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

September 18-19, 2023
Day 1

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

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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Duke | MARGOLIS CENTER for Health Policy

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#PregSafe

The Role of Postapproval Pregnancy Safety Studies

Leyla Sahin, MD, Deputy Director for Safety
Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research

Optimizing the Use of Postapproval Pregnancy Safety Studies

FDA-Duke Margolis Public Workshop September 18, 2023

Disclaimer

- 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- Overview of 2019 Postapproval Pregnancy Safety Studies Draft Guidance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  - 2019 Postapproval Pregnancy Safety Studies Draft Guidance published based on input from public meeting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)

PDS Pharmacoepidemiology & Drug Safety

ispe Official Journal of the International Society for Pharmacoepidemiology

REVIEW | Full Access

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.

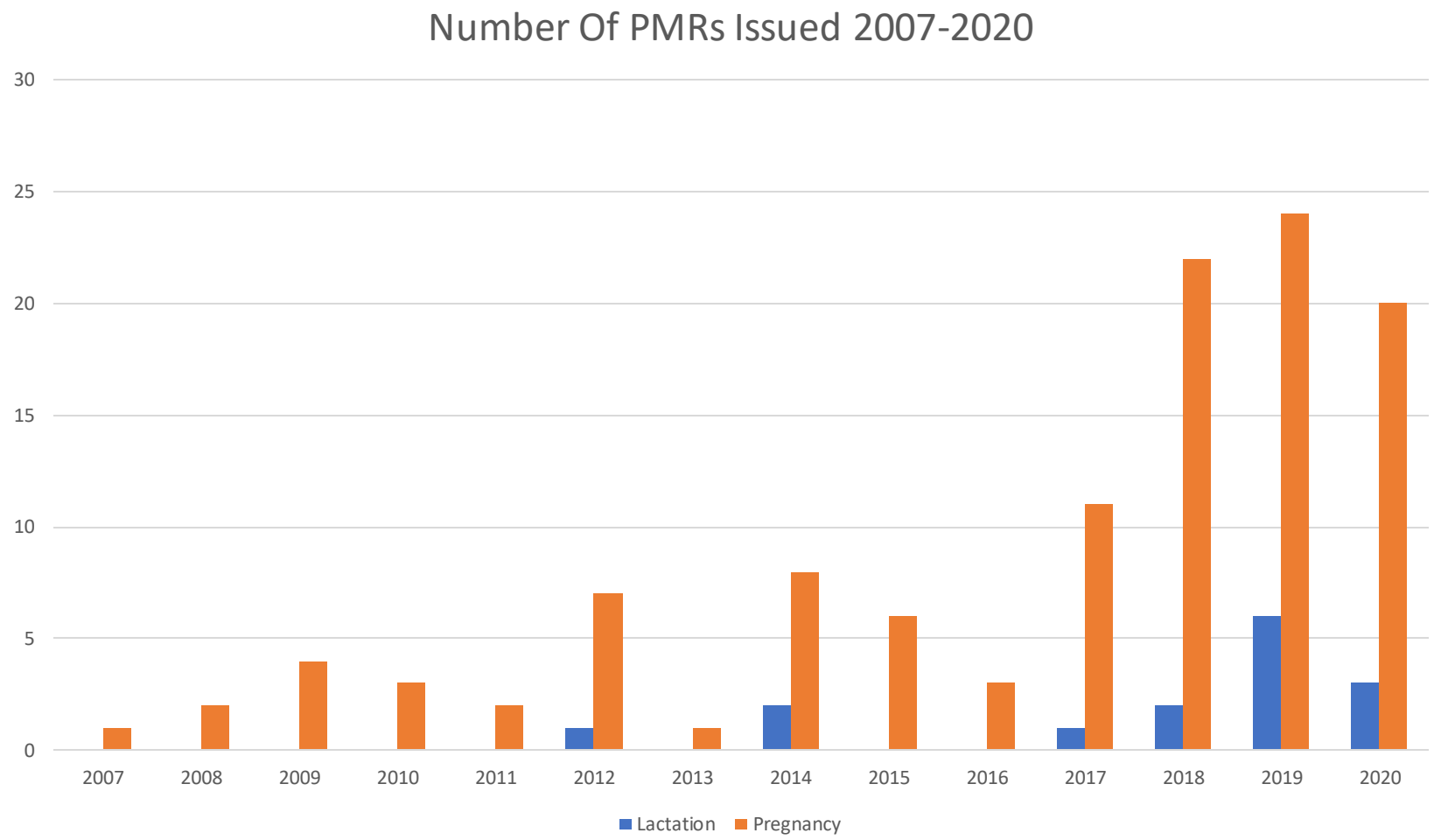
SECTIONS PDF TOOLS SHARE

Abstract

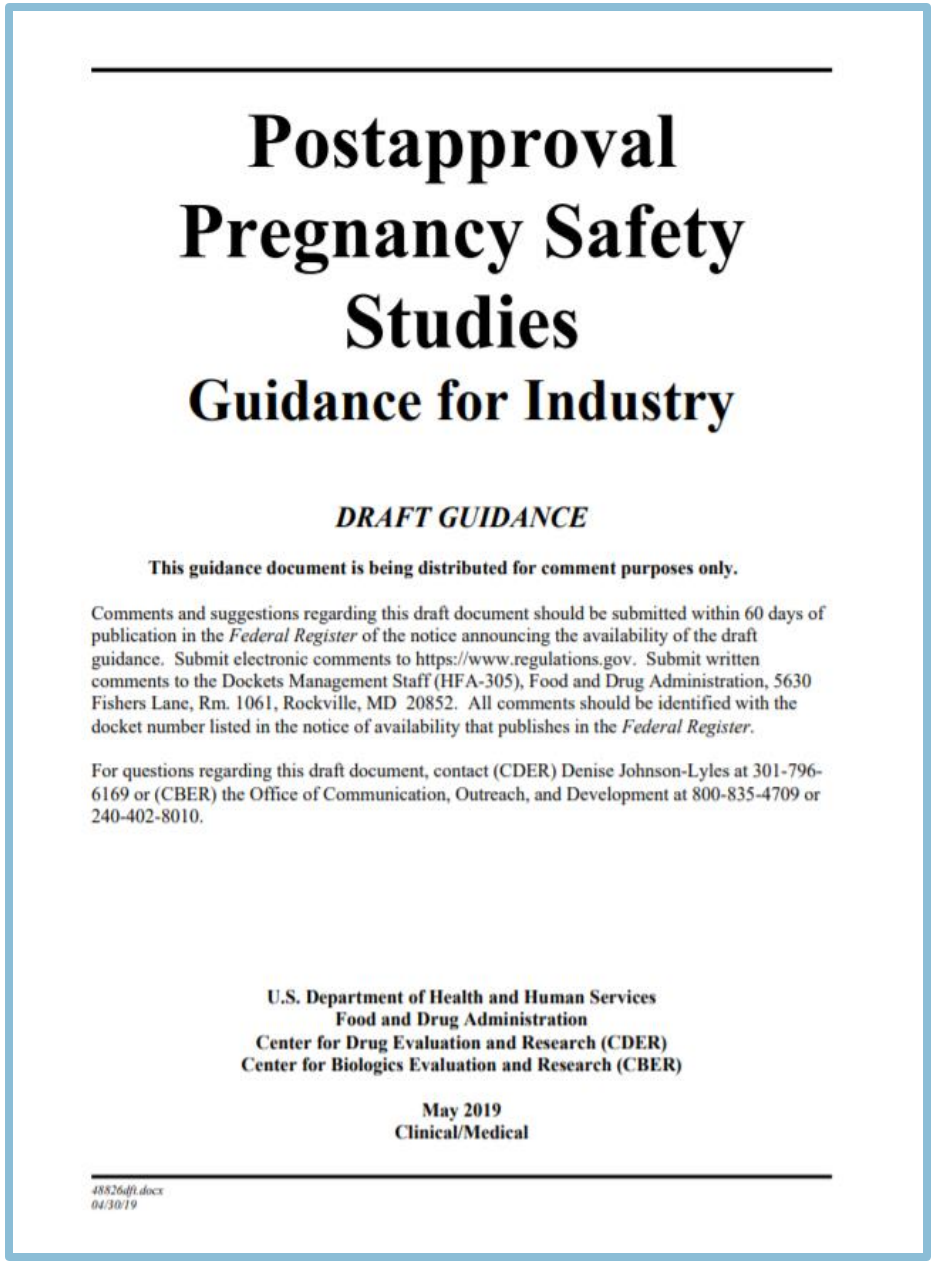
Since pregnant and lactating women have historically been excluded from drug development trials, safety studies need to be conducted postapproval. This study evaluated FDA's Post Marketing Requirements for pregnancy and lactation studies from 2007 to 2020, and identified trends and potential future opportunities. The number of

November 2022

Trends in Pregnancy and Lactation PMRs



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, Rm. 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.

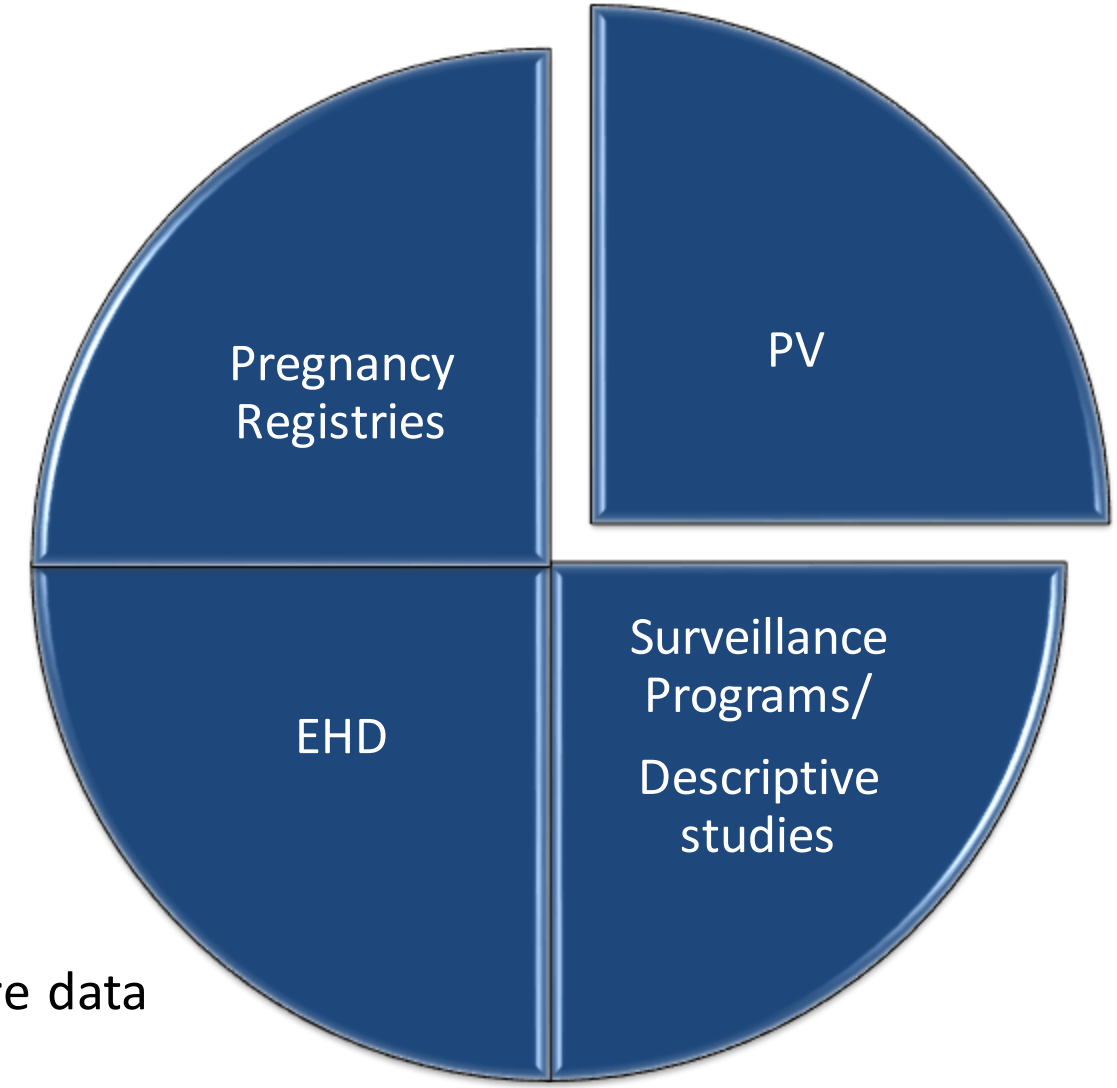
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Clinical/Medical

48826dft.docx
04/30/19

- Published in 2019
- Guidance undergoing revision

Highlights of Draft Guidance



EHD=Electronic healthcare data

PV=Pharmacovigilance

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)

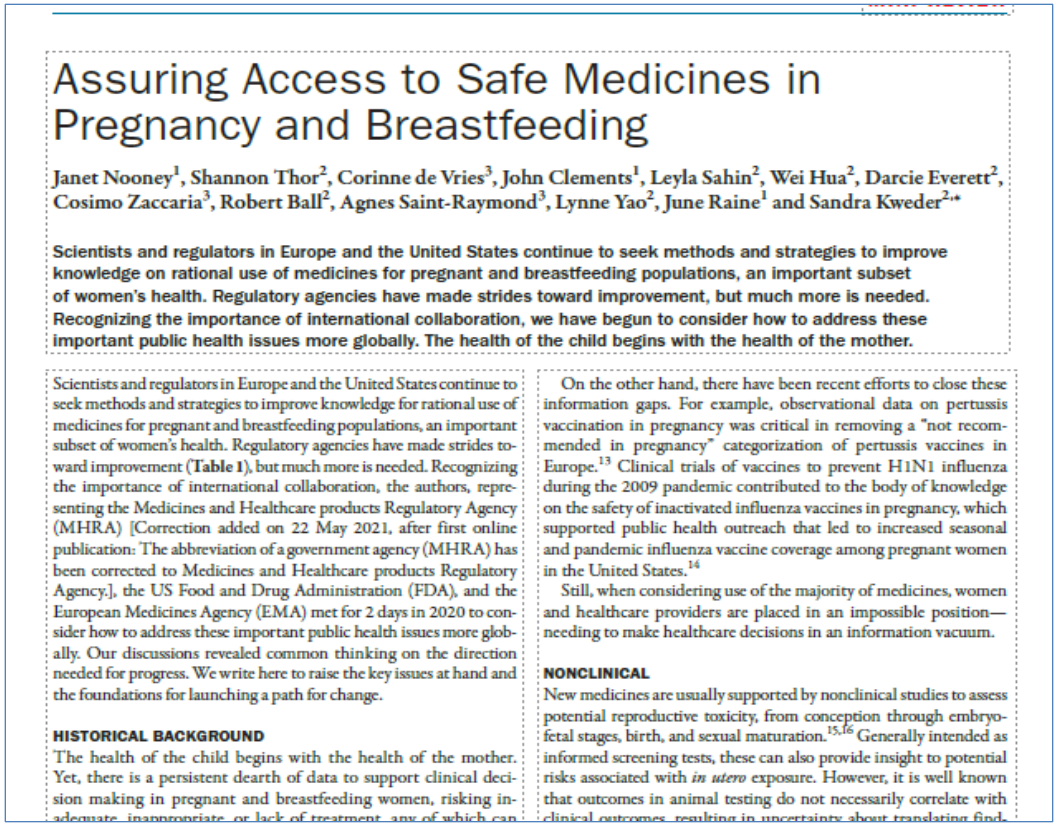
- Increase the quantity, quality, and timeliness of research involving therapeutic products used by pregnant women
- Implement a proactive approach to protocol development and study design
  - Develop a systematic plan for timely collection of data (including safety data) in pregnant women
- Optimize 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

Health Canada

FDA

MHRA



Assuring Access to Safe Medicines in Pregnancy and Breastfeeding

Janet Nooney[1], Shannon Thor[2], Corinne de Vries[3], John Clements[1], Leyla Sahin[2], Wei Hua[2], Darcie Everett[2], Cosimo Zaccaria[3], Robert Ball[2], Agnes Saint-Raymond[3], Lynne Yao[2], June Raine[1] and Sandra Kweder[2,*]

Scientists and regulators in Europe and the United States continue to seek methods and strategies to improve knowledge on rational use of medicines for pregnant and breastfeeding populations, an important subset of women's health. Regulatory agencies have made strides toward improvement, but much more is needed. Recognizing the importance of international collaboration, we have begun to consider how to address these important public health issues more globally. The health of the child begins with the health of the mother.

Scientists and regulators in Europe and the United States continue to seek methods and strategies to improve knowledge for rational use of medicines for pregnant and breastfeeding populations, an important subset of women's health. Regulatory agencies have made strides toward improvement (**Table 1**), but much more is needed. Recognizing the importance of international collaboration, the authors, representing the Medicines and Healthcare products Regulatory Agency (MHRA) [Correction added on 22 May 2021, after first online publication: The abbreviation of a government agency (MHRA) has been corrected to Medicines and Healthcare products Regulatory Agency.], the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) met for 2 days in 2020 to consider how to address these important public health issues more globally. Our discussions revealed common thinking on the direction needed for progress. We write here to raise the key issues at hand and the foundations for launching a path for change.

HISTORICAL BACKGROUND

The health of the child begins with the health of the mother. Yet, there is a persistent dearth of data to support clinical decision making in pregnant and breastfeeding women, risking inadequate, inappropriate, or lack of treatment, any of which can

On the other hand, there have been recent efforts to close these information gaps. For example, observational data on pertussis vaccination in pregnancy was critical in removing a "not recommended in pregnancy" categorization of pertussis vaccines in Europe.[13] Clinical trials of vaccines to prevent H1N1 influenza during the 2009 pandemic contributed to the body of knowledge on the safety of inactivated influenza vaccines in pregnancy, which supported public health outreach that led to increased seasonal and pandemic influenza vaccine coverage among pregnant women in the United States.[14]

Still, when considering use of the majority of medicines, women and healthcare providers are placed in an impossible position—needing to make healthcare decisions in an information vacuum.

NONCLINICAL

New medicines are usually supported by nonclinical studies to assess potential reproductive toxicity, from conception through embryo-fetal stages, birth, and sexual maturation.[15,16] Generally intended as informed screening tests, these can also provide insight to potential risks associated with *in utero* exposure. However, it is well known that outcomes in animal testing do not necessarily correlate with clinical outcomes, resulting in uncertainty about translating find-

CLINICAL PHARMACOLOGY & THERAPEUTICS |
VOLUME 110 NUMBER 4 | October 2021

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

Optimizing the Use of Postapproval Pregnancy Safety Studies

A Hybrid Public Workshop

Duke | MARGOLIS CENTER *for* Health Policy

September 18 & 19, 2023

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

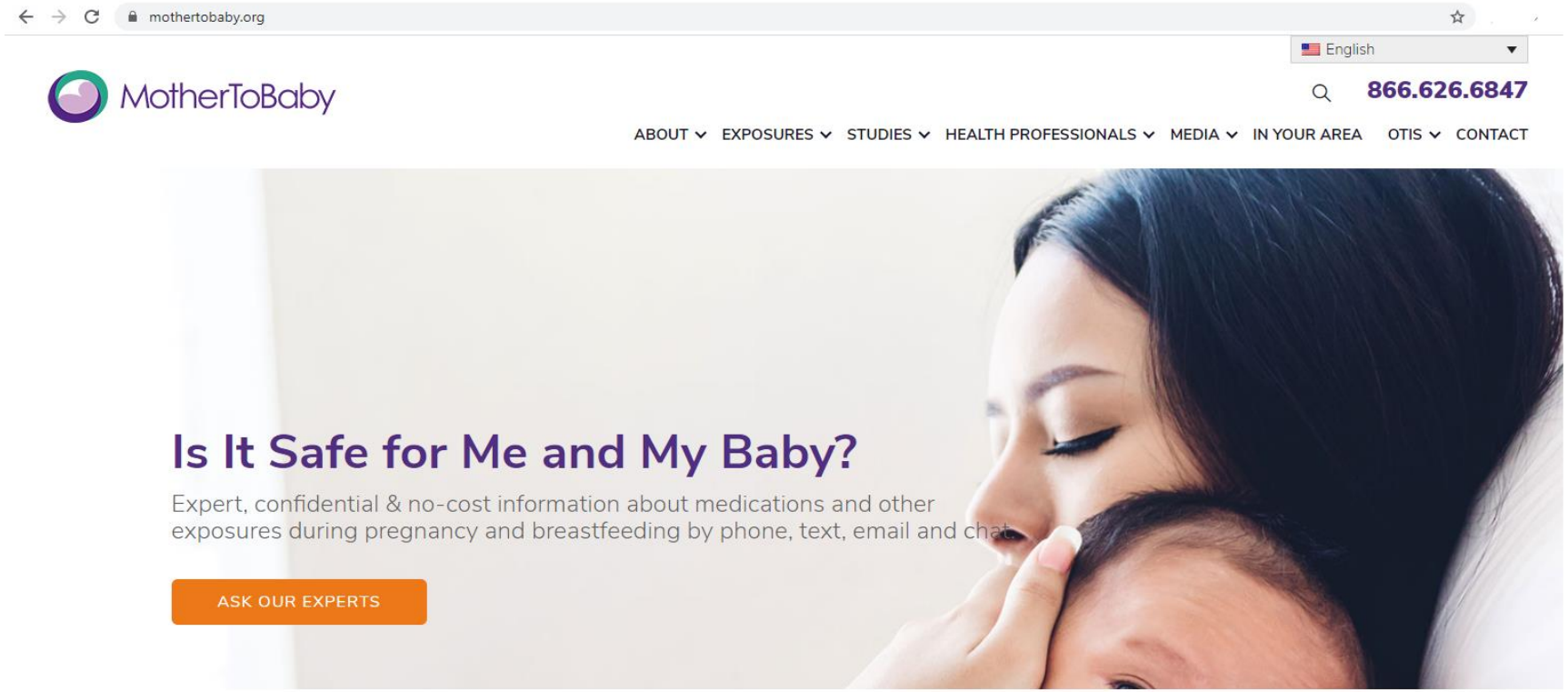
Elyse Kharbanda, HealthPartners Institute

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

UC San Diego School of Medicine
MotherToBaby Pregnancy Studies
VAMPSS Vaccines and Medications in Pregnancy Surveillance System



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UC San Diego SCHOOL OF MEDICINE

MotherToBaby PREGNANCY STUDIES

VAMPSS Vaccines and Medications in Pregnancy Surveillance System

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

English

MotherToBaby

866.626.6847

ABOUT EXPOSURES STUDIES HEALTH PROFESSIONALS MEDIA IN YOUR AREA OTIS CONTACT

MotherToBaby Pregnancy Studies

Ongoing Studies: Providing Better Information on Medication Safety in Pregnancy

LIVE CHAT

Center for Better Beginnings

UC San Diego School of Medicine

MotherToBaby Pregnancy Studies

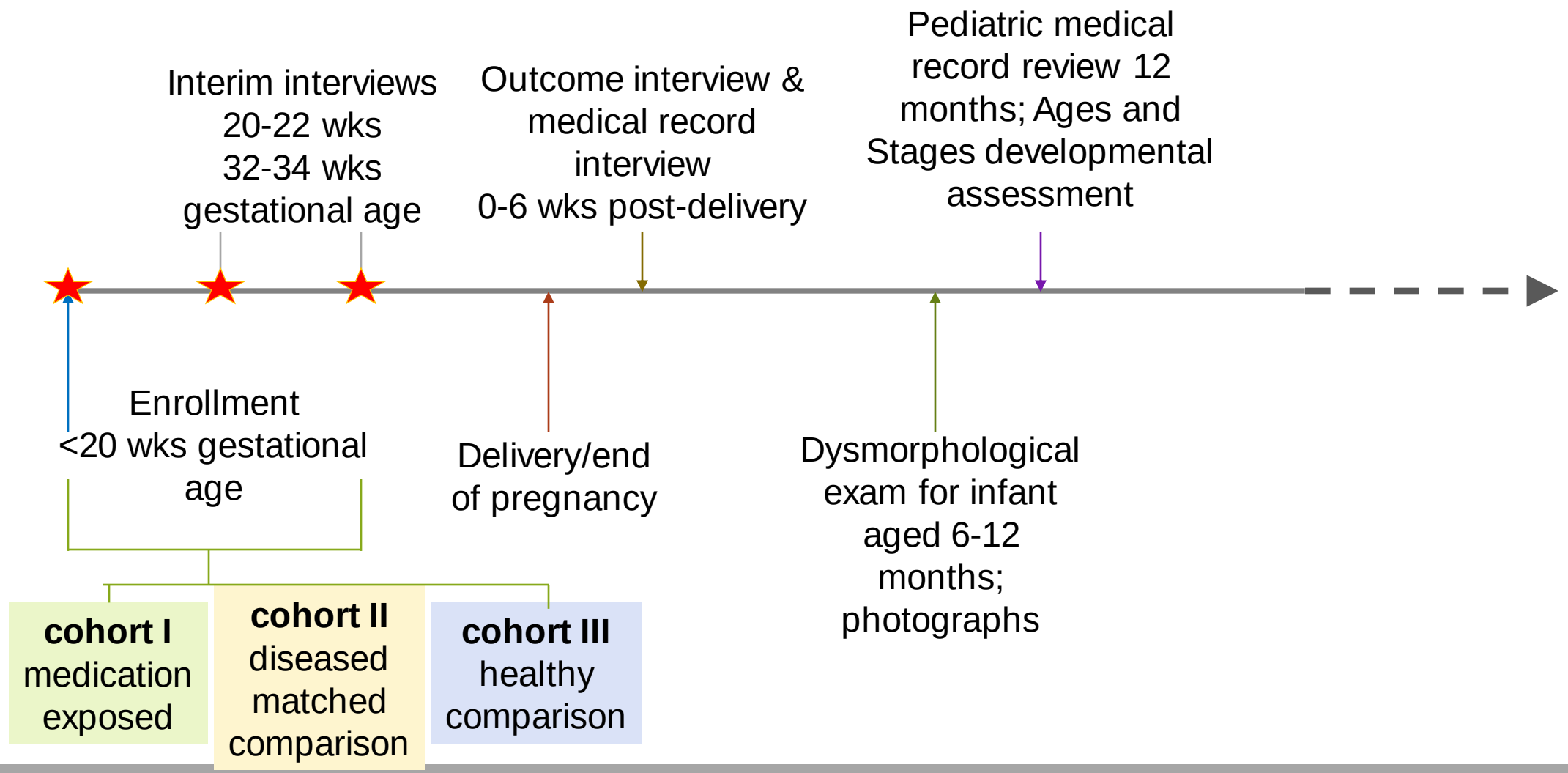
VAMPSS Vaccines and Medications in Pregnancy Surveillance System

MotherToBaby Pregnancy Registry Cohort Study Design

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



Key Assumptions

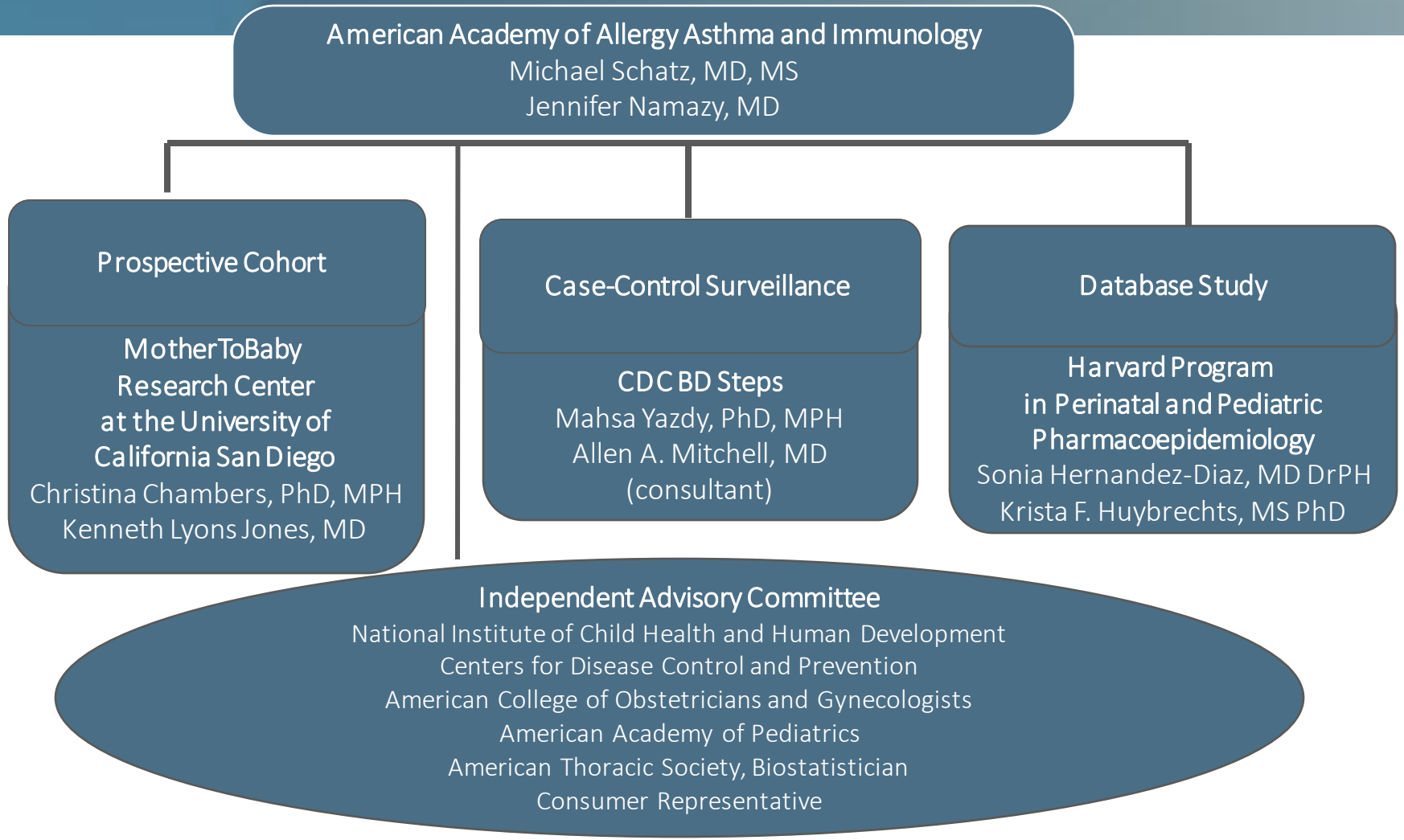
- Pregnancy registries are typically underpowered to evaluate risk/safety for specific congenital anomalies
- Even if a registry is adequately powered to rule out a 2-3 fold increased risk of major congenital anomalies combined, this is not what we expect of a teratogen – we expect that specific anomalies/clusters 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.

Key Design Features MotherToBaby Registries

- 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



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MotherToBaby
PREGNANCY STUDIES

VAMPSS
Vaccines and Medications in Pregnancy Surveillance System

Vaccine
Volume 34, Issue 37, 17 August 2016, Pages 4443-4449

Safety of the 2010–11, 2011–12, 2012–13, and 2013–14 seasonal influenza vaccines in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS ☆

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

Vaccine
Volume 34, Issue 37, 17 August 2016, Pages 4450-4459

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 [a, d], Stephen Kerr [a, d], Carla M. Van Bennekom [a, d], Christina Chambers [b, d], Kenneth L. Jones [b, d], Michael Schatz [c, d], Allen A. Mitchell [a, d]

MotherToBaby Pregnancy Studies – Examples of Registries that "Succeeded"

Product	Design	Years of Enrollment	Target Sample Size	Lost to follow-up	Results included in Product Label
Etanercept	3 prospective cohorts	2000-2012	830 (370 exposed)	4%	Yes
Adalimumab	3 prospective cohorts	2004-2016	602 (257 exposed)	7%	Yes
Vedolizumab	3 prospective cohorts	2015-2020	300 (100 exposed)	6%	Final Analysis Completed
Certolizumab	3 prospective cohorts	2012-2019	450 (150 exposed)	9%	Final Analysis Completed
Dupilimab	3 prospective cohorts	2018-date	600 (200 exposed)	3%	Expect completion 2024
Pfizer-BioNTech Covid-19 Vaccine	2 prospective cohorts	2021-2023	2000 (1100 exposed)	Not yet determined	Enrollment Completed

MotherToBaby Pregnancy Studies – Examples of Registries that "Failed"

Product	Design	Years of Enrollment	Target Sample Size	Sample Size Achieved
Tocilizumab	3 prospective cohorts	2010-2022	300 (100 exposed)	226 (34 exposed)
Tofacitinib	3 prospective cohorts	2013-2022	300 (100 exposed)	211 (11 exposed)
Mepolizumab	3 prospective cohorts	2016-2022	800 (200 exposed)	291 (23 exposed)

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"

Final Comments

- 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

Optimizing the Use of Postapproval Pregnancy Safety Studies
FDA / Duke Margolis Center for Health Policy
Washington DC **September 18, 2023**

Disclosures

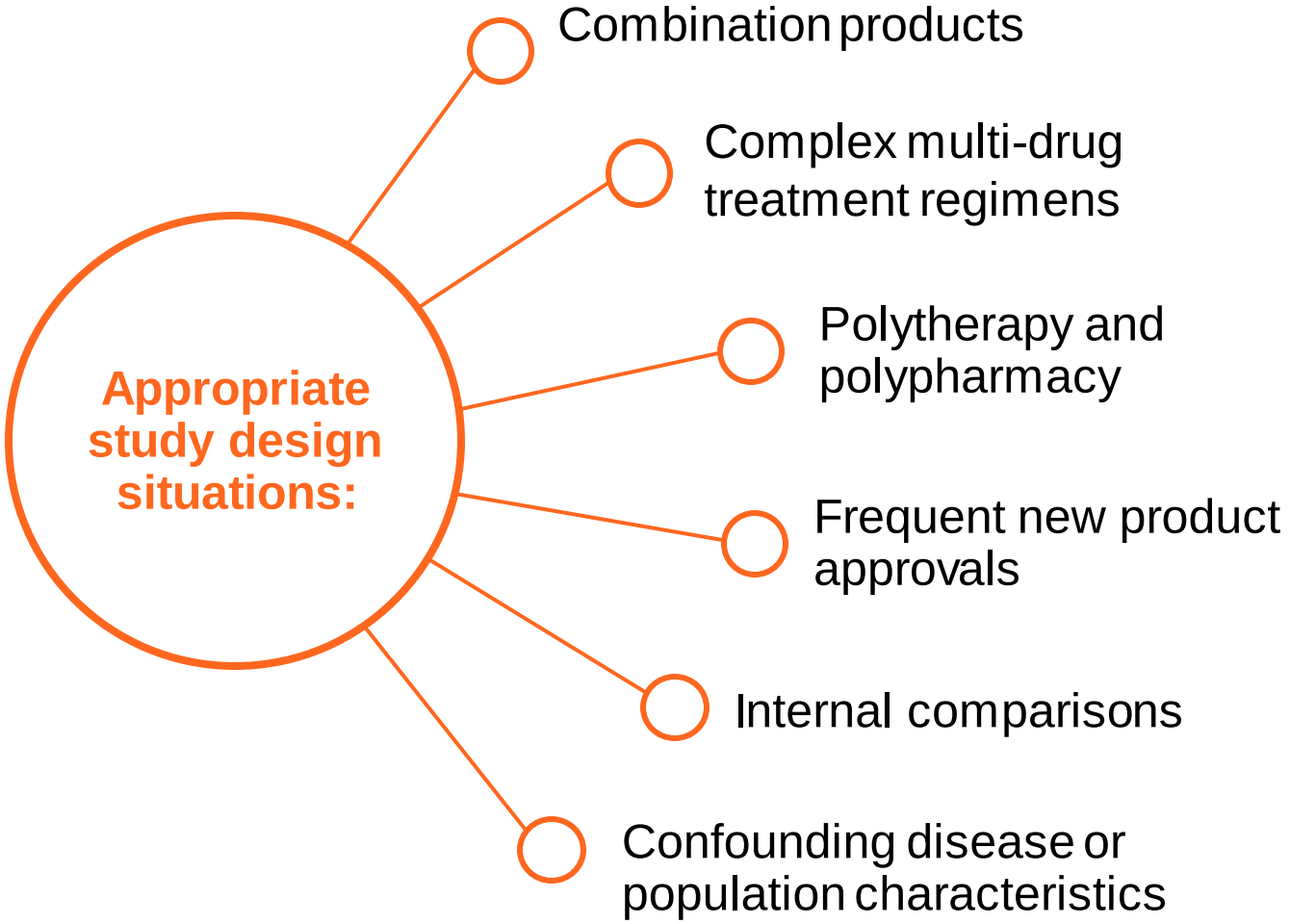
- I am a salaried employee of Syneos Health, the contract research organization that conducts the Antiretroviral Pregnancy Registry (APR); I own company stock
- The APR is a collaborative study jointly funded by the following manufacturers:

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

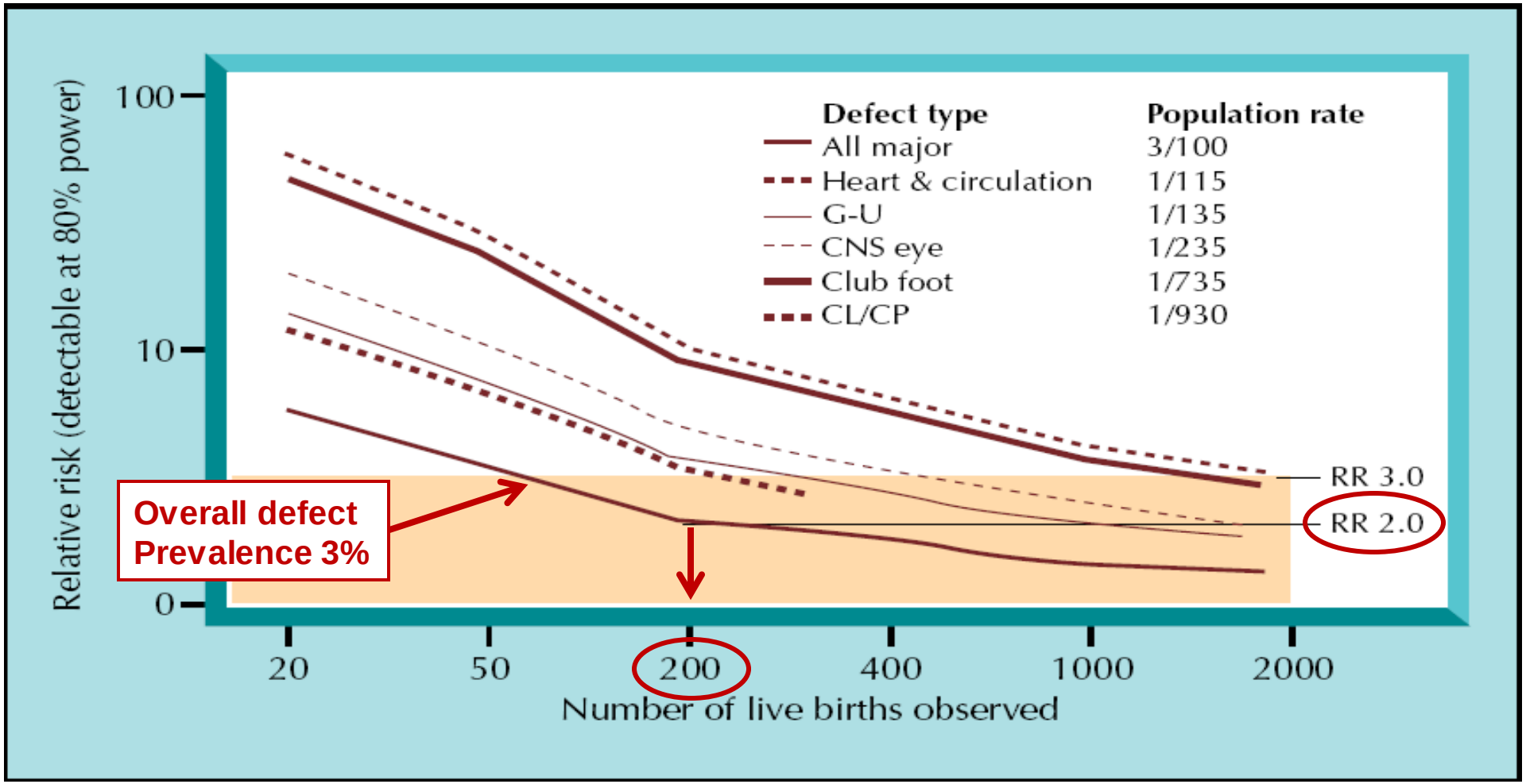
- Cohort definition:
  - exposure to specific drug(s) regardless of indication; typically all marketed brand and generic versions
  - diagnosis of a specific disease regardless if treated or untreated



Syneos Health

Introduction

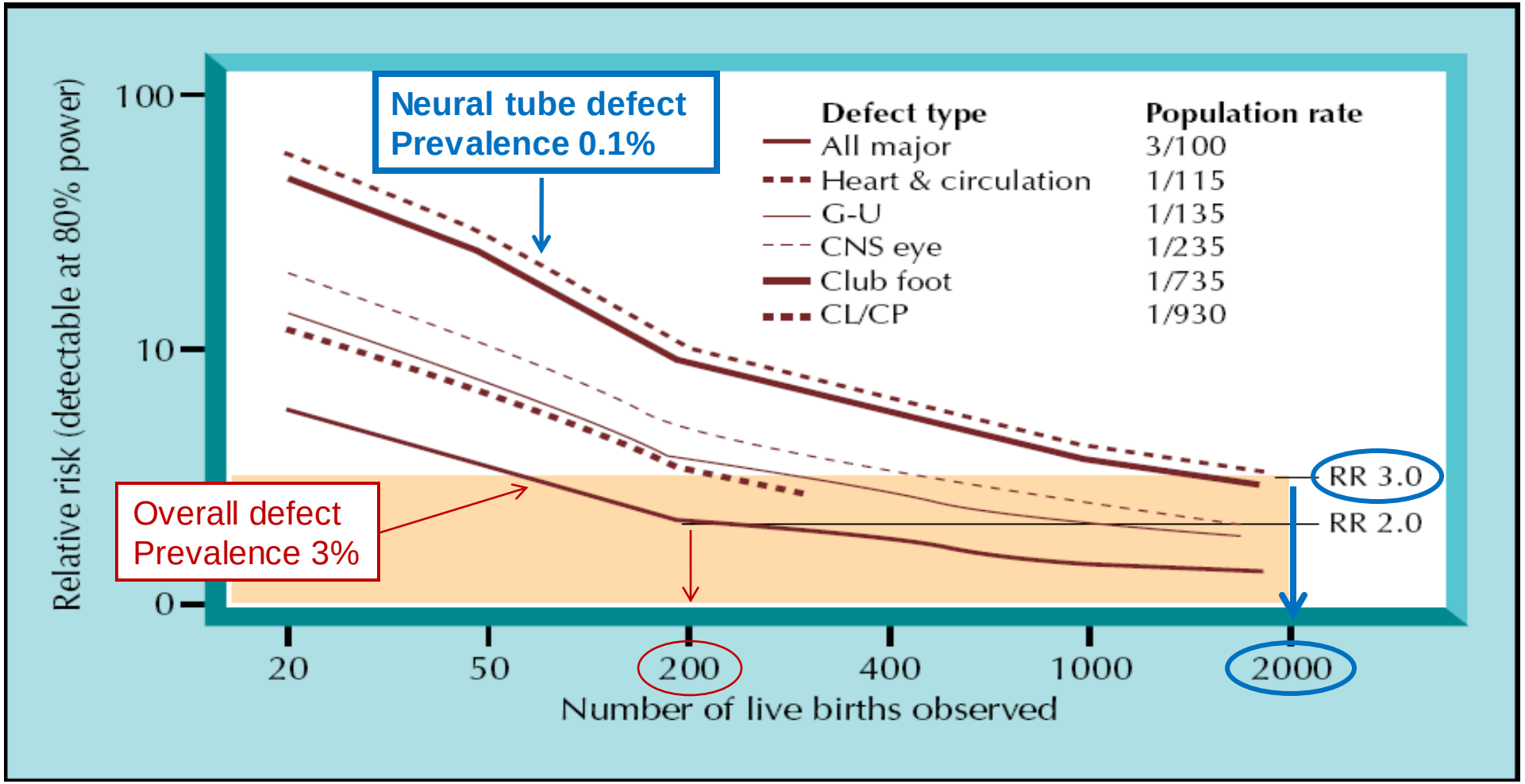
- 200 exposures can rule out a 2-fold ↑ in <u>overall</u> birth defects



Watts DH. Curr HIV/AIDS Rep 2007;4:135-140

Introduction

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



Watts DH. Curr HIV/AIDS Rep 2007;4:135-140

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; fulfils 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

Syneos Health

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)

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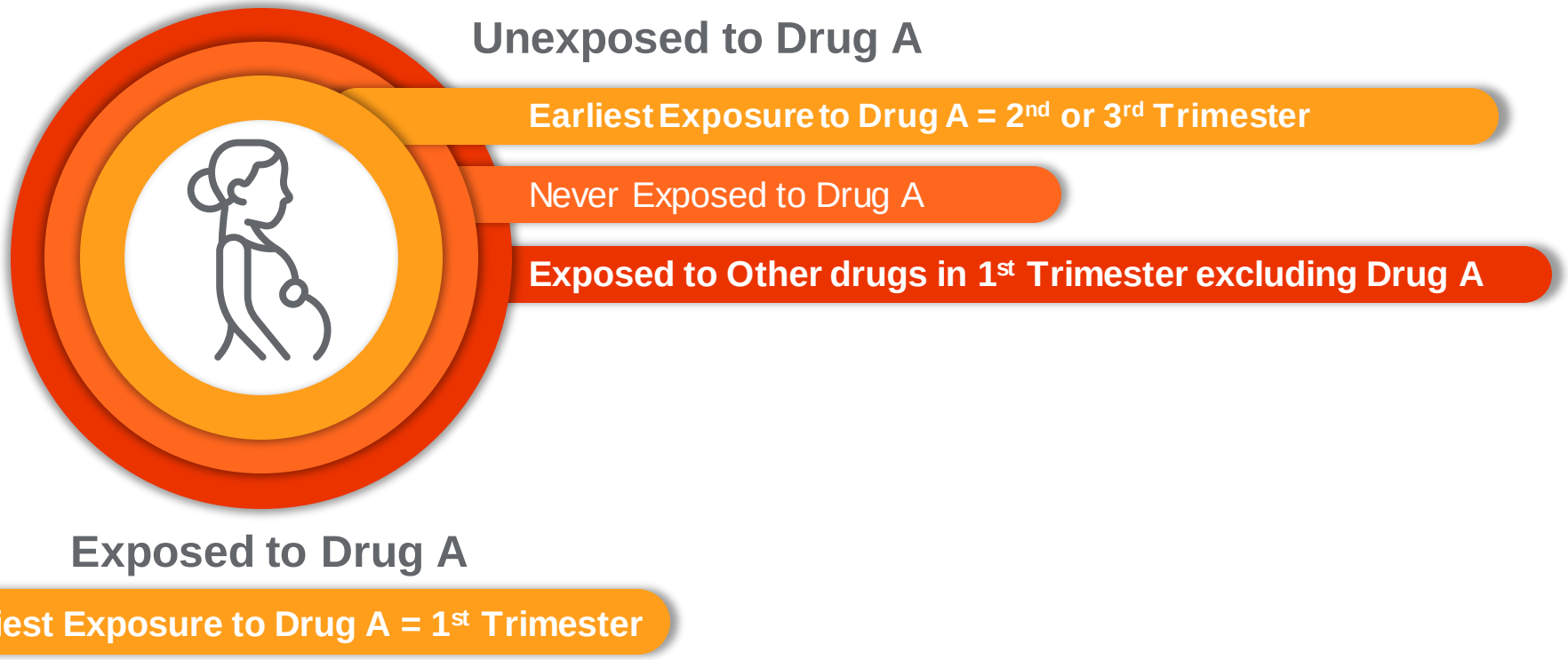
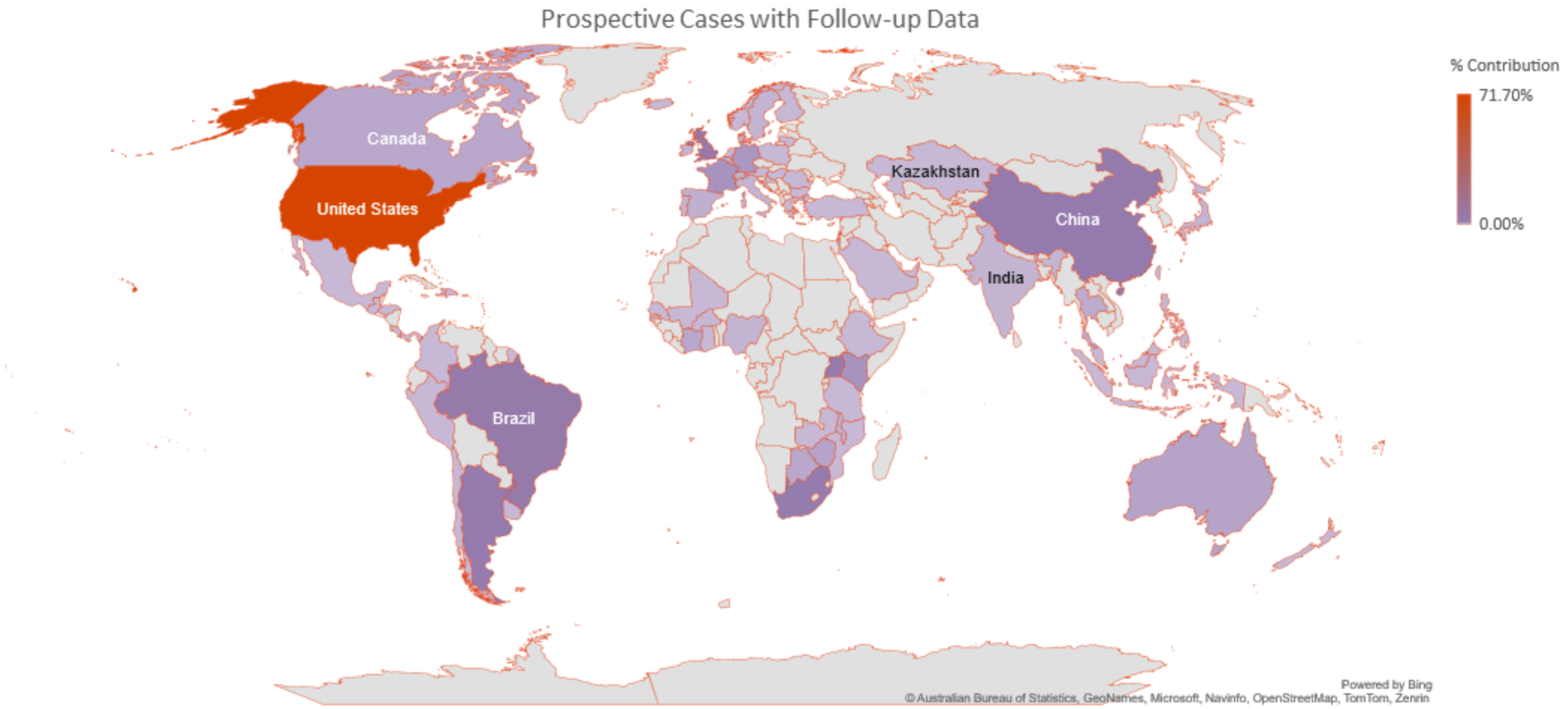
Methods: Antiretroviral Pregnancy Registry

- **Evaluating potential signals using multiple internal comparison groups**



Results: Antiretroviral Pregnancy Registry



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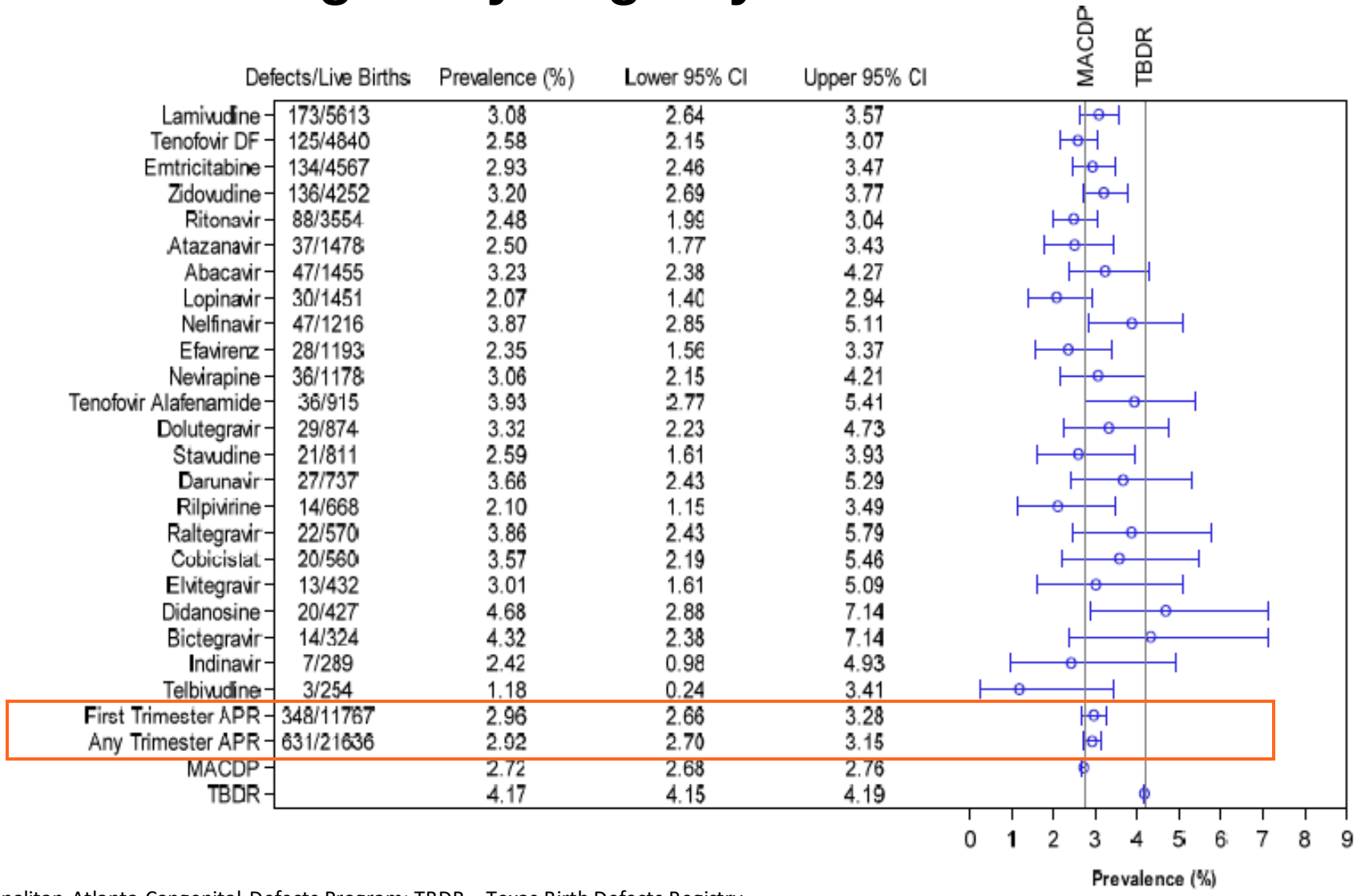
Results: Antiretroviral Pregnancy Registry

- **ARVs with ≥ 200 first trimester exposures**
- **MACDP** 2.72% (2.68, 2.76)
- **TBDR** 4.17% (4.15, 4.19)

	Defects/Live Births	Prevalence (%)	Lower 95% CI	Upper 95% CI
Lamivudine	173/5613	3.08	2.64	3.57
Tenofovir DF	125/4840	2.58	2.15	3.07
Emtricitabine	134/4567	2.93	2.46	3.47
Zidovudine	136/4252	3.20	2.69	3.77
Ritonavir	88/3554	2.48	1.99	3.04
Atazanavir	37/1478	2.50	1.77	3.43
Abacavir	47/1455	3.23	2.38	4.27
Lopinavir	30/1451	2.07	1.40	2.94
Nelfinavir	47/1216	3.87	2.85	5.11
Efavirenz	28/1193	2.35	1.56	3.37
Nevirapine	36/1178	3.06	2.15	4.21
Tenofovir Alafenamide	36/915	3.93	2.77	5.41
Dolutegravir	29/874	3.32	2.23	4.73
Stavudine	21/811	2.59	1.61	3.93
Darunavir	27/737	3.66	2.43	5.29
Rilpivirine	14/668	2.10	1.15	3.49
Raltegravir	22/570	3.86	2.43	5.79
Cobicistat	20/560	3.57	2.19	5.46
Elvitegravir	13/432	3.01	1.61	5.09
Didanosine	20/427	4.68	2.88	7.14
Bictegravir	14/324	4.32	2.38	7.14
Indinavir	7/289	2.42	0.98	4.93
Telbivudine	3/254	1.18	0.24	3.41
First Trimester APR	348/11767	2.96	2.66	3.28
Any Trimester APR	631/21636	2.92	2.70	3.15
MACDP		2.72	2.68	2.76
TBDR		4.17	4.15	4.19



MACDP = Metropolitan Atlanta Congenital Defects Program; TBDR = Texas Birth Defects Registry
Note: Confidence intervals are calculated using the Clopper-Pearson exact binomial method
Antiretroviral Pregnancy Registry; Interim Report 1 January 1989 through 31 Jan 2023

Governance Structure: Antiretroviral Pregnancy Registry

Summary: Antiretroviral Pregnancy Registry

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.

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Information Dissemination: Antiretroviral Pregnancy Registry

THE ANTIRETROVIRAL PREGNANCY REGISTRY
INTERIM REPORT

1 JANUARY 1989 THROUGH 31 JULY 2020

(Issued: June 2020 / Expiration: 6 months after issue)

For:

ABACAVIR (ZIAGEN®, ABC)
ABACAVIR•LAMIVUDINE (EPZICOM®, EPZ)
ABACAVIR•LAMIVUDINE•ZIDOVUDINE (TRIZIVIR®, TZV)
ABACAVIR•DOLUTEGRAVIR•LAMIVUDINE (TRIUMEQ®, TRI)
ADEFOVIR DIPIVOXIL (HEPSERA®, ADV)
AMPRENAVIR (AGENERASE®, APV) *(AGENERASE NO LONGER MANUFACTURED AS OF 2007)*
ATAZANAVIR (REYATAZ®, ATV)
ATAZANAVIR•COBICISTAT (EVOTAZ®, EVO)
BICTEGRAVIR•EMTRICITABINE•TENOFOVIR ALAFENAMIDE (BIKTARVY®, B/F/TAF)
COBICISTAT (TYBOST®, COBI)
DARUNAVIR (PREZISTA®, DRV)
DARUNAVIR•COBICISTAT (PREZCOBIX™, REZOLSTA™, PCX)
DARUNAVIR•COBICISTAT•EMTRICITABINE•TENOFOVIR ALAFENAMIDE (SYMTUZA®, DCF TAF)
DELAVIRDINE MESYLATE (RESCRIPTOR®, DLV)
DIDANOSINE (VIDEX®, VIDEX® EC, DDI)
DOLUTEGRAVIR (TIVICAY®, DTG)
DOLUTEGRAVIR•LAMIVUDINE (DOVATO®, D3)
DOLUTEGRAVIR•LAMIVUDINE•TENOFOVIR DISOPROXIL FUMARATE (ACRIPTEGA/TELADOMYL/TENDOLA, TLD)
DOLUTEGRAVIR•RILPIVIRINE (JULUCA ®, DTG/RPV)
DORAVIRINE (PIFELTRO™, PIF)
DORAVIRINE•LAMIVUDINE•TENOFOVIR DISOPROXIL FUMARATE (DELSTRIGO™, DEL)
EFAVIRENZ (SUSTIVA®, STOCRIN®, EFV)
EFAVIRENZ•EMTRICITABINE•TENOFOVIR DISOPROXIL FUMARATE (ATRIPLA®, ATR)
EFAVIRENZ•LAMIVUDINE•TENOFOVIR DISOPROXIL FUMARATE (SYMFI LO™, EFV/STC/TDF)
ELVITEGRAVIR (VITEKTA®, EVG)
ELVITEGRAVIR•COBICISTAT•EMTRICITABINE•TENOFOVIR ALAFENAMIDE (GENVOYA®, GEN)
ELVITEGRAVIR•COBICISTAT•EMTRICITABINE•TENOFOVIR DISOPROXIL FUMARATE (STRIBILD®, STB)
EMTRICITABINE (EMTRIVA®, FTC)
EMTRICITABINE•TENOFOVIR ALAFENAMIDE (DESCOVY®, DVY)
ENFUVIRTIDE (FUZEON®, T-20)
ENTECAVIR (BARACLUDE®, ETV)
ETRAVIRINE (INTELENCE®, ETR)
FOSAMPRENAVIR CALCIUM (LEXIVA®, FOS)
FOSTEMSAVIR (RUKOBIA, FTR)
INDINAVIR (CRIXIVAN®, IDV)
LAMIVUDINE (EPIVIR®, 3TC)
LAMIVUDINE•RALTEGRAVIR (DUTREBIS™, DUT) *(DUTREBIS NO LONGER MANUFACTURED AS OF 2017)*
LAMIVUDINE•TENOFOVIR DISOPROXIL FUMARATE (CIMDUO™, 3TC/TDF)
LAMIVUDINE•ZIDOVUDINE (COMBIVIR®, CBV)
LOPINAVIR•RITONAVIR (KALETRA®, ALUVIA®, LPV/r)
MARAVIROC (SELZENTRY®, CELSENTRI®, MVC)
NELFINAVIR (VIRACEPT®, NFV)
NEVIRAPINE (VIRAMUNE®, VIRAMUNE XR®, NVP)
RALTEGRAVIR (ISENTRESS®, RAL)
RILPIVIRINE (EDURANT®, RPV)
RILPIVIRINE•EMTRICITABINE•TENOFOVIR ALAFENAMIDE (ODEFSEY®, ODE)
RILPIVIRINE•EMTRICITABINE•TENOFOVIR DISOPROXIL FUMARATE (COMPLERA®, CPA; EVIPLERA®, EPA)
RITONAVIR (NORVIR®, RTV)
SAQUINAVIR (FORTOVASE®, SQV-SGC) *(FORTOVASE NO LONGER MANUFACTURED AS OF 2006)*
SAQUINAVIR MESYLATE (INVIRASE®, SQV-HGC)
STAVUDINE (ZERIT®, d4T)
TELBIVUDINE (SEBIVO®, TYZEKA®, LdT)
TENOFOVIR ALAFENAMIDE (VEMLIDY®, TAF)
TENOFOVIR DISOPROXIL FUMARATE (VIREAD®, TDF)
TENOFOVIR DISOPROXIL FUMARATE•EMTRICITABINE (TRUVADA®, TVD)
TIPRANAVIR (APTIVUS®, TPV)
ZALCITABINE (HIVID®, ddC) *(HIVID NO LONGER MANUFACTURED AS OF 2006)*
ZIDOVUDINE (RETROVIR®, ZDV)

Collaborative Project Sponsored by:
AbbVie, Accord Healthcare, Alvogen, Amneal Pharmaceuticals, Apotex, Aurobindo Pharma, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb Company, Cellfrion, Cipla, Gilead Sciences, Hetero Labs, Hikma Pharmaceuticals USA, Janssen Scientific Affairs, Lannett Company, Laurus Labs, Lupin Pharmaceuticals, Macleods Pharmaceuticals, Merck & Co., Mylan Laboratories, Prinston Pharmaceutical, Qilu Pharmaceutical, Sandoz, SigmaPharm Laboratories, Strides Shasun Limited, Teva Pharmaceuticals USA, and ViiV Healthcare

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AMERICAN CONFERENCE FOR THE TREATMENT OF HIV

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Is It Safe? Safety Surveillance through the Antiretroviral Pregnancy Registry

Release Date: June 2, 2023
Expiration Date: June 2, 2024
Estimated Time to Complete: 1.25 hour

VIEW ACTIVITY

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Clinical Gap and Educational Need

Learning Objectives

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Division of Genetic Diagnostics Director
Rare Disease Center of Excellence
UT Southwestern Medical Center

Target Audience

Accreditation and Credit Designation

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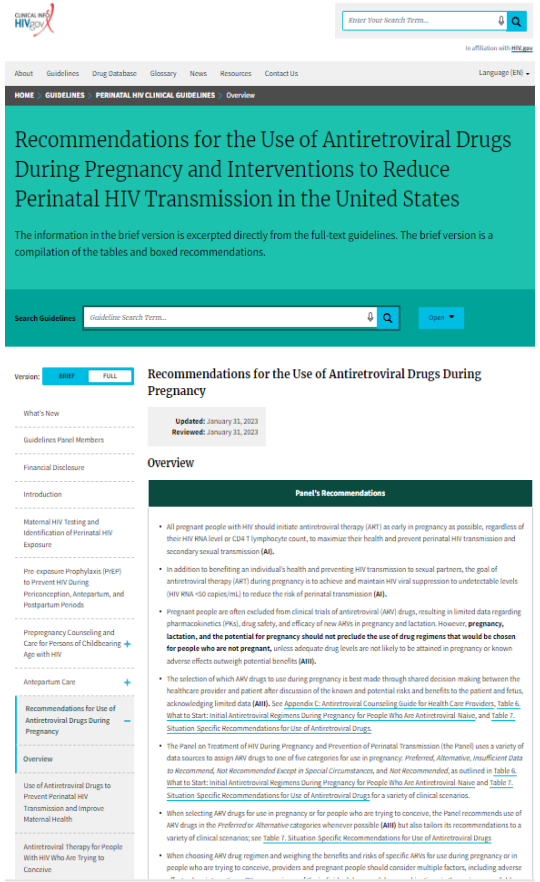
VIRTUAL GRAND ROUNDS



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HOME > GUIDELINES > PERINATAL HIV CLINICAL GUIDELINES > Overview

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

The information in the brief version is excerpted directly from the full-text guidelines. The brief version is a compilation of the tables and boxed recommendations.

Search Guidelines: Guideline Search Term... | Open

Version: BRIEF | FULL

What's New
Guidelines Panel Members
Financial Disclosure
Introduction
Maternal HIV Testing and Identification of Perinatal HIV Exposure
Pre-exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods
Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV
Antepartum Care
Recommendations for Use of Antiretroviral Drugs During Pregnancy
Overview
Use of Antiretroviral Drugs to Prevent Perinatal HIV Transmission and Improve Maternal Health
Antiretroviral Therapy for People With HIV Who Are Trying to Conceive

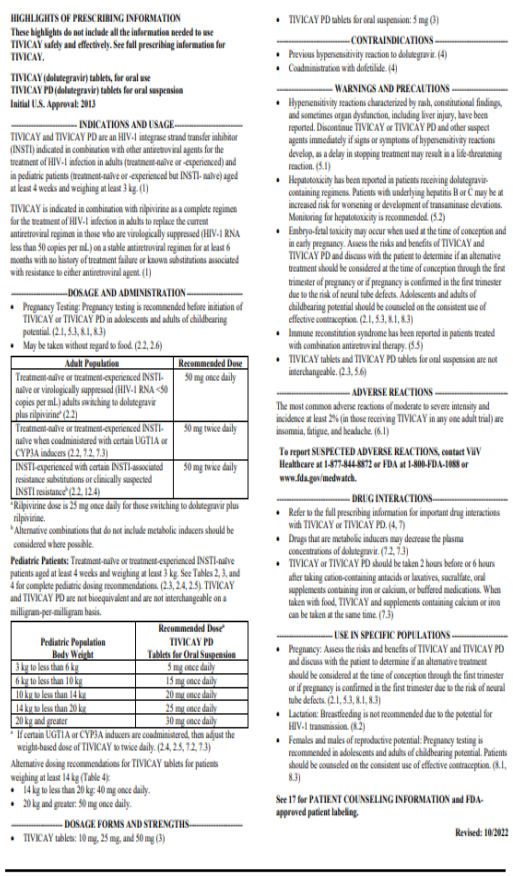
Recommendations for the Use of Antiretroviral Drugs During Pregnancy

Updated: January 31, 2023
Reviewed: January 31, 2023

Overview

Panel's Recommendations

- All pregnant people with HIV should initiate antiretroviral therapy (ART) as early in pregnancy as possible, regardless of their HIV RNA level or CD4 T lymphocyte count, to maximize their health and prevent perinatal HIV transmission and secondary sexual transmission **(AI).**
- In addition to benefiting an individual's health and preventing HIV transmission to sexual partners, the goal of antiretroviral therapy (ART) during pregnancy is to achieve and maintain HIV viral suppression to undetectable levels (HIV RNA <50 copies/mL) to reduce the risk of perinatal transmission **(AI).**
- Pregnant people are often excluded from clinical trials of antiretroviral (ARV) drugs, resulting in limited data regarding pharmacokinetics (PKs), drug safety, and efficacy of new ARVs in pregnancy and lactation. However, **pregnancy, lactation, and the potential for pregnancy should not preclude the use of drug regimens that would be chosen for people who are not pregnant,** unless adequate drug levels are not likely to be attained in pregnancy or known adverse effects outweigh potential benefits **(AIII).**
- The selection of which ARV drugs to use during pregnancy is best made through shared decision making between the healthcare provider and patient after discussion of the known and potential risks and benefits to the patient and fetus, acknowledging limited data **(AIII).** See Appendix C: Antiretroviral Counseling Guide for Health Care Providers, Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral Naive, and Table 7. Situation Specific Recommendations for Use of Antiretroviral Drugs.
- The Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) uses a variety of data sources to assign ARV drugs to one of five categories for use in pregnancy: *Preferred, Alternative, Insufficient Data to Recommend, Not Recommended Except in Special Circumstances,* and *Not Recommended,* as outlined in Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral Naive and Table 7. Situation Specific Recommendations for Use of Antiretroviral Drugs for a variety of clinical scenarios.
- When selecting ARV drugs for use in pregnancy or for people who are trying to conceive, the Panel recommends use of ARV drugs in the *Preferred* or *Alternative* categories whenever possible **(AIII)** but also tailors its recommendations to a variety of clinical scenarios; see Table 7. Situation Specific Recommendations for Use of Antiretroviral Drugs
- When choosing ARV drug regimen and weighing the benefits and risks of specific ARVs for use during pregnancy or in people who are trying to conceive, providers and pregnant people should consider multiple factors, including adverse



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TIVICAY safely and effectively. See full prescribing information for TIVICAY.

TIVICAY (dolutegravir) tablets, for oral use
TIVICAY PD (dolutegravir) tablets for oral suspension
Initial U.S. Approval: 2013

INDICATIONS AND USAGE

TIVICAY and TIVICAY PD are an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults (treatment-naïve or -experienced) and in pediatric patients (treatment-naïve or -experienced but INSTI- naïve) aged at least 4 weeks and weighing at least 3 kg. (1)

TIVICAY is indicated in combination with rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent. (1)

DOSAGE AND ADMINISTRATION

- Pregnancy Testing: Pregnancy testing is recommended before initiation of TIVICAY or TIVICAY PD in adolescents and adults of childbearing potential. (2.1, 5.3, 8.1, 8.3)
- May be taken without regard to food. (2.2, 2.6)

Adult Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirine[a] (2.2)	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers (2.2, 7.3, 7.3)	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b] (2.2, 12.4)	50 mg twice daily

[a] Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.
[b] Alternative combinations that do not include metabolic inducers should be considered where possible.

Pediatric Patients: Treatment-naïve or treatment-experienced INSTI-naïve patients aged at least 4 weeks and weighing at least 3 kg. See Tables 2, 3, and 4 for complete pediatric dosing recommendations. (2.3, 2.4, 2.5). TIVICAY and TIVICAY PD are not bioequivalent and are not interchangeable on a milligram-per-milligram basis.

Pediatric Population Body Weight	Recommended Dose[a] TIVICAY PD Tablets for Oral Suspension
3 kg to less than 6 kg	5 mg once daily
6 kg to less than 10 kg	15 mg once daily
10 kg to less than 14 kg	20 mg once daily
14 kg to less than 20 kg	25 mg once daily
20 kg and greater	30 mg once daily

[a] If certain UGT1A or CYP3A inducers are coadministered, then adjust the weight-based dose of TIVICAY to twice daily. (2.4, 2.5, 7.2, 7.3)

Alternative dosing recommendations for TIVICAY tablets for patients weighing at least 14 kg (Table 4):
- 14 kg to less than 20 kg: 40 mg once daily.
- 20 kg and greater: 50 mg once daily.

DOSAGE FORMS AND STRENGTHS

- TIVICAY tablets: 10 mg, 25 mg, and 50 mg (3)
- TIVICAY PD tablets for oral suspension: 5 mg (3)

CONTRAINDICATIONS

- Previous hypersensitivity reaction to dolutegravir. (4)
- Coadministration with dofetilide. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue TIVICAY or TIVICAY PD and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.1)
- Hepatotoxicity has been reported in patients receiving dolutegravir-containing regimens. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Monitoring for hepatotoxicity is recommended. (5.2)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.3, 8.1, 8.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.5)
- TIVICAY tablets and TIVICAY PD tablets for oral suspension are not interchangeable. (2.3, 5.6)

ADVERSE REACTIONS

The most common adverse reactions of moderate to severe intensity and incidence at least 2% (in those receiving TIVICAY in any one adult trial) are insomnia, fatigue, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with TIVICAY or TIVICAY PD. (4, 7)
- Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. (7.2, 7.3)
- TIVICAY or TIVICAY PD should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. When taken with food, TIVICAY and supplements containing calcium or iron can be taken at the same time. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1, 8.3)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing is recommended in adolescents and adults of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

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Conclusions

Making the Case for Consolidated Collaborative Registries

Challenges

Complexity	Collaboration	Communication	Competition	Confidentiality	Commitment
• Operationally and analytically complex • Requires high degree of expertise to implement	• Marketplace competitors must agree to work together • Adopt and adhere to common processes, policies and timelines	• Respect established lines of communication • Documentation is critical	• Innovator companies have onus to set-up and implement	• Necessary to be sensitive to proprietary aspects of drug discovery, marketing, life-cycle management	• Various stakeholders may have different priorities and levels of interests

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Chambers, et al. J Allergy Clin Immunol 2021;147:2009-20.

Making the Case for Consolidated Collaborative Registries

Advantages

Logical	Economical	Efficient	Recruitment	Methodological	Consistency
• 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

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Chambers, et al. J Allergy Clin Immunol 2021;147:2009-20.

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CDC COVID-19 Vaccine Pregnancy Registry

Optimizing the Use of Post-approval Pregnancy Safety Studies

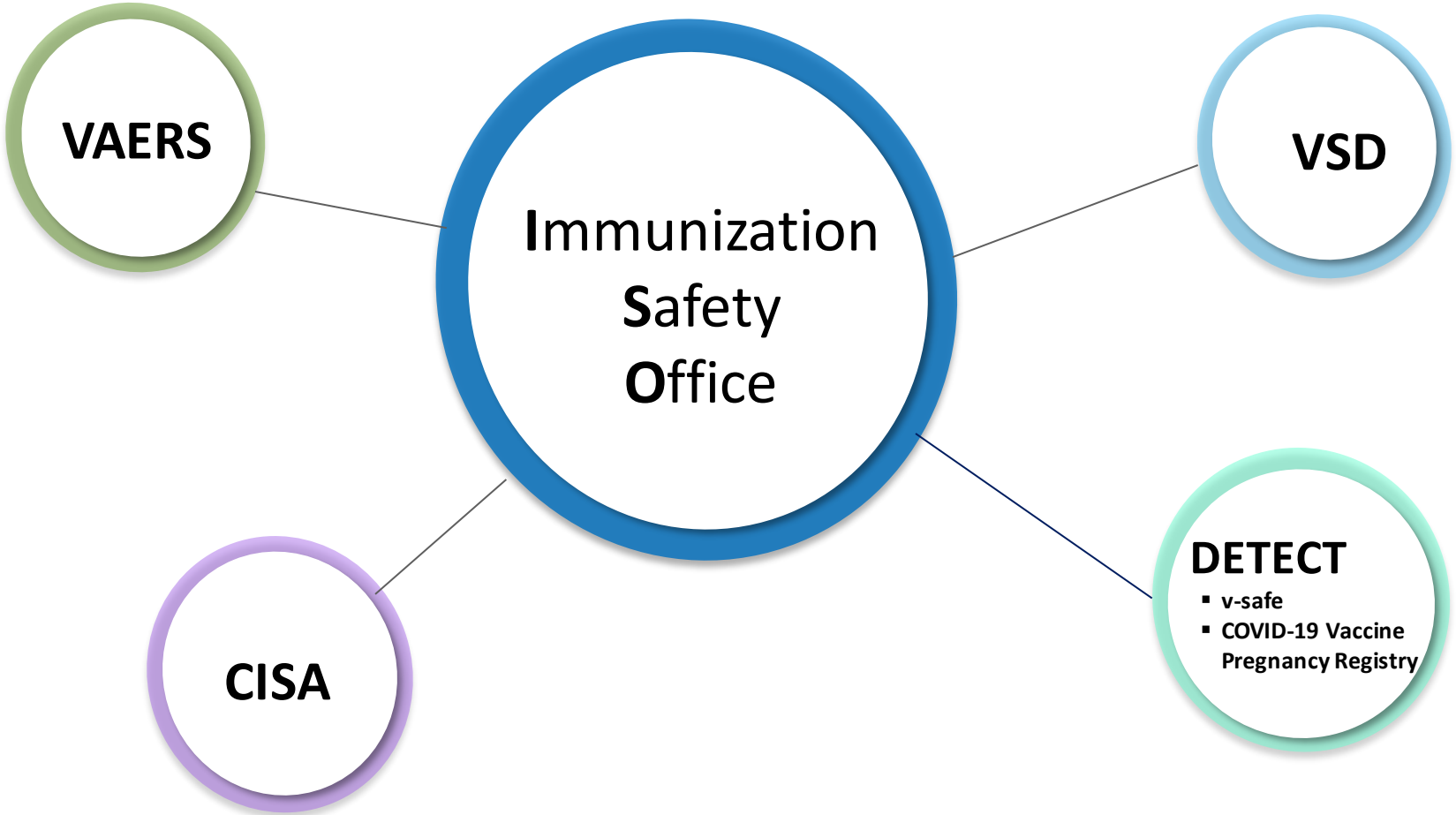
September 18, 2023

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

v-safe after vaccination health checker

- Active, smart-phone based monitoring system for COVID-19 vaccines
- Voluntary self-enrollment
- Started DEC 14, 2020

Individuals Reporting Pregnancy*

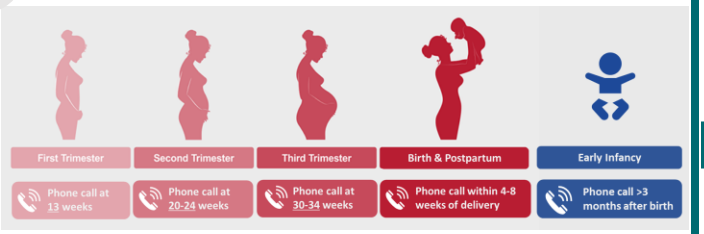
Eligibility Screening[Ŧ]

- 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

Eligible Individuals

Phase 1: Preconception to 3 months

Consent for registry enrollment and follow-up

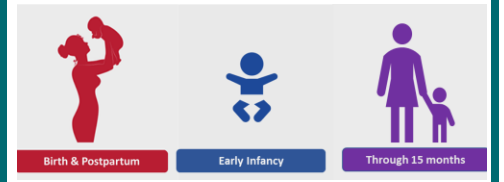


- Survey included:
  - Demographics, health over pregnancy
  - Pregnancy outcome
  - Birth hospitalization, postpartum
  - Infant health to 3 months of age
- Consent obtained for medical records

Eligibility: Participants who were not lost to follow-up or did not opt out of follow-up

Phase 2: Through 15 months

Extended follow-up



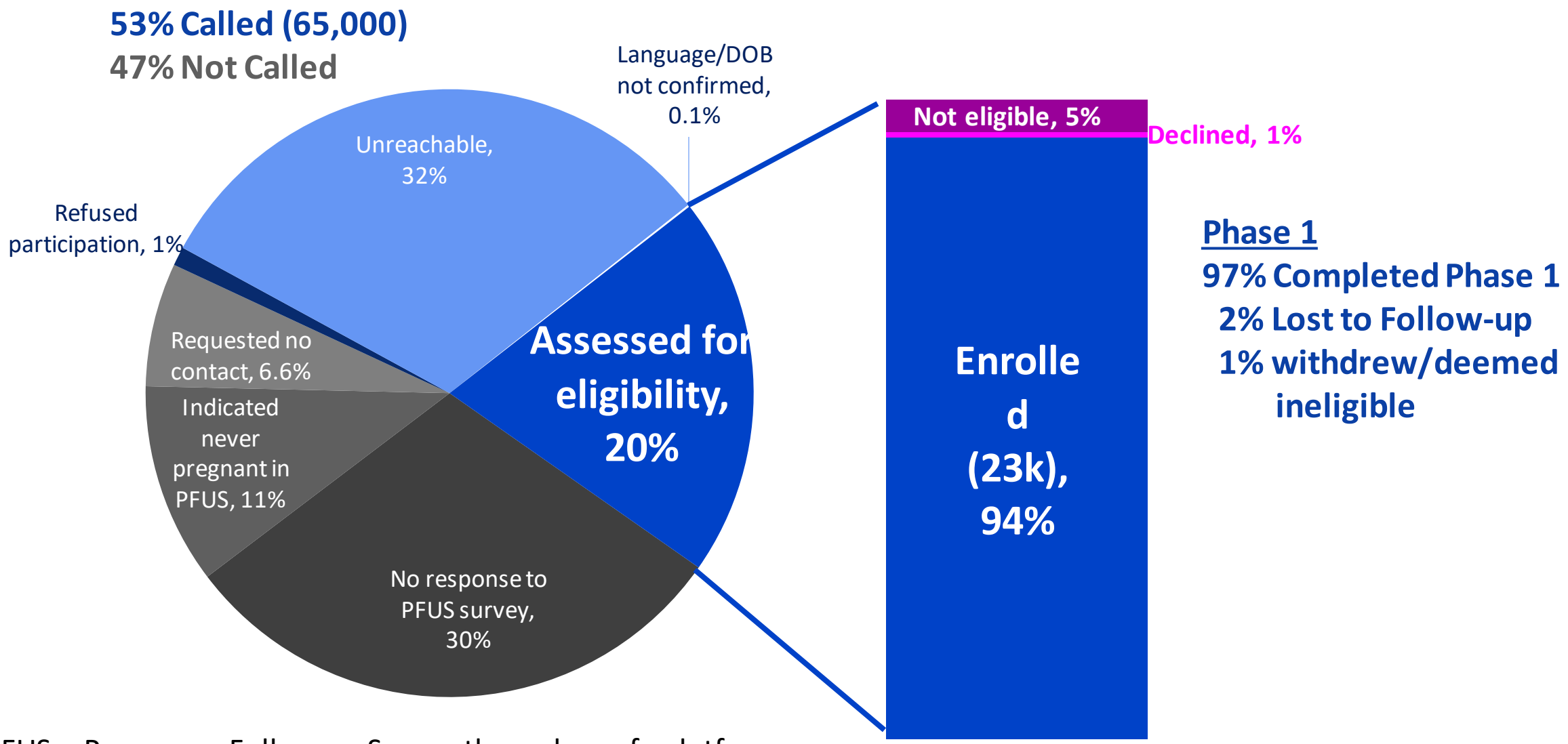
- Survey included:
  - Pregnancy outcome (if unknown)
  - Maternal health
  - Infant health through 15 months of age
  - Additional details on possible /probable birth defect from Phase 1
- Consent for medical records

*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

Ŧ 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

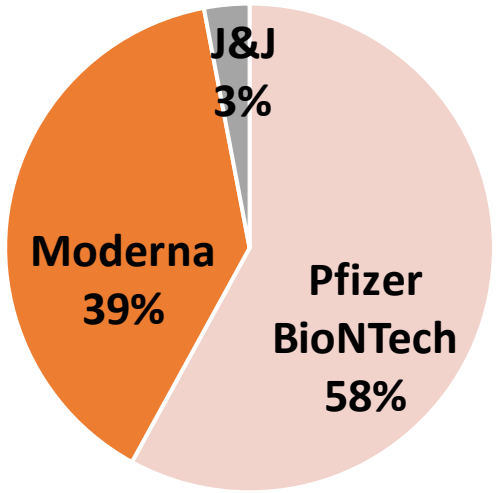
123,609 pregnancies reported into v-safe, Dec 2020 –Jun 2021

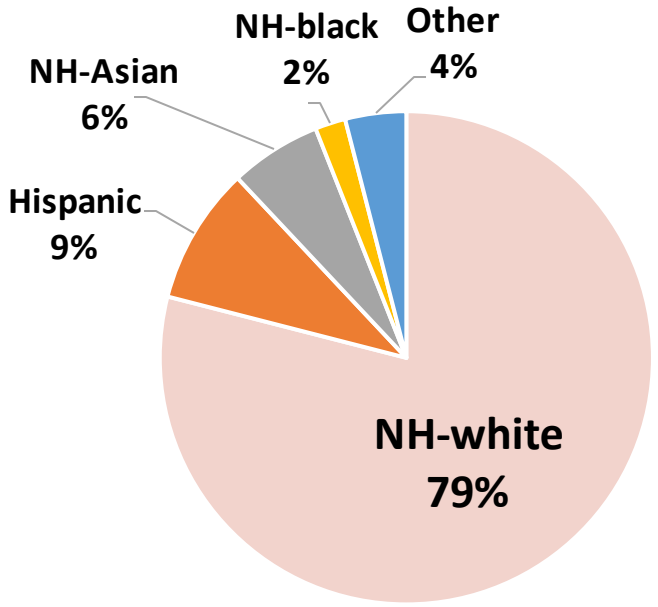


PFUS – Pregnancy Follow-up Survey through v-safe platform

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%

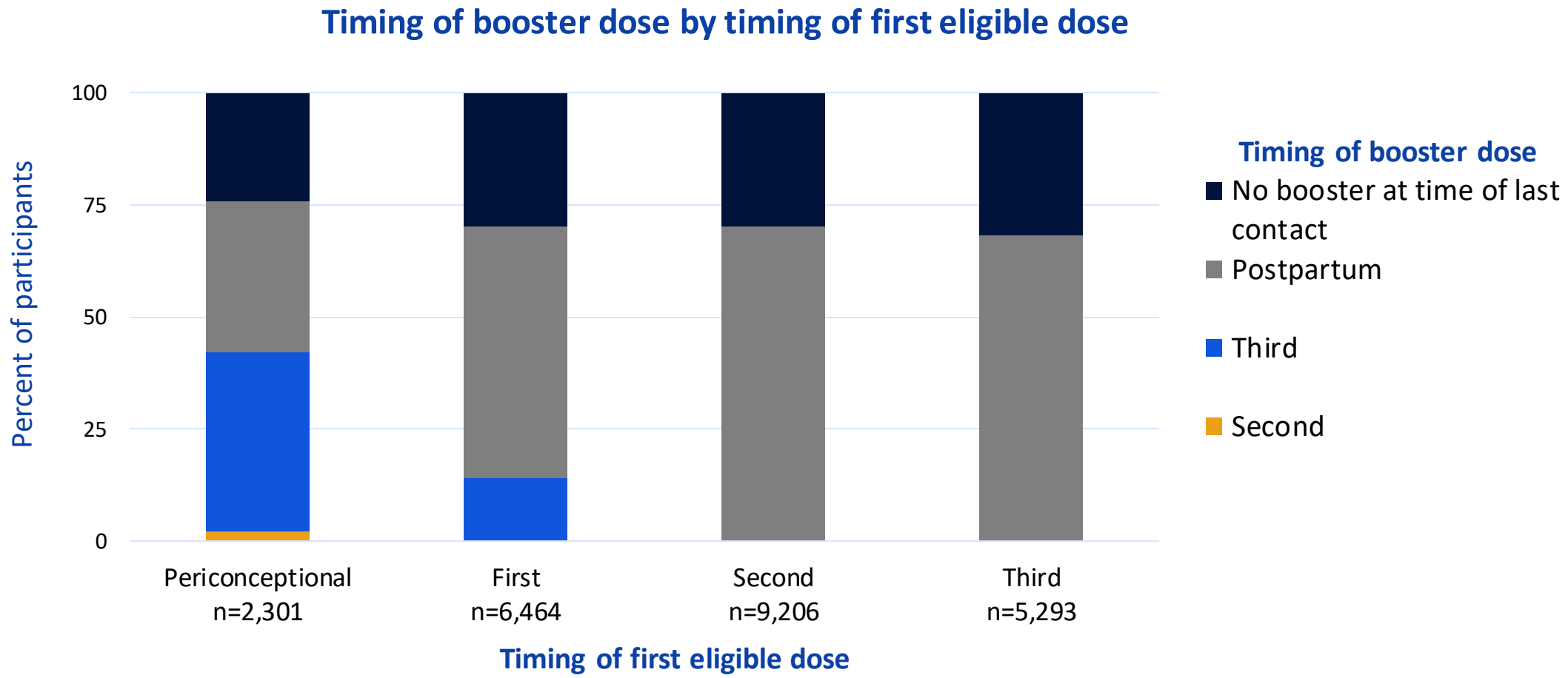
Third Trimester

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

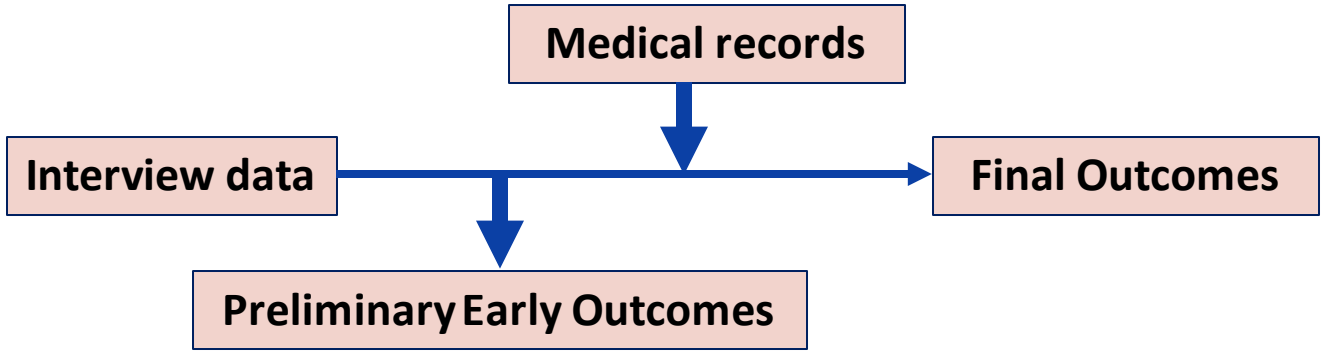
- Among enrolled participants, 8% received a booster during pregnancy; 62% received a booster after pregnancy

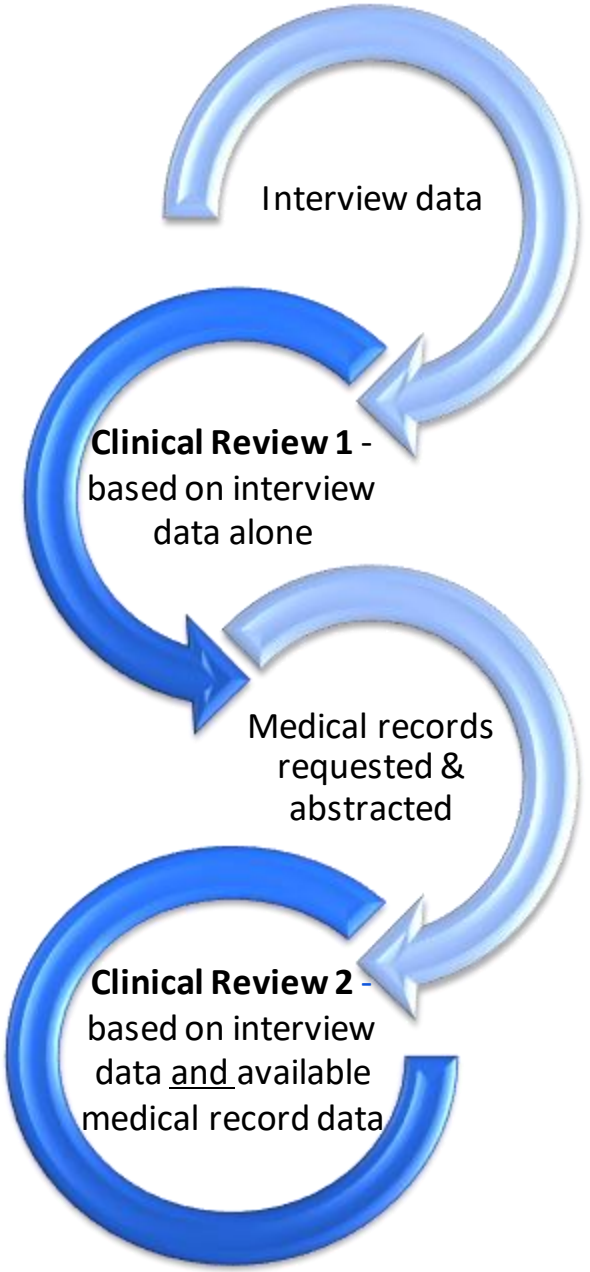


Phase 2 (Extended Follow-up)

- 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





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 Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons, *NEJM* June 2021
  - Receipt of mRNA COVID-19 vaccines preconception and during pregnancy and risk of self-reported spontaneous abortions, CDC v-safe COVID-19 Vaccine Pregnancy Registry 2020–21, *NEJM* Oct 2021
- 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

- CDC COVID-19 Vaccine Pregnancy Registry Participants
- CDC COVID-19 Vaccine Pregnancy Registry staff and contributors
  - Andrea Sharma
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  - Jennita Reefhuis
  - Jan Cragan
  - Cynthia Moore
  - Shana Godfred Cato
  - Sascha Ellington
  - David Shay

Resources

- ACIP 9-22-21: COVID-19 vaccine safety in pregnancy: Updates from the v-safe COVID-19 vaccine pregnancy registry
- ACIP 10-19-22: Updates on COVID-19 vaccine safety in pregnancy: • Vaccine Safety Datalink • v-safe COVID-19 Vaccine Pregnancy Registry
- ACIP- COVID-19 Vaccine Safety Technical (VAST) Subgroup Discussion and Interpretation-March 1, 2021 (cdc.gov)
- Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons, NEJM June 2021
- 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)
TTY: 1-888-232-6348 www.cdc.gov

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

HealthPartners®

Largest consumer-governed nonprofit health care organization in the nation, founded in 1957, based in Bloomington, MN

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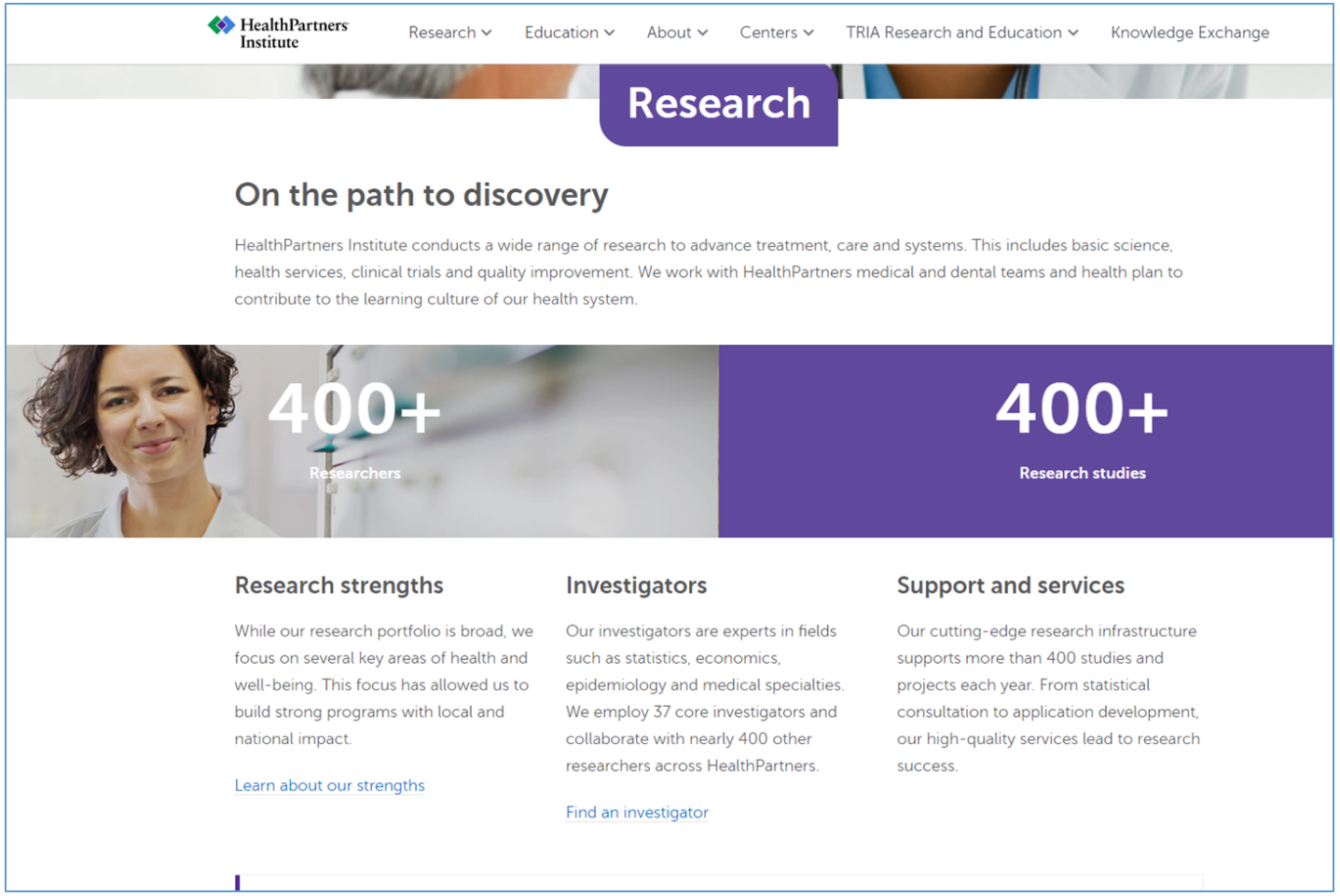


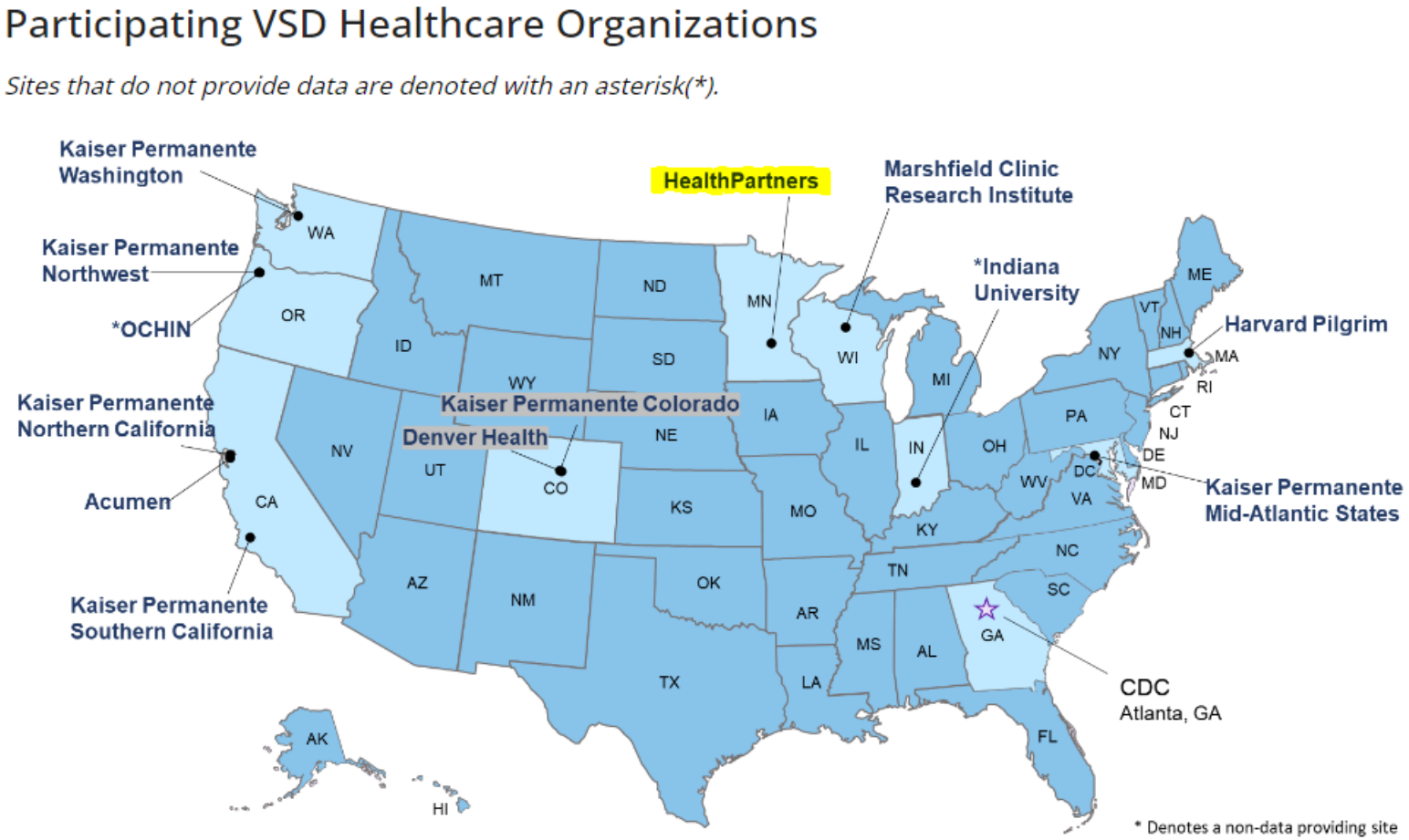
Nonprofit institute within HealthPartners dedicated to high-quality, public-domain health research

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)**

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.**



HealthPartners VSD team includes collaborators at Yale University, Cornell University, University of Minnesota, University of Iowa, Children's Minnesota and Gillette Children's

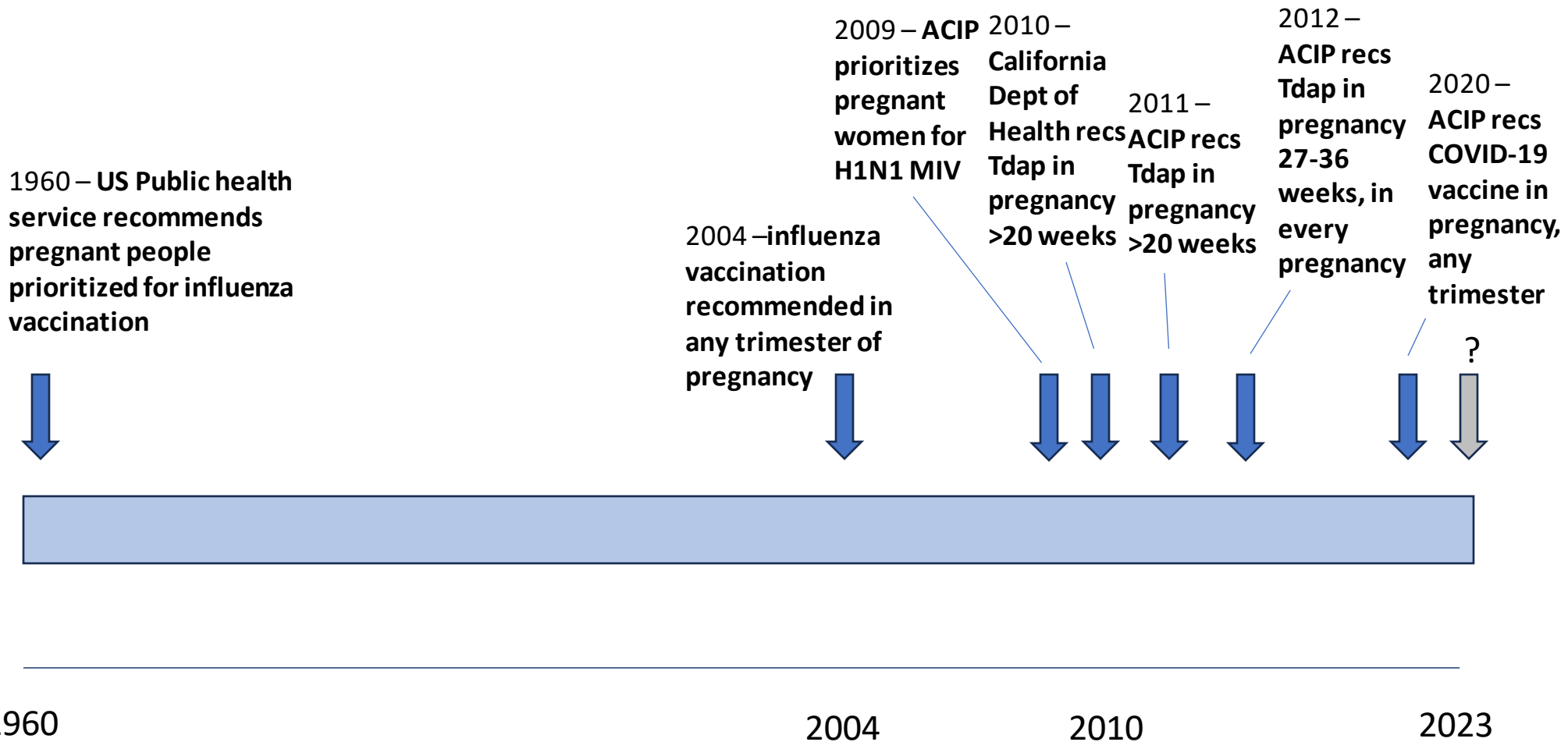
Vaccine Safety Datalink (VSD) data structure

- **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



VSD studies of vaccine safety in pregnancy - Influenza

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

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

James D. Nordin, MD, MPH[1], Elyse Olshen Kharbanda, MD, MPH[1], Gabriela Vazquez Benitez, PhD[1], Heather Lipkind, MD, MS[2], Claudia Vellozzi, MD, MPH[3], and Frank DeStefano, MD, MPH[3], 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).*

VSD studies of vaccine safety in pregnancy - Influenza

ORIGINAL ARTICLES

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First Trimester Influenza Vaccination and Risks for Major Structural Birth Defects in Offspring

Elyse Olshen Kharbanda, MD, MPH[1], Gabriela Vazquez-Benitez, PhD[1], Paul A. Romitti, PhD[2], Allison L. Naleway, PhD[3], T. Craig Cheetham, PharmD[4], Heather S. Lipkind, MD, MS[5], Nicola P. Klein, MD, PhD[6], Grace Lee, MD, MPH[7], Michael L. Jackson, PhD, MPH[8], Simon J. Hambidge, MD, PhD[9], Natalie McCarthy, MPH[10], Frank DeStefano, MD, MPH[10], and James D. Nordin, MD, MPH[1], 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 insurance enrollment were followed to 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.[1] 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.[2] Although initial adherence with these guidelines was low,[3] a national survey of women pregnant during the 2014-2015 influenza season noted that about 50% reported receiving IIV before or during pregnancy.[4]

VSD studies of vaccine safety in pregnancy - Tdap

Original Investigation

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

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

Supplemental content at jama.com

IMPORTANCE In 2010, due to a pertussis outbreak and neonatal deaths, the California Department of Health recommended that the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) be administered during pregnancy. Tdap is now recommended by the Advisory Committee on Immunization Practices for all pregnant women, preferably between 27 and 36 weeks' gestation. Limited data exist on Tdap safety during pregnancy.

OBJECTIVE To evaluate whether maternal Tdap vaccination during pregnancy is associated with increased risks of adverse obstetric events or adverse birth outcomes.

DESIGN AND SETTING Retrospective, observational cohort study using administrative health

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).

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).

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VSD studies of vaccine safety in pregnancy - Tdap

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Tdap vaccination during pregnancy and risk of chorioamnionitis and related infant outcomes

Victoria Greenberg [a,*], Gabriela Vazquez-Benitez [b], Elyse O. Kharbanda [b], Matthew F. Daley [c], Hung Fu Tseng [d], Nicola P. Klein [e], Allison L. Naleway [f], Joshua T.B. Williams [g], James Donahue [h], Lisa Jackson [i], Eric Weintraub [j], Heather Lipkind [k], Malini B. DeSilva [l]

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[d] Kaiser Permanente Southern California, Pasadena, CA, United States
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[f] Center for Health Research, Kaiser Permanente Northwest, Portland, OR, United States
[g] Ambulatory Care Services, Denver Health, Denver, CO, United States
[h] Marshfield Clinic, Research Institute, Marshfield, WI, United States
[i] Kaiser Permanente Washington, Seattle, WA, United States
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[k] Weill Cornell Medicine, New York, NY, United States
[l] HealthPartners Institute, Bloomington, MN, United States

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.

nitis in people receiving tetanus toxoid, reduced diphthe-
e during pregnancy has been reported. The importance of
has not demonstrated increased adverse infant outcomes
.

ational cohort study of pregnant people ages 15–49 years
n who were members of 8 Vaccine Safety Datalink (VSD)
e used a time-dependent covariate Cox model with stabi-
luate associations between Tdap vaccination during preg-
th outcomes. We used Poisson regression with robust
ights applied to evaluate the association of Tdap vaccina-
ormed medical record reviews on a random sample of
nionitis to determine positive predictive values (PPV) of
horioamnionitis," "possible clinical chorioamnionitis," or

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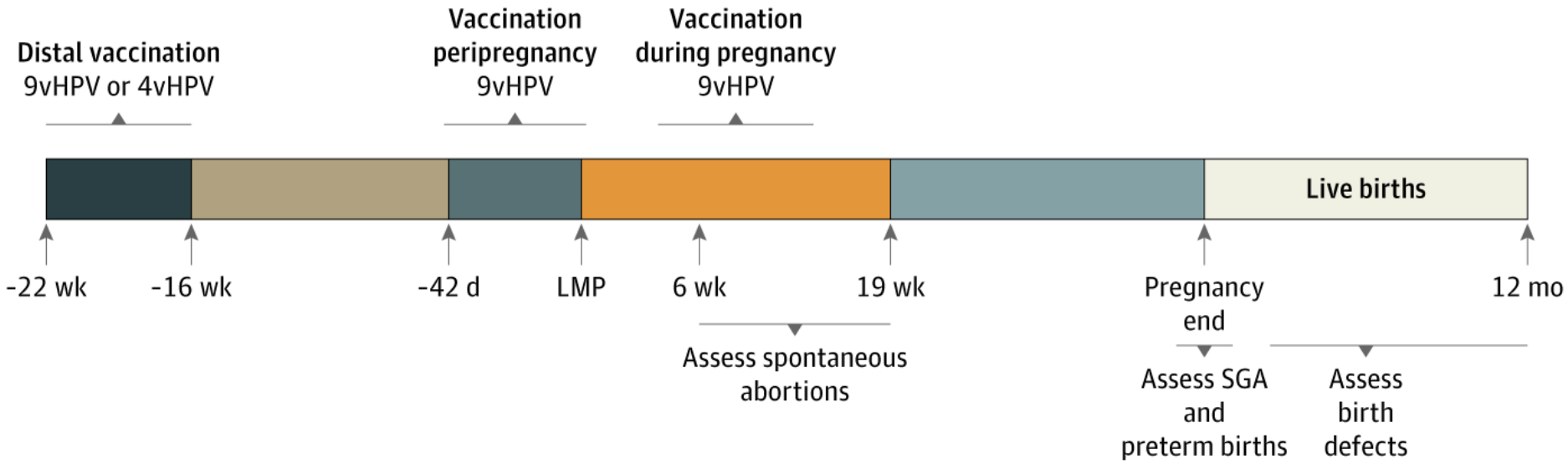
VSD studies of vaccine safety in pregnancy – Inadvertent exposures to HPV vaccine

- 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



Variable	No. (%)			Risk of event		
	Distal exposure	Peripregnancy exposure	During-pregnancy exposure	Peripregnancy vs distal exposure	During pregnancy vs distal exposure	During pregnancy or peripregnancy vs distal exposure
Pregnancies, No.	552	496	445	NA	NA	NA
SAB	33 (6.0)	22 (4.4)	25 (5.6)	RR (95% CI): 0.72 (0.42-1.24)[b]	HR (95% CI): 1.12 (0.66-1.93)[c]	HR (95% CI): 1.20 (0.77-1.88)[c]
Live births with gestational age, No.	518	474	418	NA	NA	NA
Preterm births[d]	42 (8.1)	27 (5.7)	26 (6.2)	RR (95% CI): 0.72 (0.45-1.17)[c]	RR (95% CI): 0.73 (0.44-1.20)[c]	RR (95% CI): 0.75 (0.50-1.13)[c]
Live births with gestational age and birth weight, No.	425	388	341	NA	NA	NA
SGA births[e]	27 (6.4)	27 (7.0)	29 (8.5)	RR (95% CI): 1.10 (0.65-1.88)[c]	RR (95% CI): 1.31 (0.78-2.20)[c]	RR (95% CI): 1.18 (0.75-1.85)[c]
Live births with follow-up, No.[f]	414	363	320	NA	NA	NA
Major structural birth defects	4 (1.0)	4 (1.1)	4 (1.3)	PR (95% CI): 1.03 (0.26-4.07)[g]	PR (95% CI): 1.30 (0.36-4.69)[g]	PR (95% CI): 1.06 (0.34-3.33)[g]

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.

[g] Using 9vHPV or 4vHPV vaccine, with inverse probability weights for age, race/ethnicity, hospitalization before pregnancy, smoking, and site.

VSD studies of COVID-19 vaccine safety in pregnancy

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

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

HealthPartners Institute
- Elyse Kharbanda
- Malini DeSilva
- Gabriela Vazquez-Benitez
- Jim Nordin
- Leslie Kuckler
- Jingyi Zhu
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- Sunita Thapa
- Nicole Trower
- Yuan Yuan Olsen

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- Heather Lipkind
- Christina Ackerman
- Sangini Sheth
- Annalies DeNoble
- Victoria Greenberg

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- Kimberly Vesco
- 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

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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

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

PDUFA: Prescription Drug User Fee Act

Understanding the Current State of Using Postapproval Pregnancy Safety Studies for FDA's Decision-making

Analysis #	Title	Presenter
1	Analysis of how different types postapproval pregnancy safety studies have been used by FDA	Dr. Adebola Ajao
2	Review of types of postapproval safety data that have been included in pregnancy labeling	Dr. Aida Kuzucan
3	Preliminary analysis of drug utilization data to inform the development of the pregnancy safety study framework	Dr. José J. Hernández-Muñoz

Analysis of Postapproval Pregnancy Safety Studies Associated with FDA Approved Products

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Epidemiologist
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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

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[1]

- 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,[2] 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#:~:text=The%20phrase%20postmarketing%20requirements%20and,%2C%20efficacy%2C%20or%20optimal%20use.
2. Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry. Assessed at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-studies-and-clinical-trials-implementation-section-505o3-federal-food-drug-and-0

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

Data source	Search criteria
FDA PMR/PMC database[1]	• Patient population = pregnant • Study/trial include pregnant/pregnancy • PMR/PMC description mentions pregnant/pregnancy
FDA Office of Women's Health (OWH) Pregnancy Registry database[2]	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

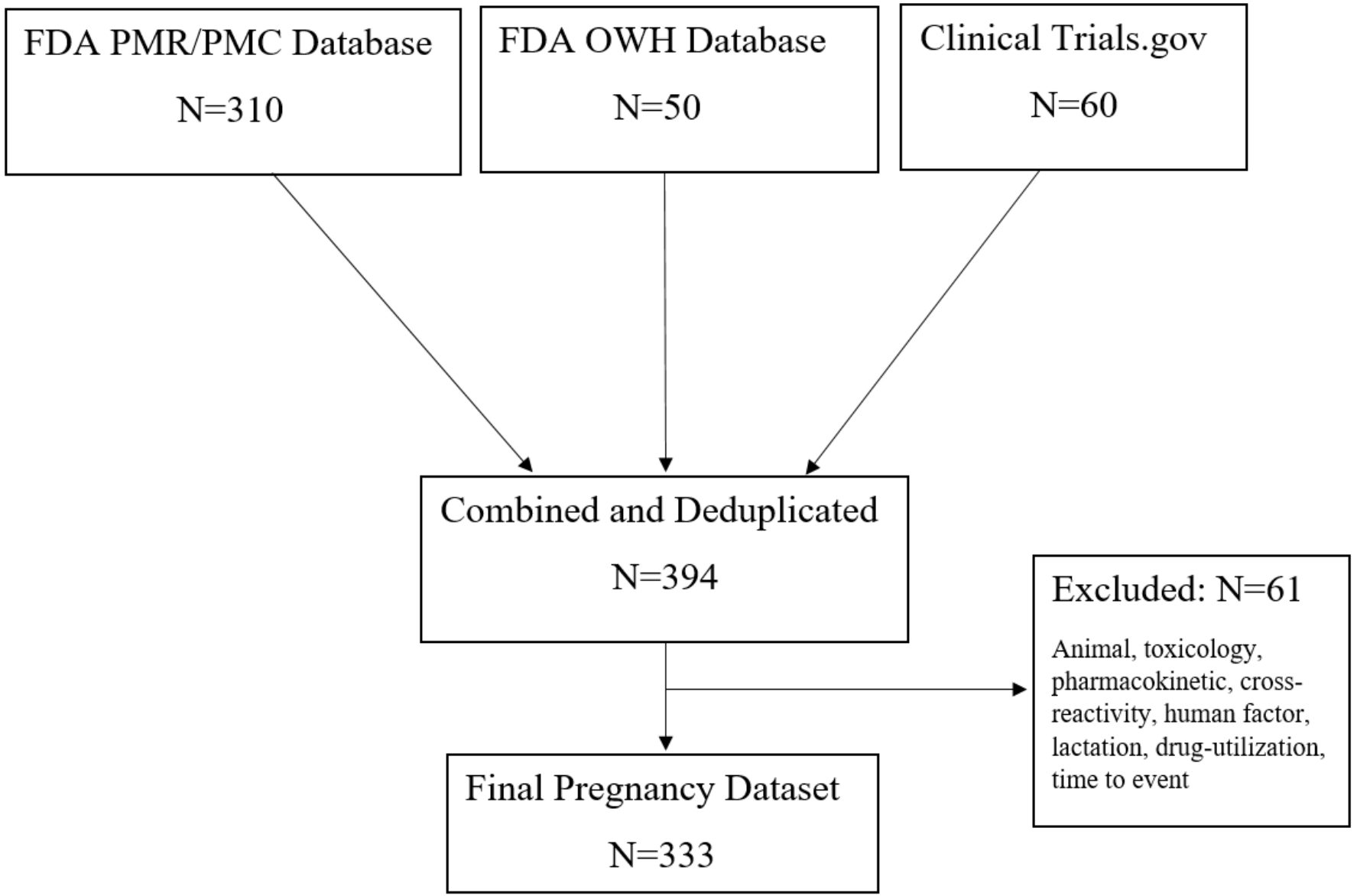
- Animal studies, toxicology studies, pharmacokinetic studies, cross-reactivity studies, lactation studies

Study Variables

- Study Type
- Study Goal
- Therapeutic Class
- Study Status
- Study Establishment Year
- Reasons for Study Termination[1]
- 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



Study Type

	N (333)	%
Pregnancy Exposure Registry (PER) Study	**209**	**63%**
Descriptive Pregnancy Safety Study	69	21%
Database Study/Pre-specified Outcome	52	15%
Randomized Clinical Trial	3	1%

Study Goal

	N (333)	%
Safety Signal Detection/Identification	**330**	**99%**
Safety Signal Evaluation/Confirmation	3	1%

- **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

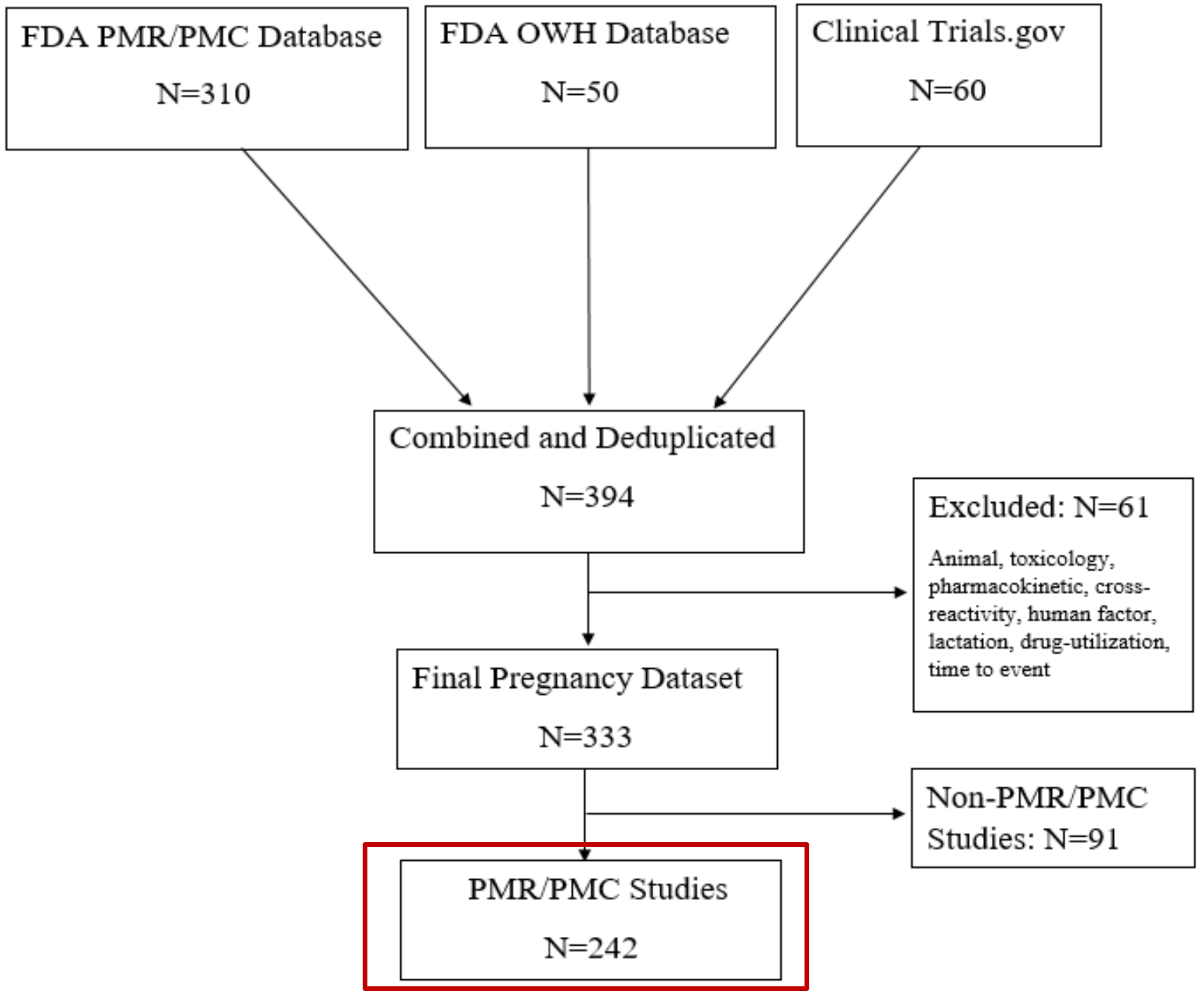
	N 333	%
Psychiatry	**71**	**21%**
Neurology	61	18%
Prophylactic Vaccines and Related Biologic Products	48	14%
Dermatology	25	8%
Metabolic	22	7%
Reproductive	16	5%
Genetic/Inborn Error	16	5%
Rheumatology	15	4%
Others	59	18%

Study Status as of July 2023

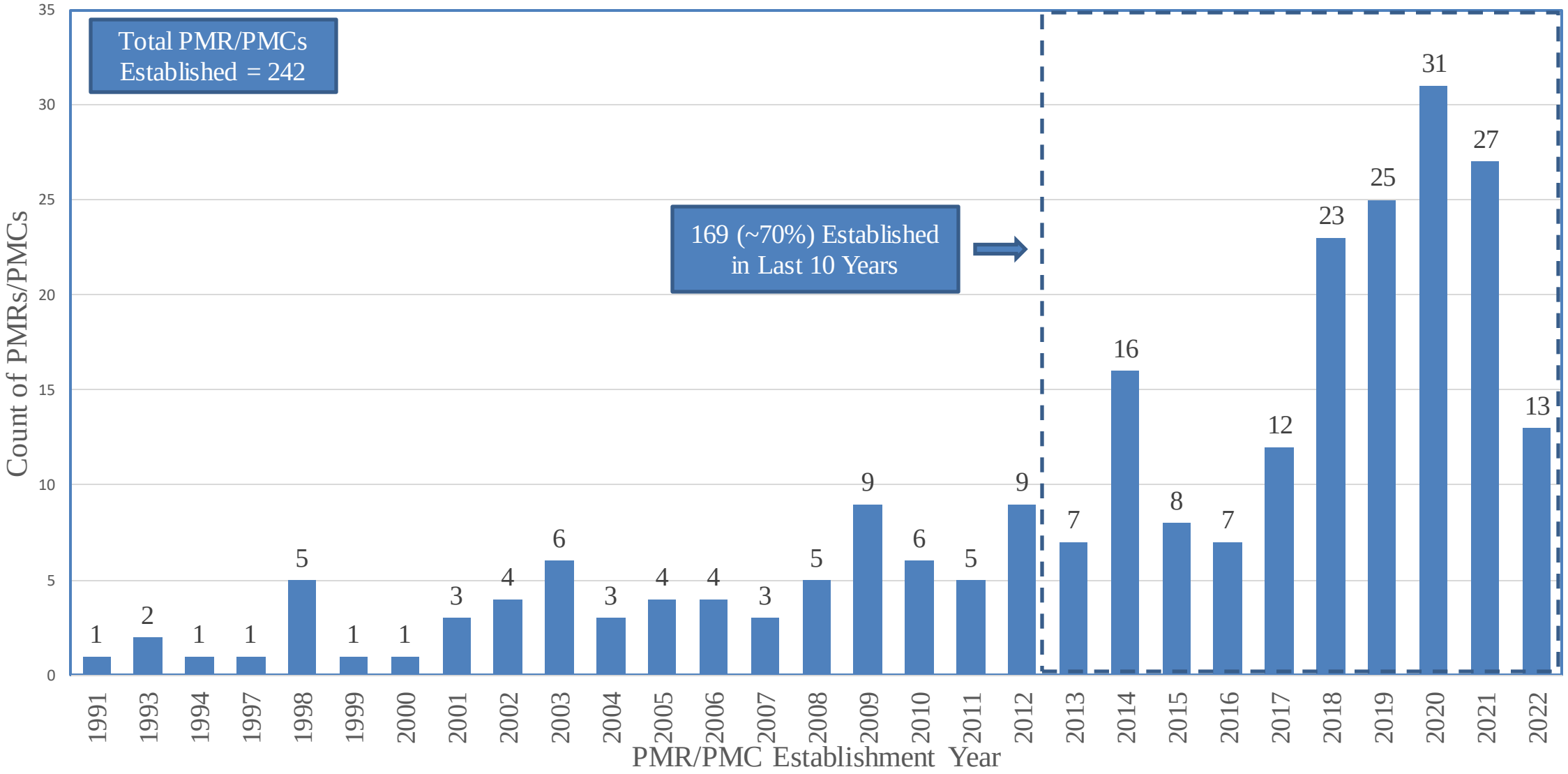
	N (333)	%
Terminated[1]	38	11%
Completed[2]	65	20%
Ongoing	230	69%

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

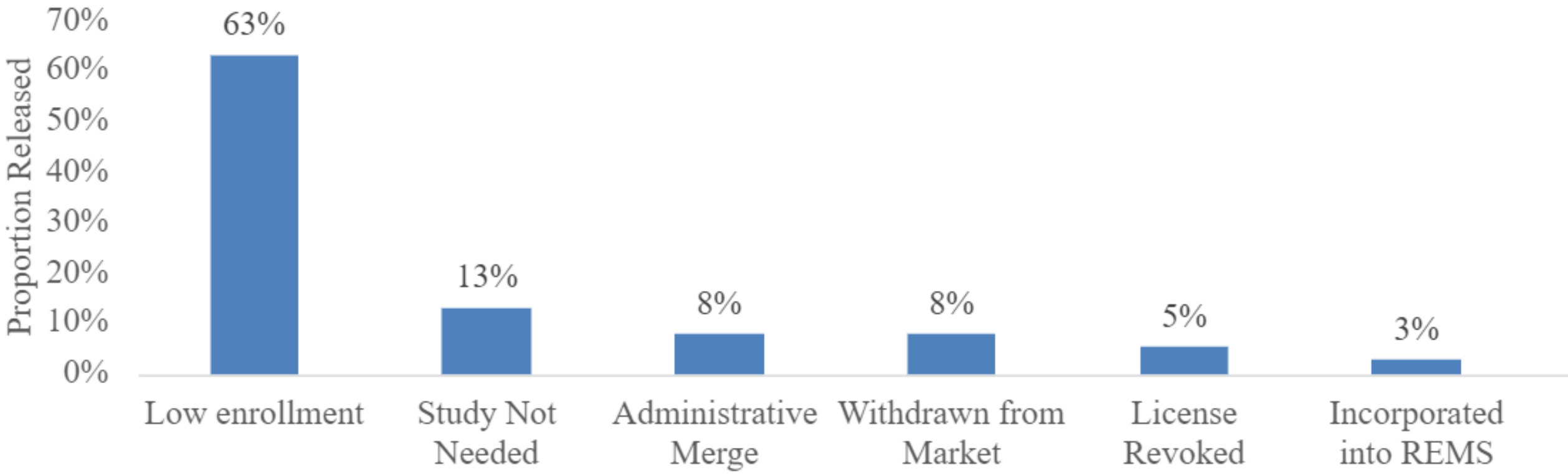


Study Establishment Year (PMR/PMC)



Terminated Studies (N=38)

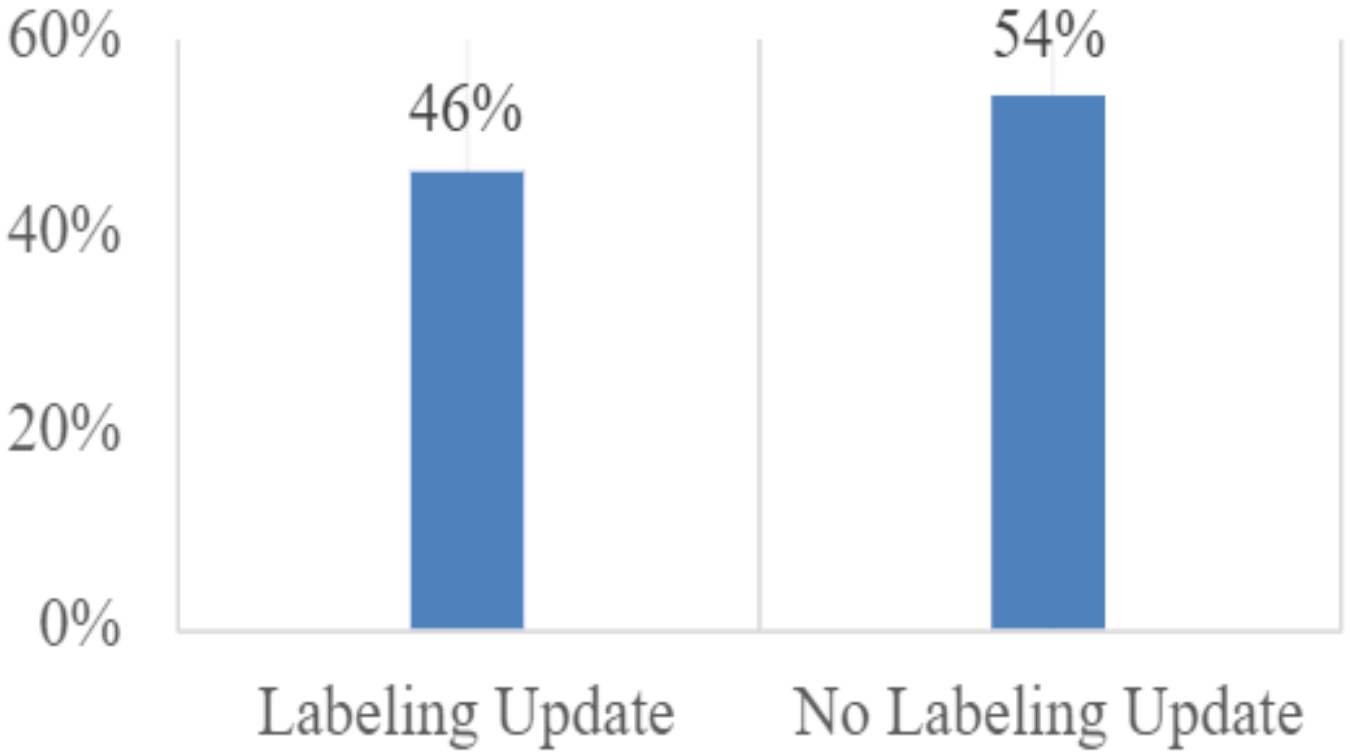
- 24 (63%) of released/terminated studies not feasible due to low enrollment
  - Of these studies, 14 (58%) were replaced by a different study design
- Average time from study establishment to release: 8 years (range 2 – 14 years)



Completed Studies

		N (65)	%
Study Type	**Pregnancy Exposure Registry (PER)**	**44**	**68%**
	Descriptive Pregnancy Safety Study	12	18%
	Database Study/Pre-specified outcome	7	11%
	Clinical Trial	2	3%

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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FDA
U.S. FOOD & DRUG
ADMINISTRATION

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

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Division of Pediatrics and Maternal Health (DPMH), Office of New Drugs (OND):
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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

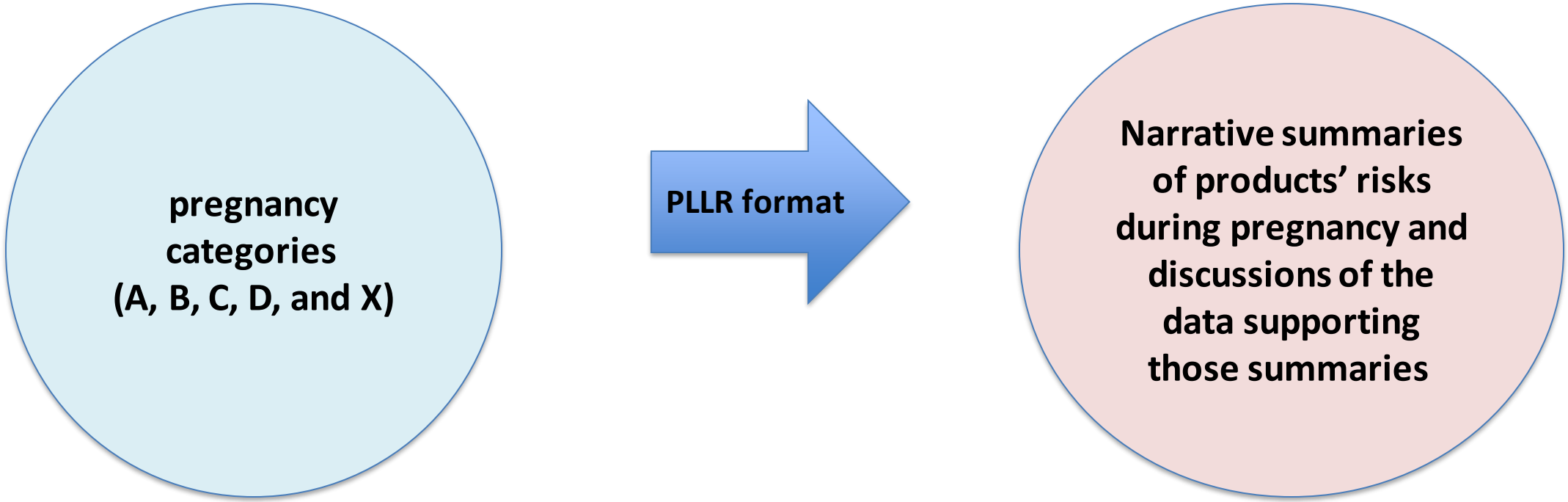
Outline

- 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

PLLR format


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.

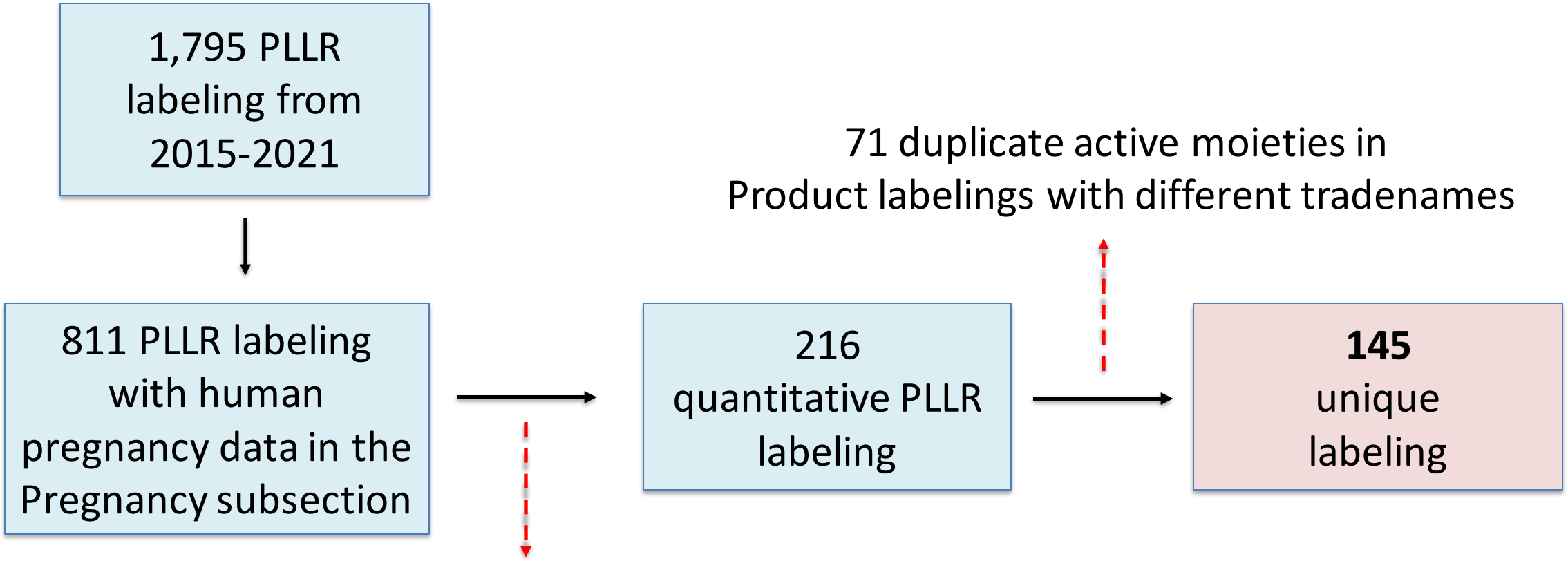
- Multiple quality checkpoints to ensure accurate and consistent capture of characteristics.

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



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

Standardized extraction sheets used to identify product labeling characteristics and studies reflected in labeling

Three epidemiologists used standardized definitions to identify study characteristics.

Quality Control

Quality Control

Step 1: Characterize Product Labelings and Identify Study

Step 2: Extract Study Characteristrics

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

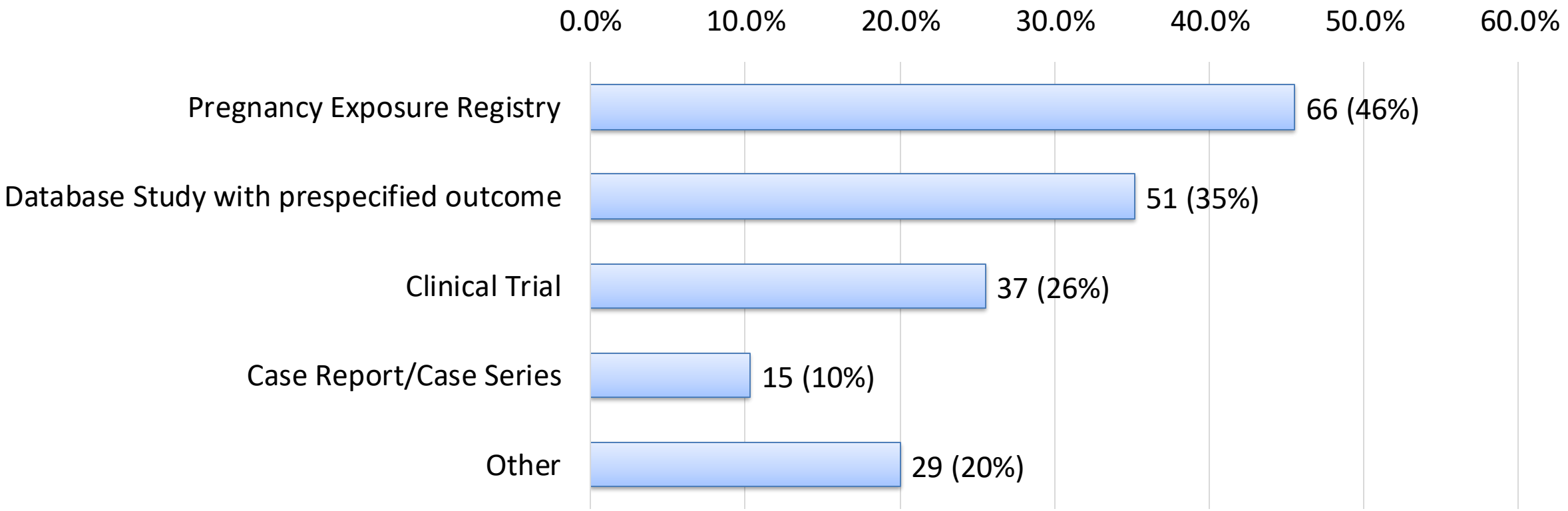
RESULTS

Product Labelings and Studies Evaluated in Analysis

PLLR Labeling- years included: 2015-2021

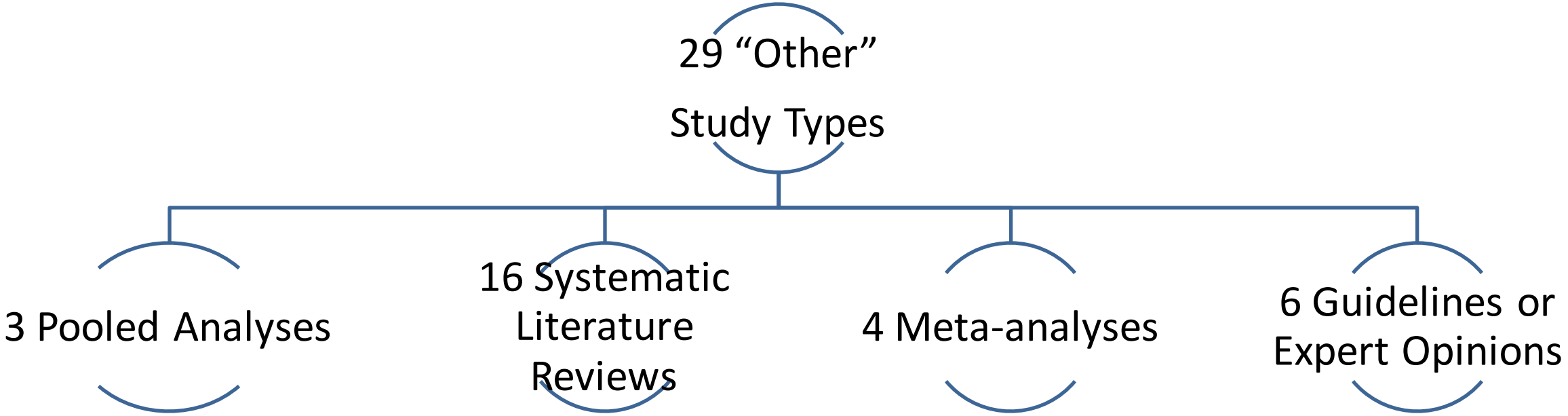
- 145 product labelings
- 177 unique studies

Product Labeling Characteristics: Frequency of Data from Different Study Types (N=145 labelings)*



*Product labelings could have one or more "quantitative" human safety statements supported by one or more studies, so these proportions do not equal 100.

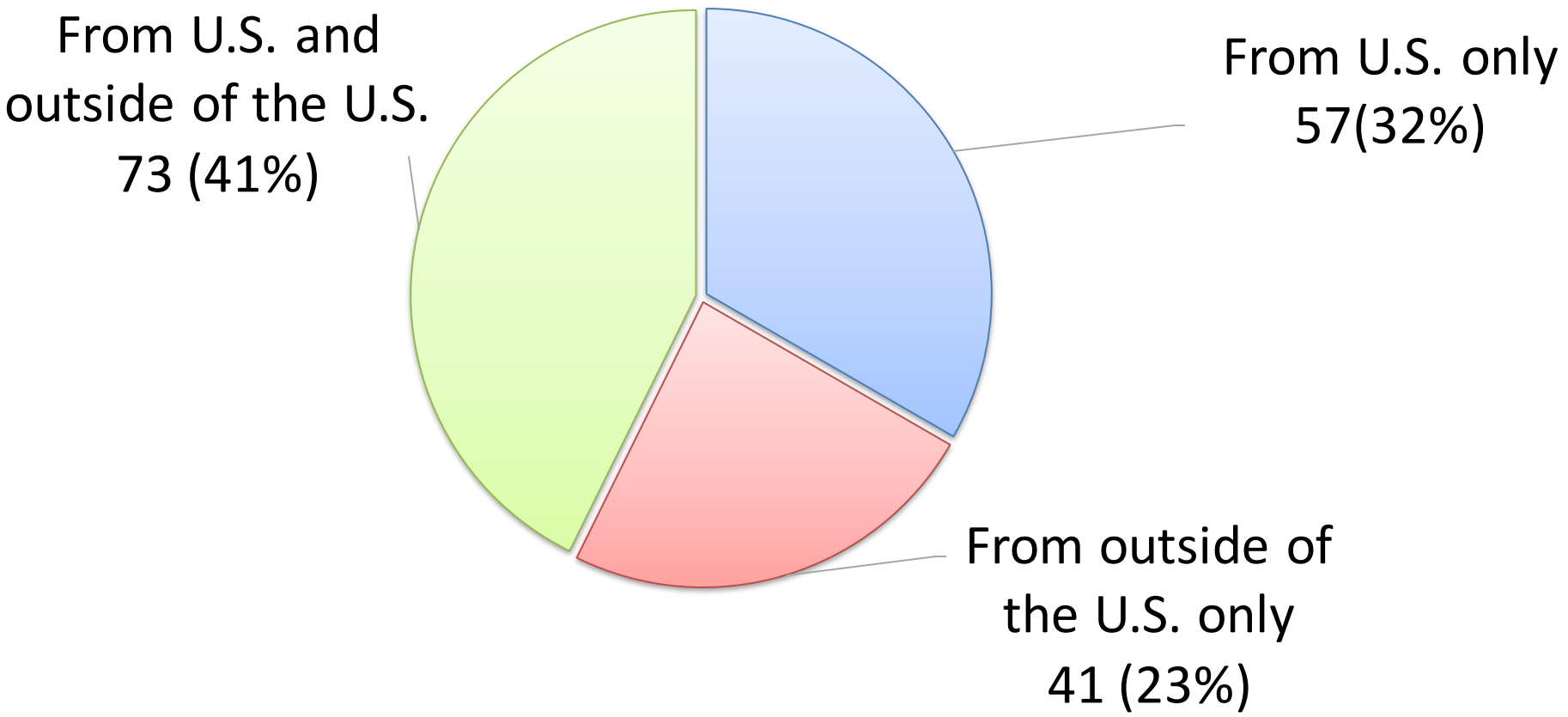
Product Labeling Characteristics: Other Study Types



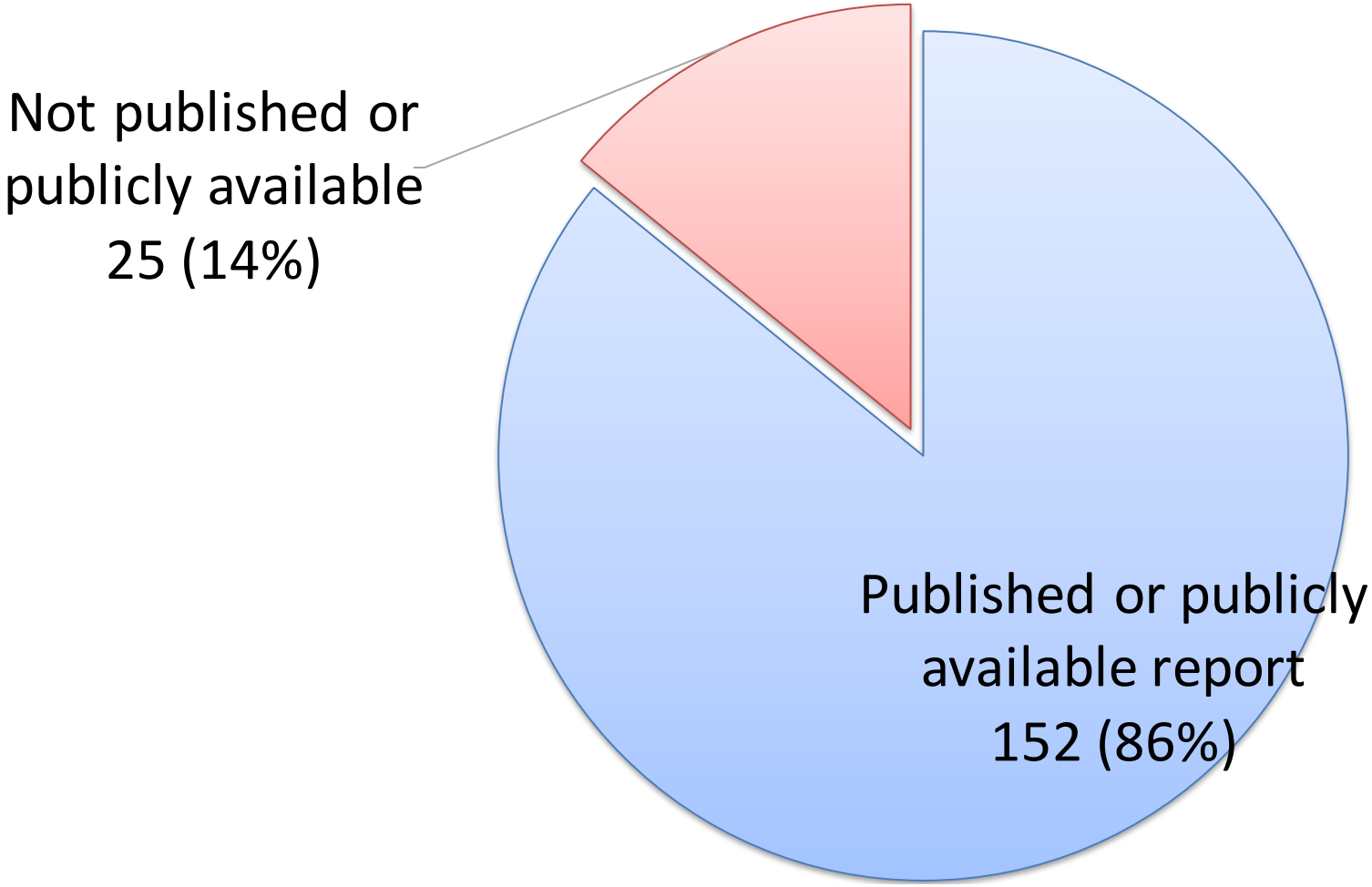
Product Labeling Characteristics: Top Therapeutic Class/ Organ System (N=145 labelings)

Therapeutic class/ organ system	Count	Proportion
Antiviral Agents	40	27.6%
Cardiovascular	10	6.9%
Gastrointestinal	12	8.3%
Psychiatric	12	8.3%
Reproductive and Urologic Agents	9	6.2%
Other	62	42.8%

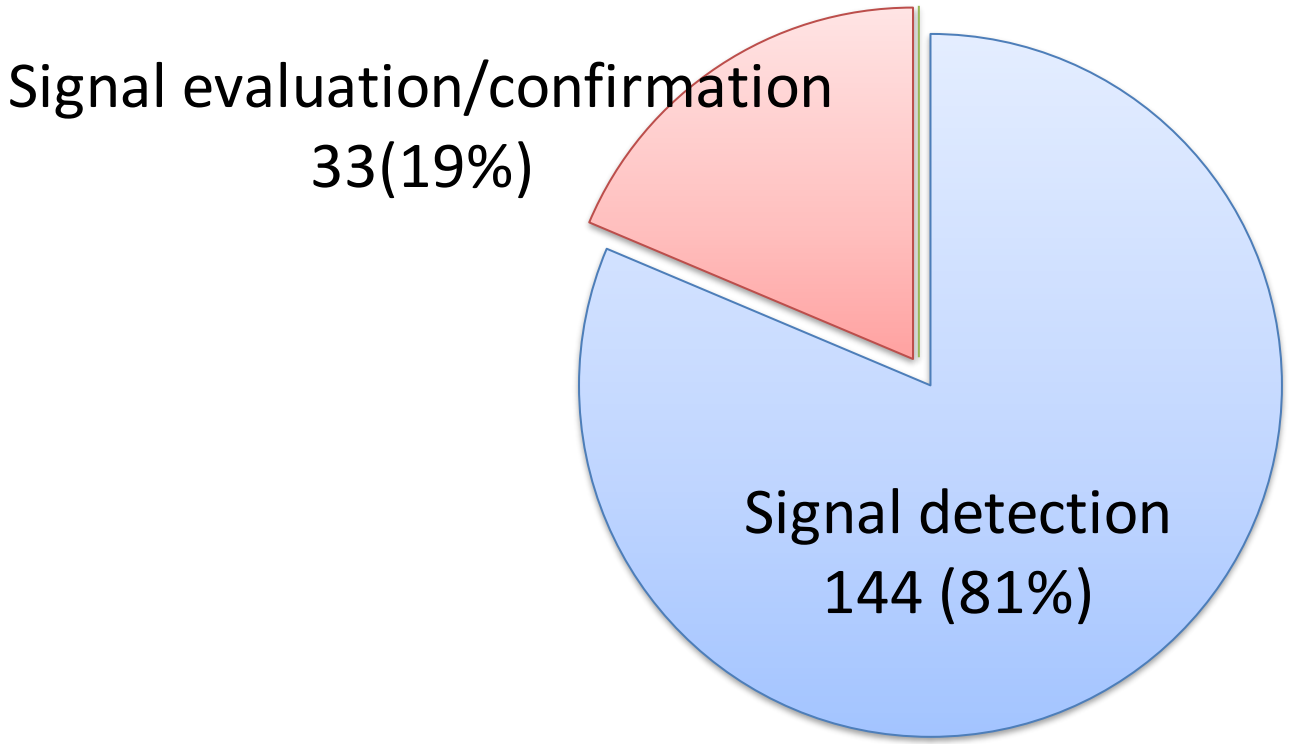
Study Characteristics: Geographic Location of Study Population (N=177 studies)



Study Characteristics: Publication (N=177 Studies)



Study Characteristics: Study Goal (N=177 Studies)



EXAMPLES: COMMONLY USED DATA SOURCES

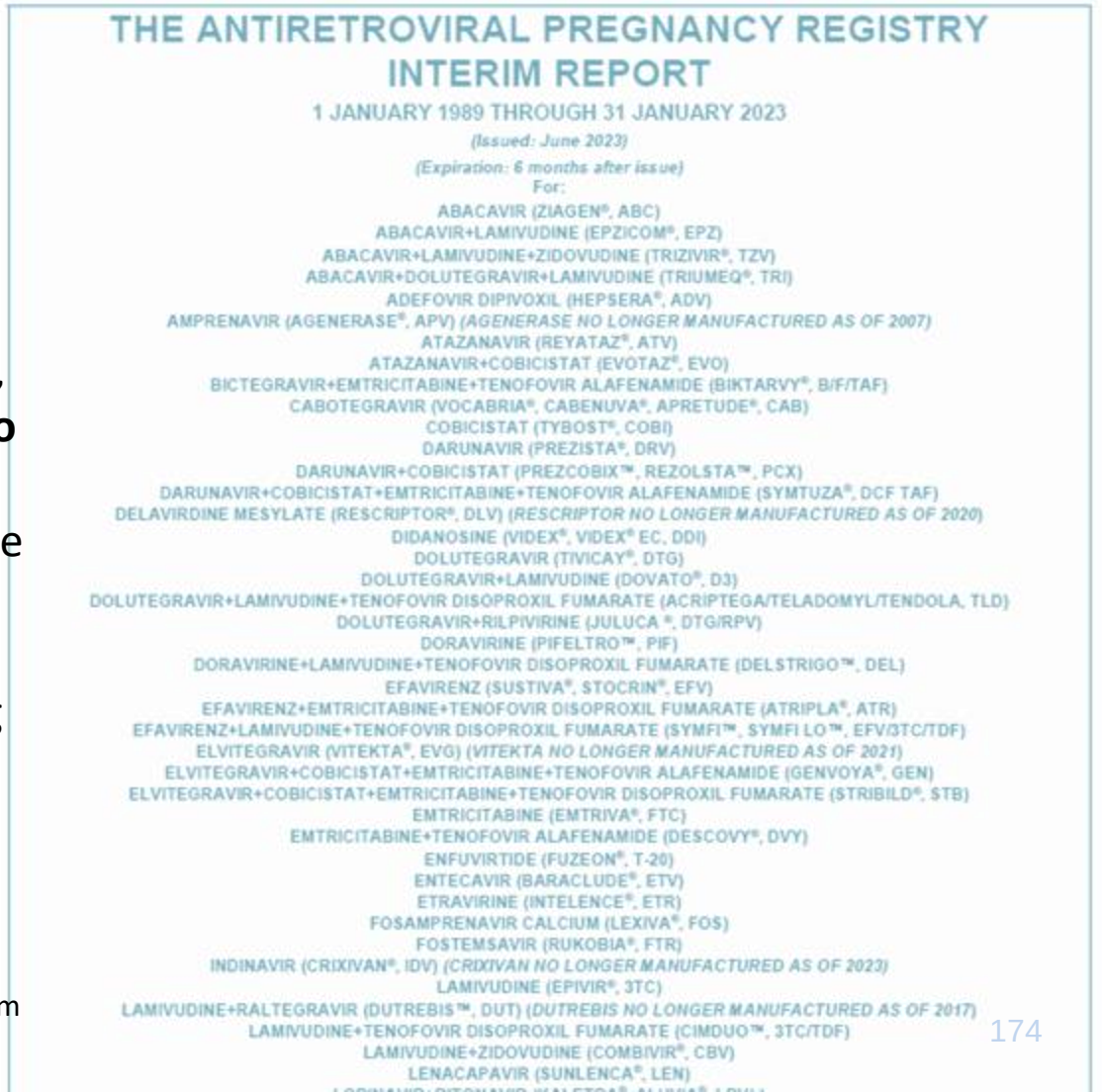
Antiretroviral Pregnancy Registry (APR) (N=38 Product Labelings)

Example: EPIVIR-HBV (lamivudine)

<u>Excerpt from the Human Data subheading in the Pregnancy subsection of labeling:</u>

> 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.

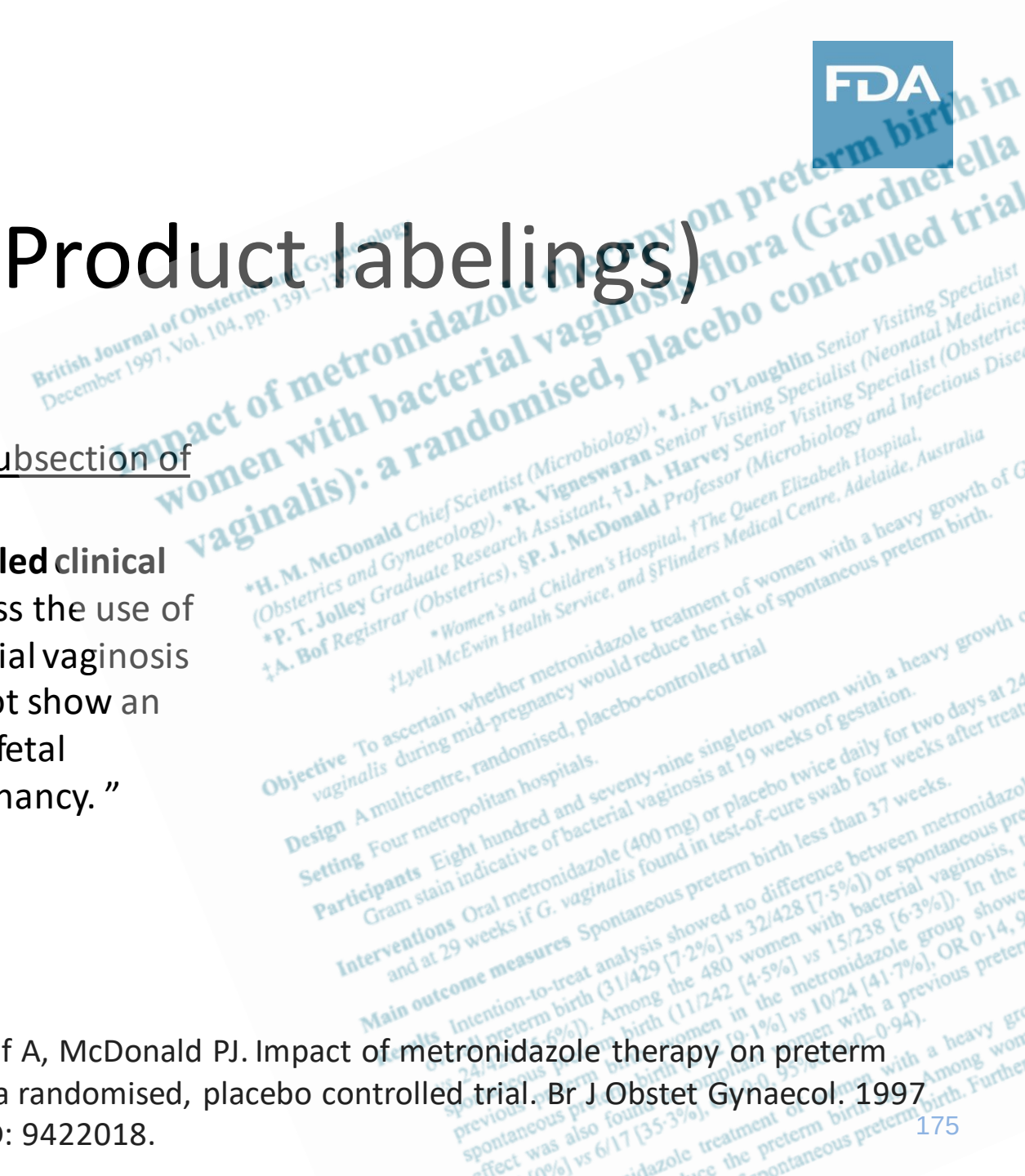

THE ANTIRETROVIRAL PREGNANCY REGISTRY
INTERIM REPORT
1 JANUARY 1989 THROUGH 31 JANUARY 2023
(Issued: June 2023)
(Expiration: 6 months after issue)
For:
ABACAVIR (ZIAGEN®, ABC)
ABACAVIR+LAMIVUDINE (EPZICOM®, EPZ)
ABACAVIR+LAMIVUDINE+ZIDOVUDINE (TRIZIVIR®, TZV)
ABACAVIR+DOLUTEGRAVIR+LAMIVUDINE (TRIUMEQ®, TRI)
ADEFOVIR DIPIVOXIL (HEPSERA®, ADV)
AMPRENAVIR (AGENERASE®, APV) *(AGENERASE NO LONGER MANUFACTURED AS OF 2007)*
ATAZANAVIR (REYATAZ®, ATV)
ATAZANAVIR+COBICISTAT (EVOTAZ®, EVO)
BICTEGRAVIR+EMTRICITABINE+TENOFOVIR ALAFENAMIDE (BIKTARVY®, B/F/TAF)
CABOTEGRAVIR (VOCABRIA®, CABENUVA®, APRETUDE®, CAB)
COBICISTAT (TYBOST®, COBI)
DARUNAVIR (PREZISTA®, DRV)
DARUNAVIR+COBICISTAT (PREZCOBIX™, REZOLSTA™, PCX)
DARUNAVIR+COBICISTAT+EMTRICITABINE+TENOFOVIR ALAFENAMIDE (SYMTUZA®, DCF TAF)
DELAVIRDINE MESYLATE (RESCRIPTOR®, DLV) *(RESCRIPTOR NO LONGER MANUFACTURED AS OF 2020)*
DIDANOSINE (VIDEX®, VIDEX® EC, DDI)
DOLUTEGRAVIR (TIVICAY®, DTG)
DOLUTEGRAVIR+LAMIVUDINE (DOVATO®, D3)
DOLUTEGRAVIR+LAMIVUDINE+TENOFOVIR DISOPROXIL FUMARATE (ACRIPTEGA/TELADOMYL/TENDOLA, TLD)
DOLUTEGRAVIR+RILPIVIRINE (JULUCA ®, DTG/RPV)
DORAVIRINE (PIFELTRO™, PIF)
DORAVIRINE+LAMIVUDINE+TENOFOVIR DISOPROXIL FUMARATE (DELSTRIGO™, DEL)
EFAVIRENZ (SUSTIVA®, STOCRIN®, EFV)
EFAVIRENZ+EMTRICITABINE+TENOFOVIR DISOPROXIL FUMARATE (ATRIPLA®, ATR)
EFAVIRENZ+LAMIVUDINE+TENOFOVIR DISOPROXIL FUMARATE (SYMFI™, SYMFI LO™, EFV/3TC/TDF)
ELVITEGRAVIR (VITEKTA®, EVG) *(VITEKTA NO LONGER MANUFACTURED AS OF 2021)*
ELVITEGRAVIR+COBICISTAT+EMTRICITABINE+TENOFOVIR ALAFENAMIDE (GENVOYA®, GEN)
ELVITEGRAVIR+COBICISTAT+EMTRICITABINE+TENOFOVIR DISOPROXIL FUMARATE (STRIBILD®, STB)
EMTRICITABINE (EMTRIVA®, FTC)
EMTRICITABINE+TENOFOVIR ALAFENAMIDE (DESCOVY®, DVY)
ENFUVIRTIDE (FUZEON®, T-20)
ENTECAVIR (BARACLUDE®, ETV)
ETRAVIRINE (INTELENCE®, ETR)
FOSAMPRENAVIR CALCIUM (LEXIVA®, FOS)
FOSTEMSAVIR (RUKOBIA®, FTR)
INDINAVIR (CRIXIVAN®, IDV) *(CRIXIVAN NO LONGER MANUFACTURED AS OF 2023)*
LAMIVUDINE (EPIVIR®, 3TC)
LAMIVUDINE+RALTEGRAVIR (DUTREBIS™, DUT) *(DUTREBIS NO LONGER MANUFACTURED AS OF 2017)*
LAMIVUDINE+TENOFOVIR DISOPROXIL FUMARATE (CIMDUO™, 3TC/TDF)
LAMIVUDINE+ZIDOVUDINE (COMBIVIR®, CBV)
LENACAPAVIR (SUNLENCA®, LEN)

Clinical Trial (N=37 Product labelings)

Example: METRONIDAZOLE

<u>Excerpt from the Human Data subheading in the Pregnancy subsection of labeling:</u>

> "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. "



McDonald HM, O'Loughlin JA, Vigneswaran R, Jolley PT, Harvey JA, Bof A, McDonald PJ. Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis flora (Gardnerella vaginalis): a randomised, placebo controlled trial. Br J Obstet Gynaecol. 1997 Dec;104(12):1391-7. doi: 10.1111/j.1471-0528.1997.tb11009.x. PMID: 9422018.

Scandinavian Birth Register (N=21 Product labelings)

Example: Sertraline Hydrochloride Capsule (sertraline)

<u>Excerpt from the Human Data subheading in the Pregnancy subsection of labeling:</u>

> "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"."

Källén B, Olausson PO. Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn. Pharmacoepidemiology and drug safety. 2008 Aug;17(8):801-6.

Medicaid (N=11 Product labelings)

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.

Huybrechts KF, Hernández-Díaz S, Patorno E, Desai RJ, Mogun H, Dejene SZ, Cohen JM, Panchaud A, Cohen L, Bateman BT. Antipsychotic use in pregnancy and the risk for congenital malformations. JAMA psychiatry. 2016 Sep 1;73(9):938-46.

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.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

U.S. FOOD & DRUG ADMINISTRATION

Backup slides

Background: PDUFA VII Commitment Letter

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.

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

EXTRACTION SHEET DRAFT Version 5 (3/10/2023)

1. Save extraction sheet as "tradename_NDA/BLAnumber_extraction" in the following folder: Study ID Extraction Sheets

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

IND	
NDA	
BLA	

3. Tradename (application number) of product used to answer questions 4 through 11:

4. Generic name:

5. Applicant:

6. Label link:

7. Label year (year label converted to PLLR in DARRTS. Date can be found in column F in the "Copy of PLLR 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 on front page of label?

Pregnancy contraindication?	☐Yes	☐No
Pregnancy mention in "WARNINGS AND PRECAUTIONS" section	☐Yes	☐No
"May cause fetal harm" statement in "HIGHLIGHTS – USE IN SPECIAL POPULATIONS" section	☐Yes	☐No

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

1

EXTRACTION SHEET DRAFT Version 5 (3/10/2023)

12. Quantitative information in Section 8.1 text (multiple pieces of quantitative information may come from a single study. group multiple datapoints only if explicit that in label that information came from the same source):

Quantitative data #	Excerpt from label (section 8.1)
Data 1	
Data 2	
Data 3	
Data 4	
Data 5	

13. Were Relevant Internal Documents Identified?

☐YES	☐No

Was a DPMH review identified?

☐YES	☐No

What types of documents were identified?
DPMH, DEPI, Labeling supplement from applicant, other (please specify):

☐DPMH review	☐Labeling supplement from applicant
☐DEPI review	☐Other (please specify):

List and provide links to reviews or supplement identified [save copy of identified reviews to Reviews and literature —name files using this format: tradename_NDA/BLA_review type(month,year)]:

Review or supplement (month,year)	link to review

Data sources mentioned that support quantitative data presented in label (there may be more than one study source per quantitative data listed in question 12):

Study #	Data #	Review or supplement [review type (month, year)]	Excerpt from review or relevant table/ figure or page number
Study 1			
Study 2			
Study 3			
Study 4			

2

EXTRACTION SHEET DRAFT Version 5 (3/10/2023)

Study 5			

14. Literature search:
Were we able to identify published literature to support quantitative data in label:

☐YES	☐No

If yes, citation and location of quantitative information in that citation:

Study #	Data #	link to study	page where we can find quantitative information
Study 1			
Study 2			
Study 3			
Study 4			
Study 5			

15. Is there quantitative human data in section 8.1 (listed in question 11/12) where no specific study or data source could be identified?

☐Yes	☐No

If yes, which data (from Q. 11/12)?

Data #	Excerpt from label

16. Is the products associated with a pregnancy-related PMR/PMC [please use the following link to identify any PMR/PMCs associated with this product: Pregnancy_studies_PMRPMC_506B_2022-05-31.xlsx (sharepoint.com)

☐Yes	☐No

If yes, is the above mentioned PMR/PMC associated with a study used to inform PLLR labeling?

☐Yes	☐No

If yes, list the studies?

Study #	Requirement Description [copy and paste from Column AC (PMX_UNREDACT_DESCR)]	PMR/PMC Status [copy and paste from column AS (PMX_UNREDACT_STAT_EXPLN)]

3

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

Example: Qualitative Statement

ACTEMRA® (tocilizumab) injection, for intravenous or subcutaneous use
Initial U.S. Approval: 2010

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

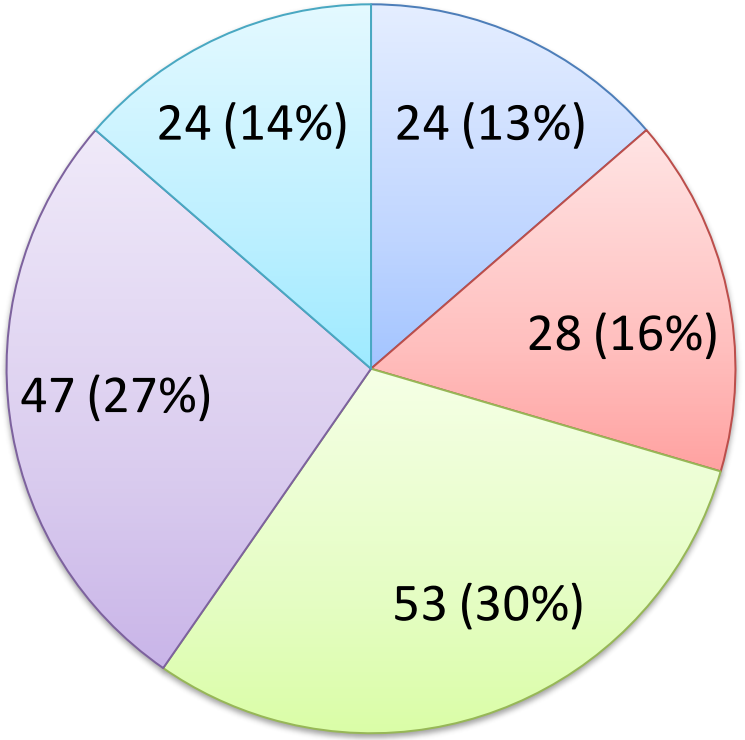
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Healthcare providers are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

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
- Pregnancy exposure registry
- Database Study with prespecified outcome
- Clinical Trial
- Other



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

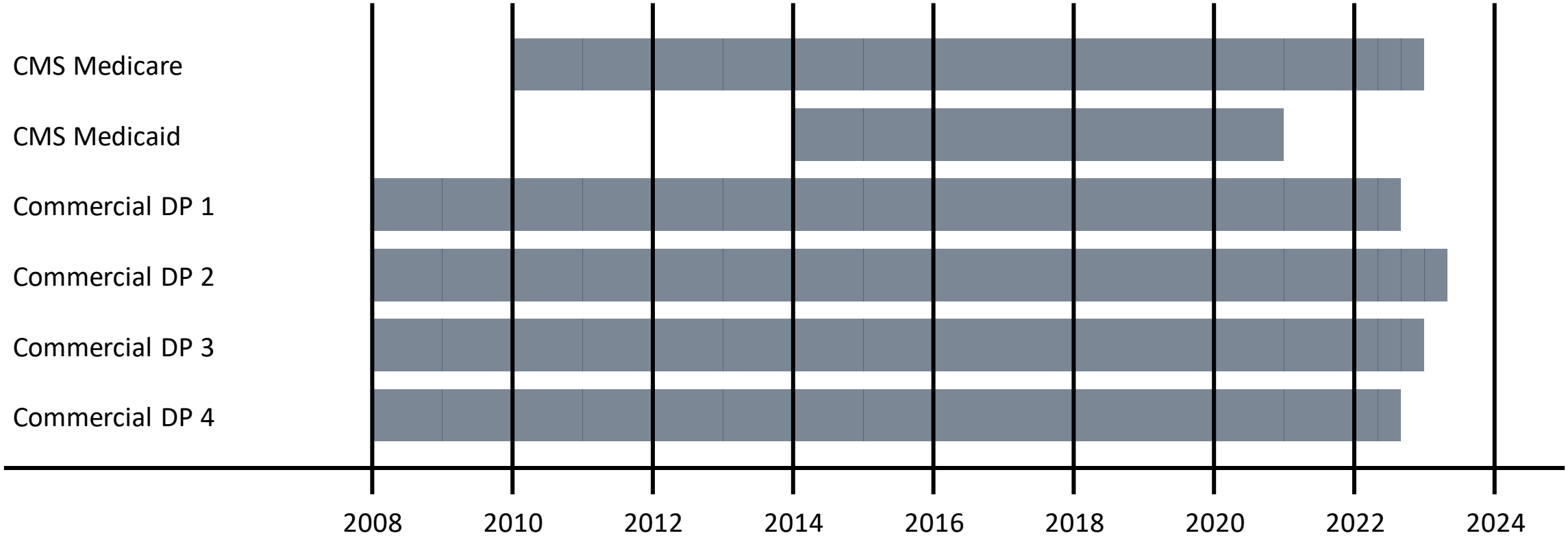
- Inclusion: A total of 249 products associated with studies in the analysis of postapproval pregnancy safety were identified for this preliminary analysis
- Exclusion: Products with pregnancy exposures ranging from 0 and 2,500 during the 15-year query period were not included in this analysis
  - The 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

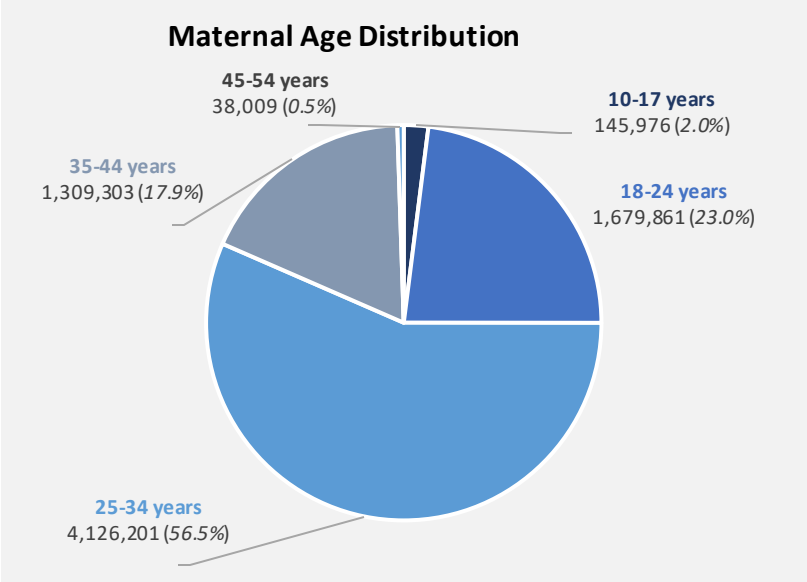


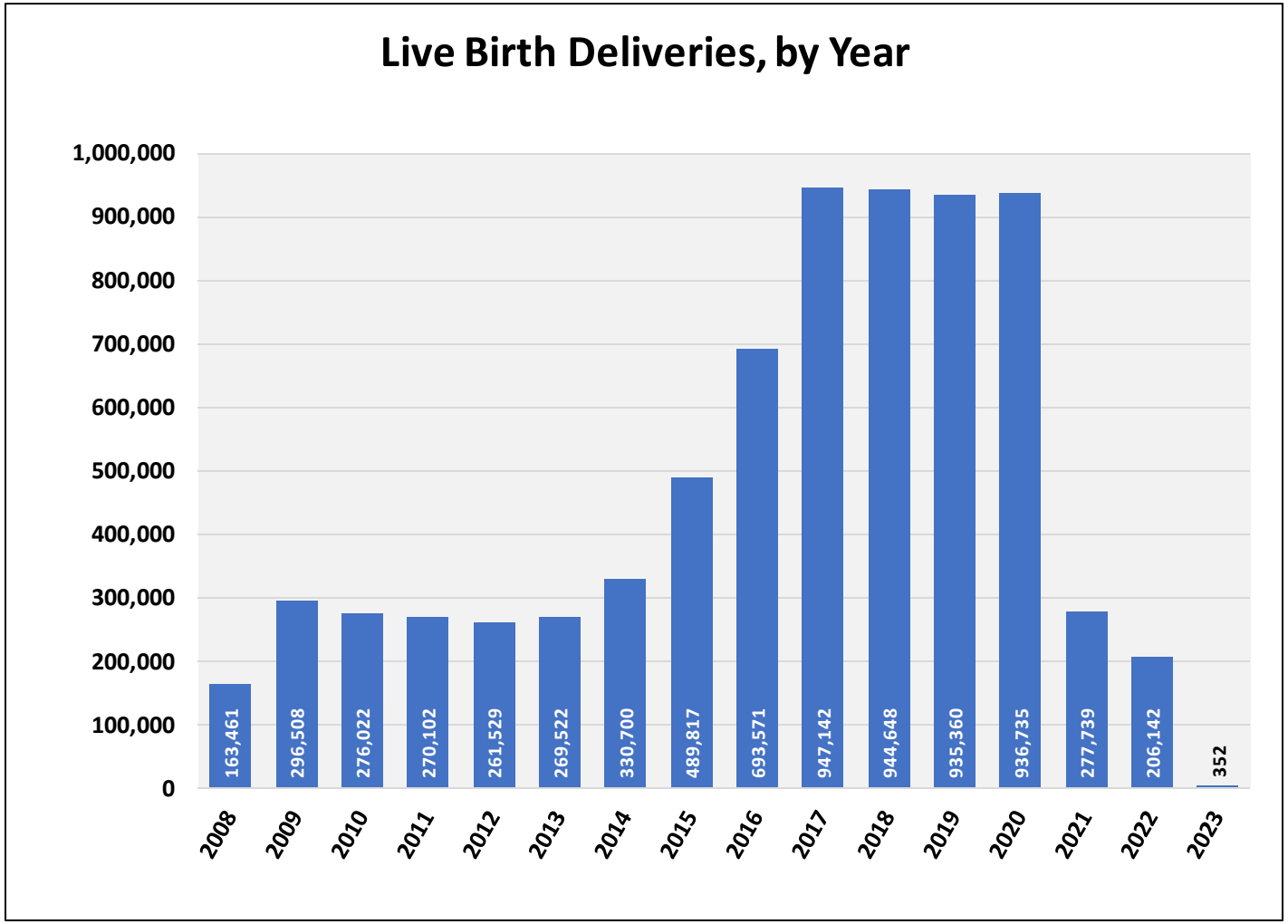
* Data prior to January 1, 2008, not utilized; dates are current as of August 4, 2023, query distribution
CMS: Centers for Medicare and Medicaid Services; DP: Data Partner; FFS: Fee-for-service

Characterization of Live Birth Deliveries in the Sentinel Distributed Database: January 1, 2008 – January 31, 2023

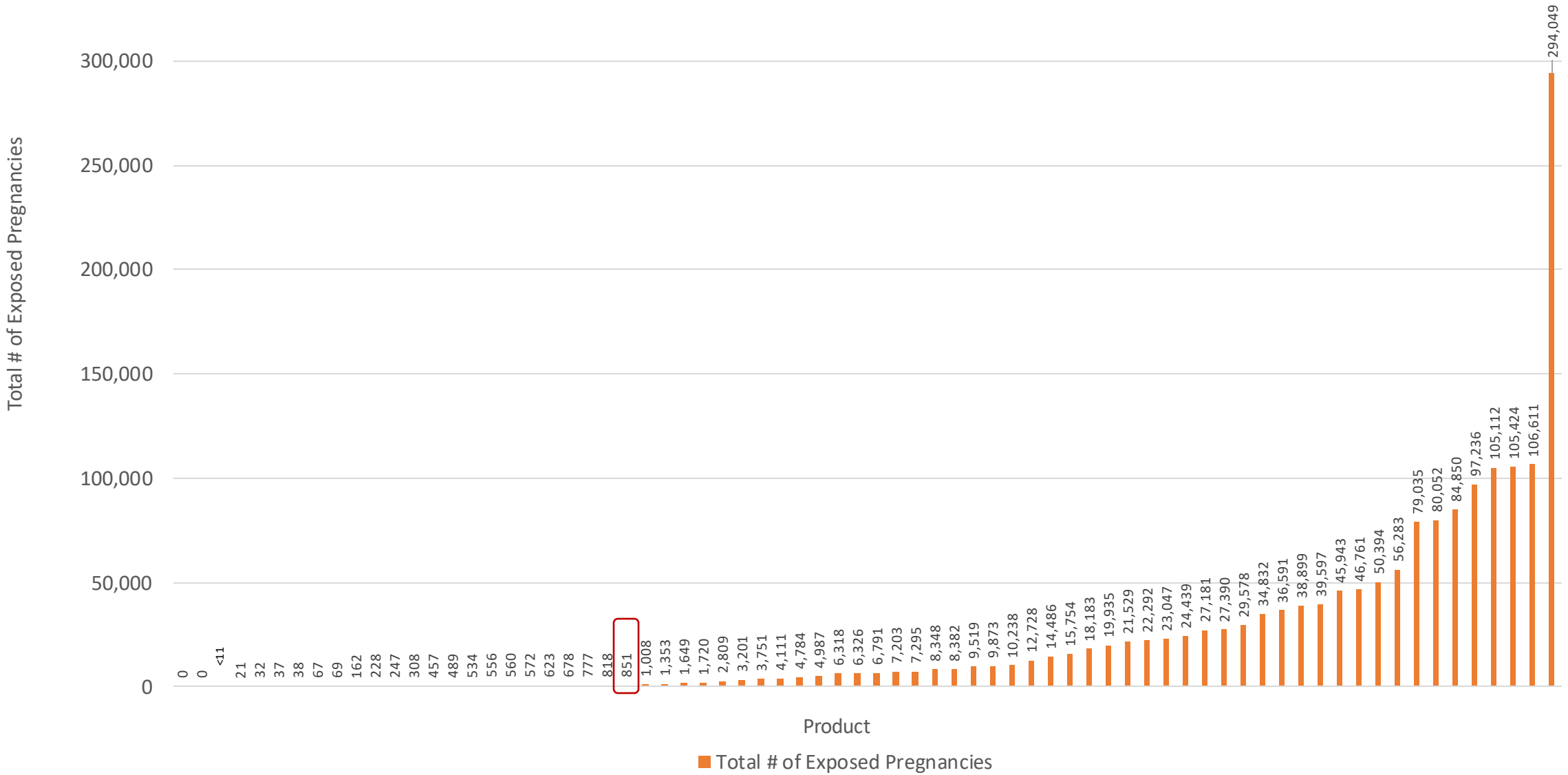
6,165,744
unique patients

7,299,350
live birth deliveries





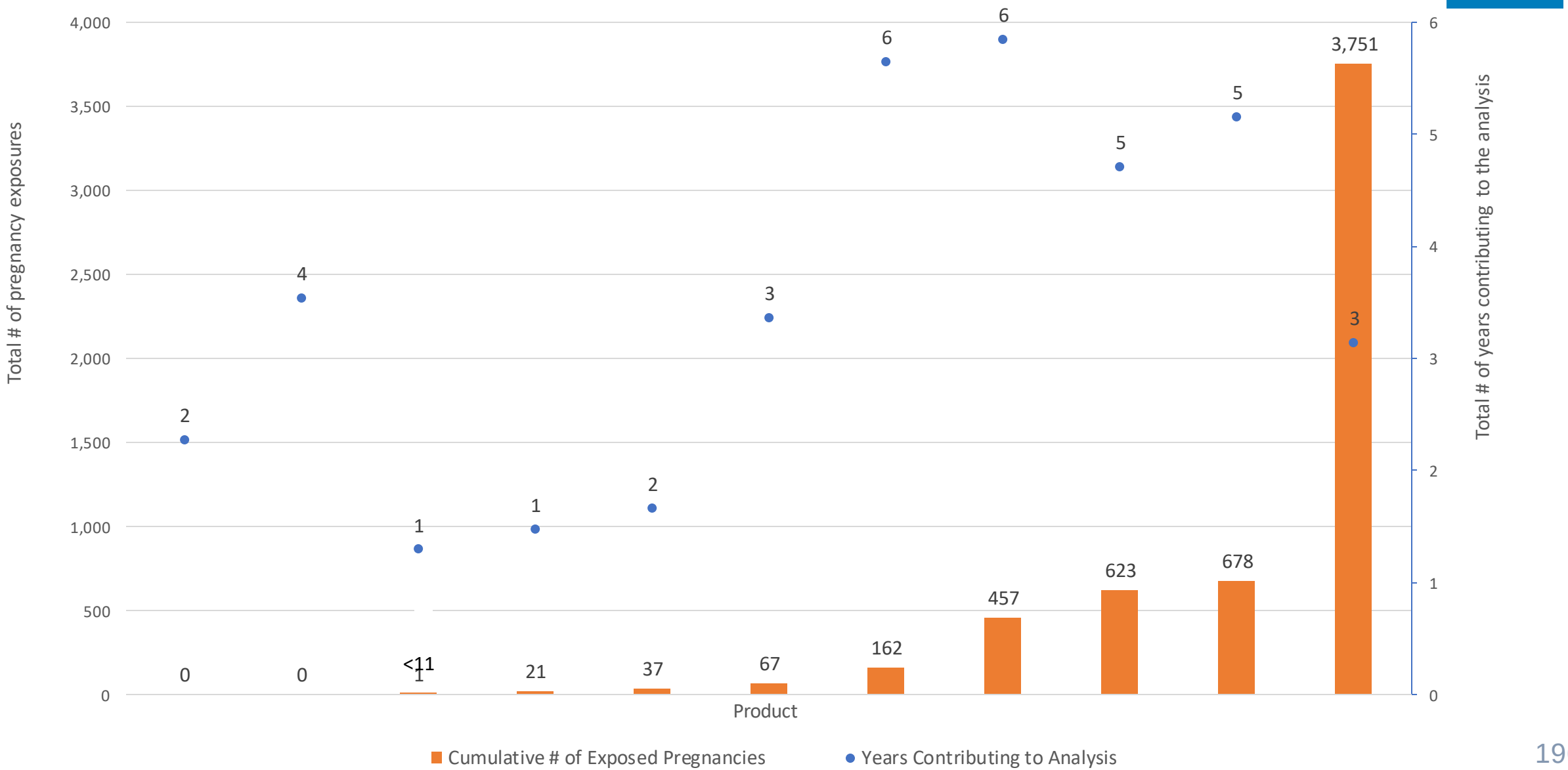
Total Number of Exposed Pregnancies from 2008-2023 for each of the 72 Products from the Convenience Sample



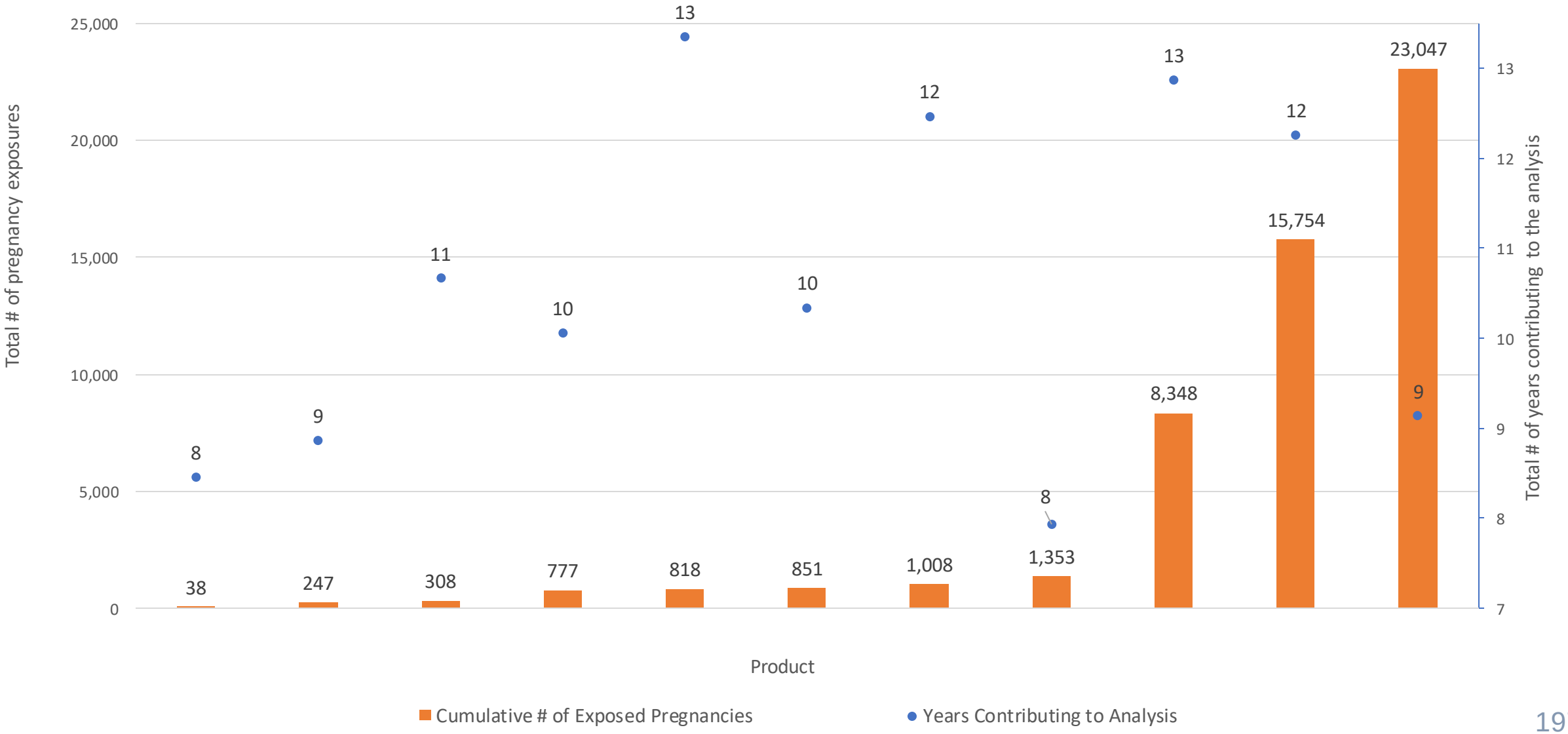
Characterization of utilization during pregnancy

- 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

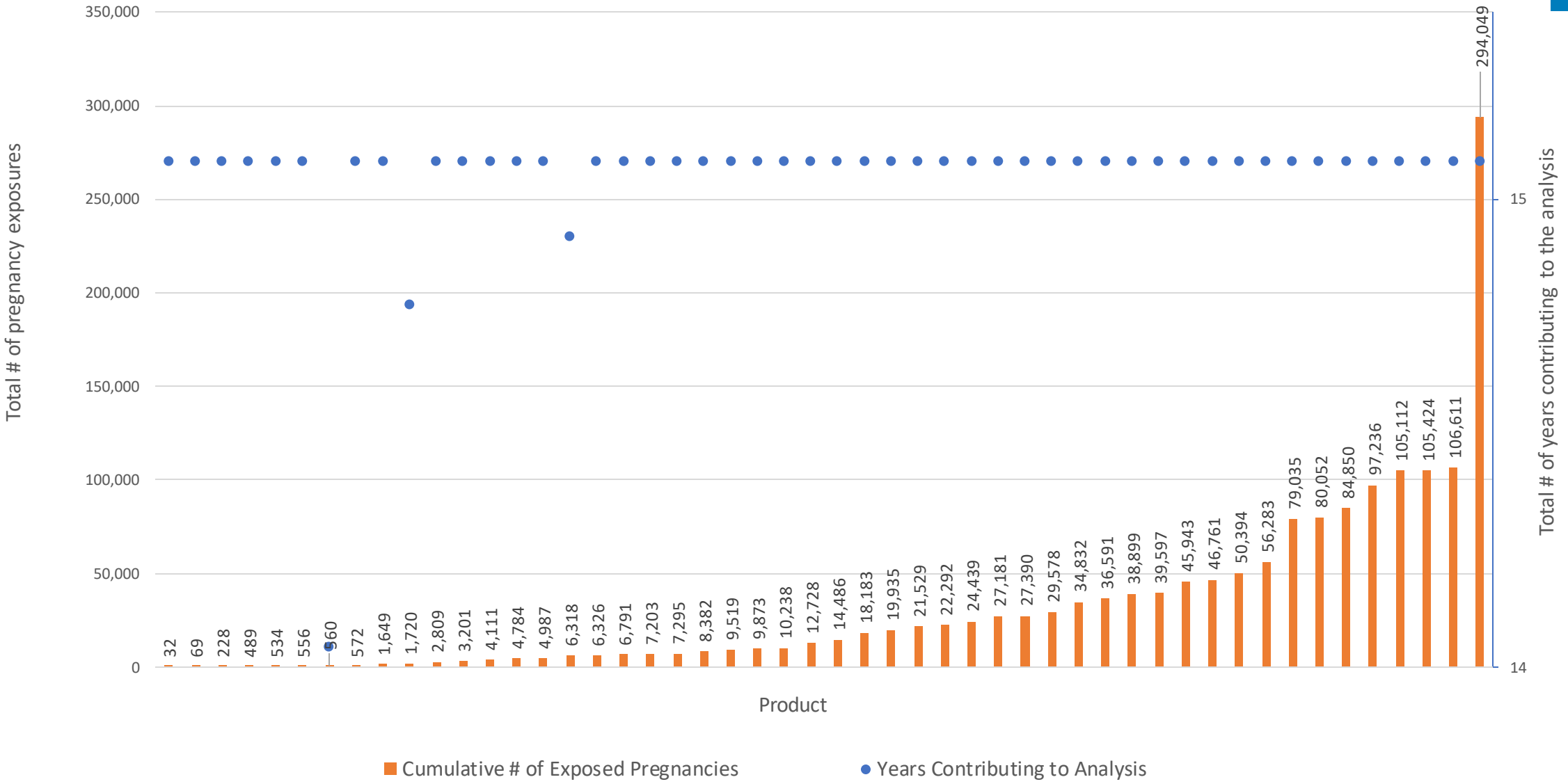
Total Number of Exposed Pregnancies for Products Contributing 0 to 6 Years of Utilization Data to the Analysis from the Convenience Sample



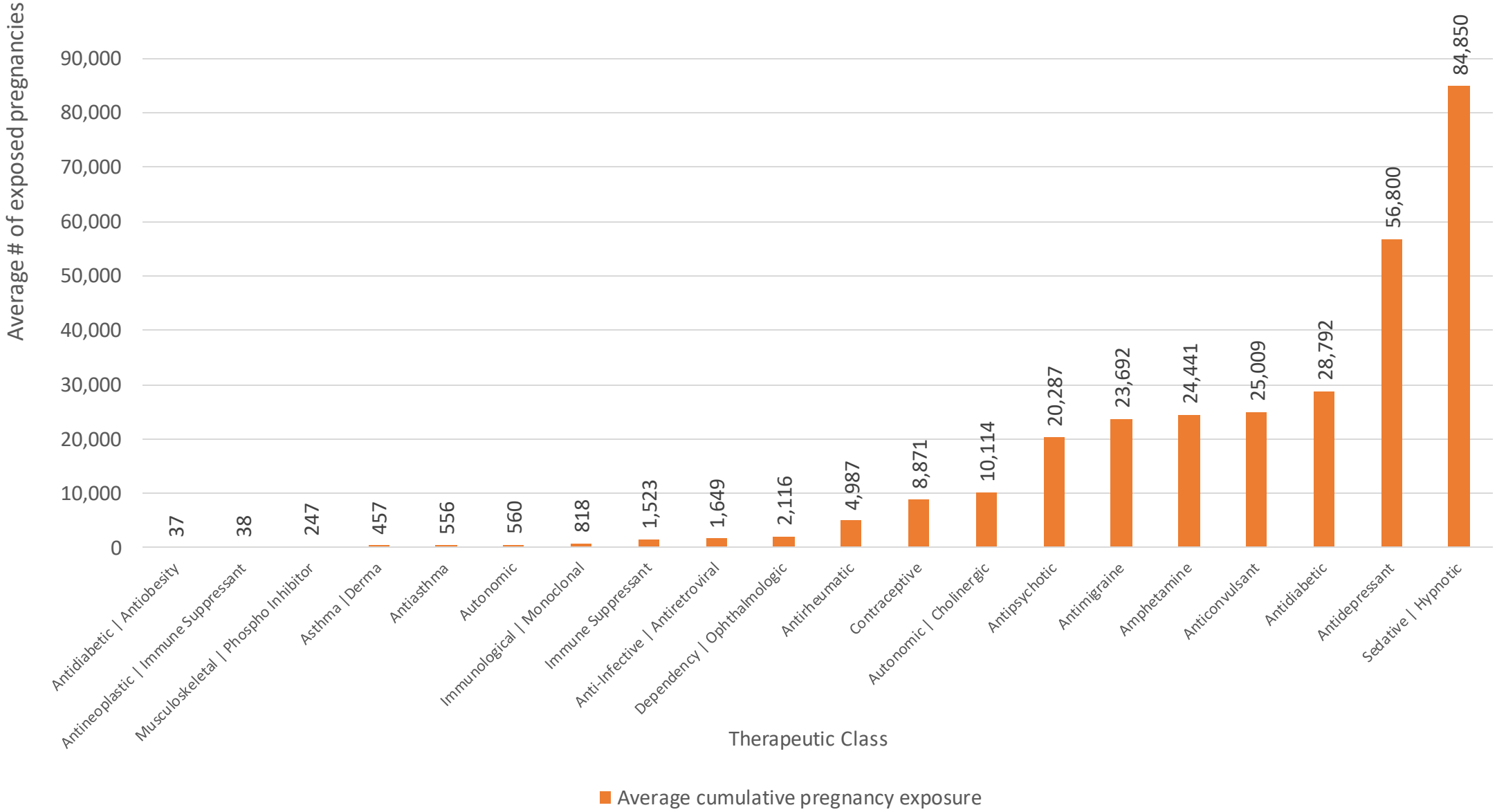
Total Number of Exposed Pregnancies for Products Contributing 7 to 13 Years of Utilization Data to the Analysis from the Convenience Sample



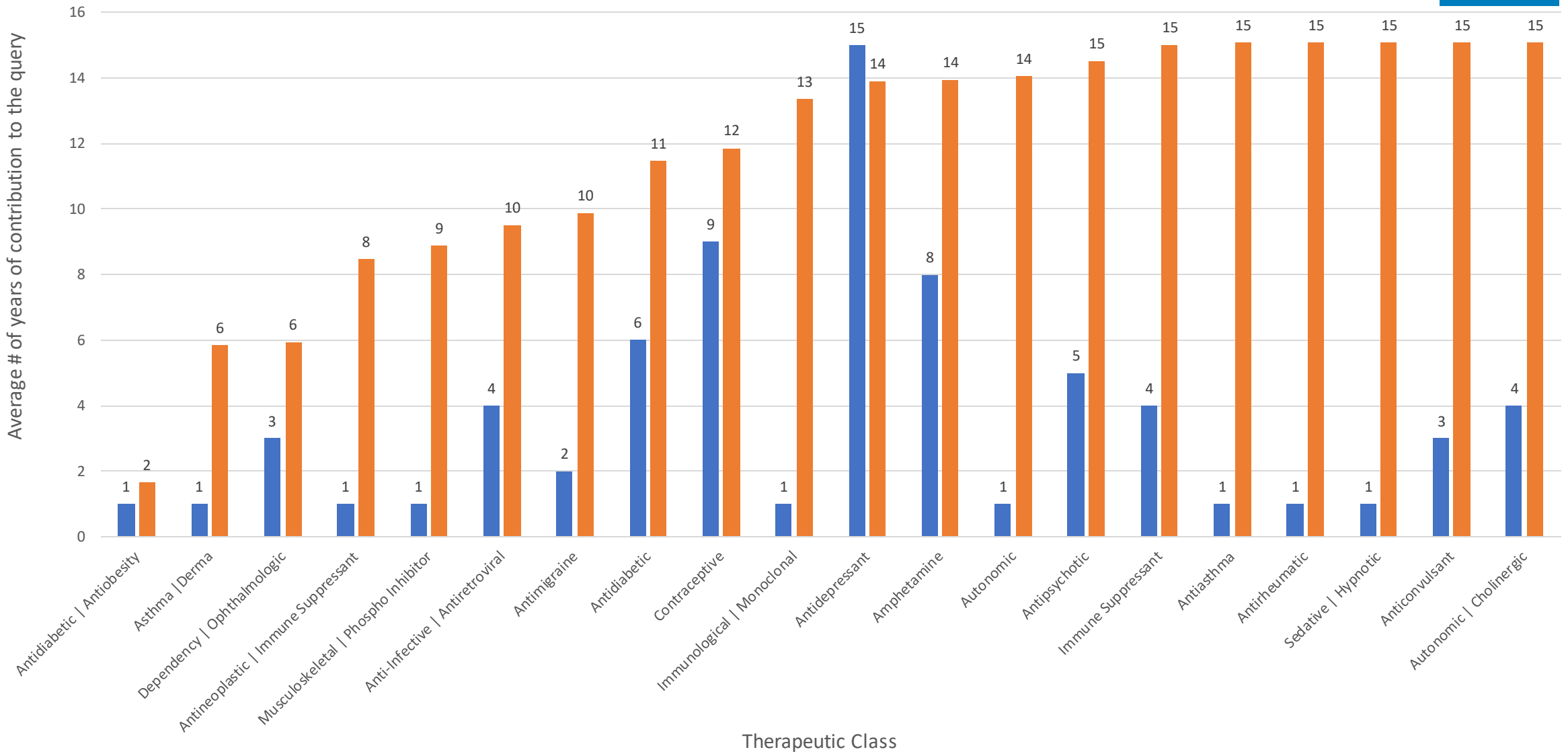
Total Number of Exposed Pregnancies for Products Contributing 14 to 15 Years of Utilization Data to the Analysis from the Convenience Sample



Average Number of Exposed Pregnancies by Therapeutic Class during the Query Period



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



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

FDA Query Team

Sentinel Operations Center

Participating Sentinel Data Partners

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.

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.

Session 3: FDA's Considerations for Constructing a Pregnancy Safety Study Framework

Introduction to Session 3

Wei Hua, MD, PhD, MS, MHS
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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

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

PDUFA: Prescription Drug User Fee Act

Understanding the Current State of Using Postapproval Pregnancy Safety Studies for FDA's Decision-making

Analysis #	Title	Presenter
1	Analysis of how different types postapproval pregnancy safety studies have been used by FDA	Dr. Adebola Ajao
2	Review of types of postapproval safety data that have been included in pregnancy labeling	Dr. Aida Kuzucan
3	Preliminary analysis of drug utilization data to inform the development of the pregnancy safety study framework	Dr. José J. Hernández-Muñoz

Three Presentations

U.S. FOOD & DRUG ADMINISTRATION

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
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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

FAERS: FDA Adverse Event Reporting System; VAERS: Vaccine Adverse Event Reporting System

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

How much do we know about the risk based on available information?	Study Goal
❑ Adequate evidence of an association	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

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

	Signal Detection	Signal Evaluation
Large effect	**High**	**Low to Medium**
Small effect	**Medium to High**	**Low**

  - 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

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

* 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		
Very rare exposure in pregnancy	**Uncertain exposure in pregnancy**	**Very common exposure in pregnancy**

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

Analysis #1:
A convenience sample of studies used by FDA

Study types used by FDA

- Pregnancy registry 63%
- Descriptive study 21%
- Database study with prespecified outcome 15%
- Clinical trial 1%

Study goal

- Signal detection 99.1%
- Signal evaluation 0.9%

Analysis #2:
A sample of PLLR labeling with quantitative human data

Study types informed PLLR

- Pregnancy registry 46%
- Database study with prespecified outcome 35%
- Clinical trial 26%
- Case report/case series 10%
- Other 20%

Study goal

- Signal detection 81.4%
- Signal evaluation 18.6%

Analysis #3:
Drug utilization of a convenience sample of products

Magnitude of exposure

- Drug utilization in pregnancy was low, especially among products approved after 2008
- Sedative/hypnotic and antidepressant products showed the highest exposure during pregnancy
- Utilization pattern cannot be explained by years on the market; other disease, patient, and product related factors will be explored

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

Optimizing the Use of Postapproval Pregnancy Safety Studies

A Hybrid Public Workshop

Duke | MARGOLIS CENTER *for* Health Policy

September 18 & 19, 2023

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
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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

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

* 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

Factor	Definition and Scope
Outcome of interest	Pregnancy-related maternal, fetal, and infant outcomes, prespecified or non-prespecified, determined by available information (or lack of information)
Study goal	Signal detection or signal evaluation
Technical capability	The ability of a study to achieve necessary level of certainty, accounting for potential sources of bias
Magnitude of drug exposure	Expected utilization of this drug by pregnant individuals, over time
▪ Study exposure capture	Fraction of magnitude of drug exposure that a given study expects to capture by year, depending on data source and data collection methods

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?

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?

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.?

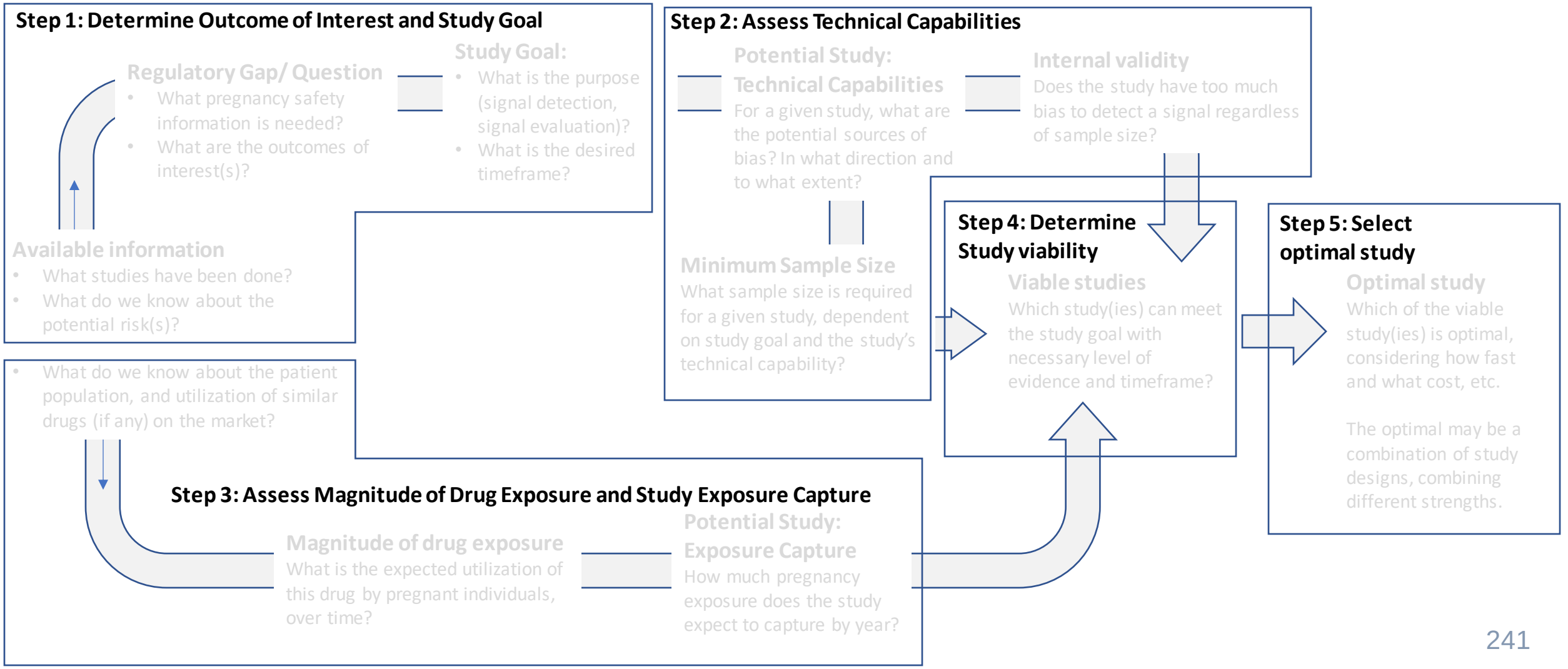
The optimal may be a combination of studies, combining different strengths.

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

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

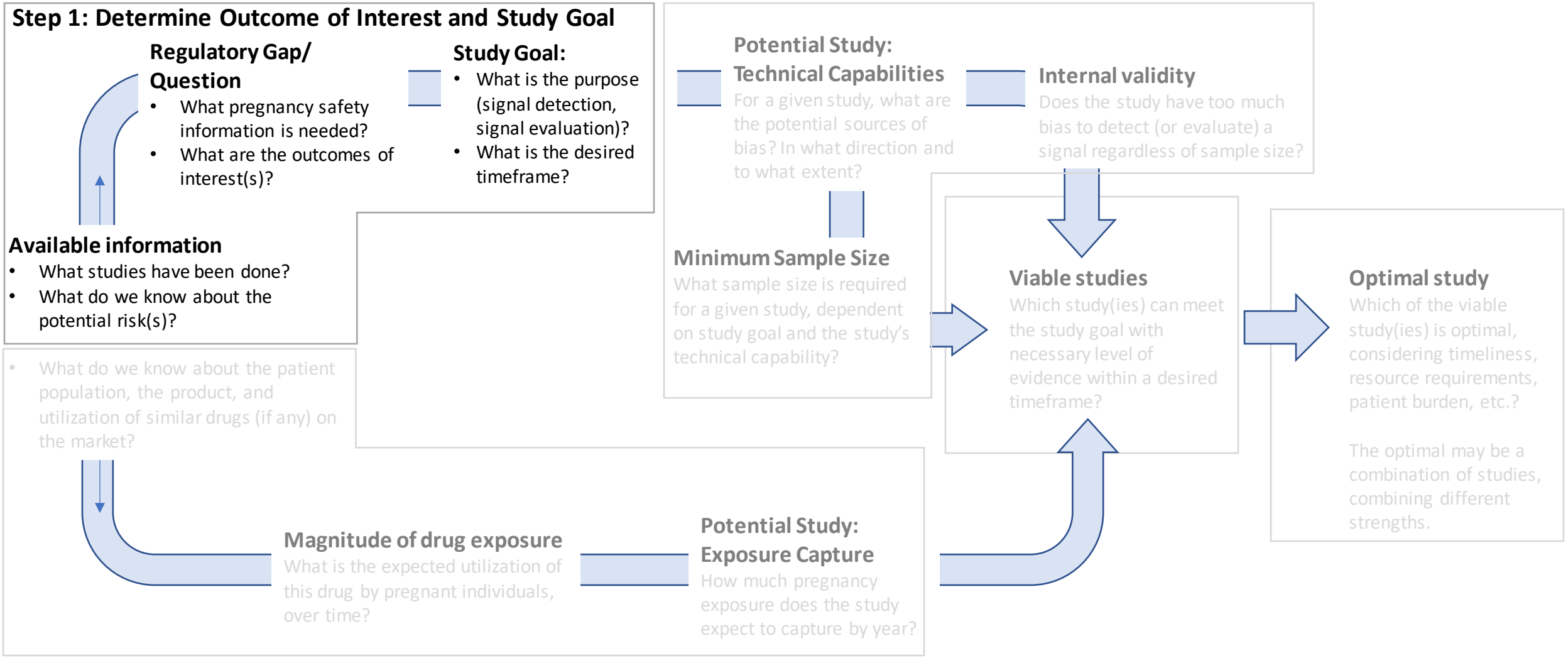
Preliminary Framework

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



Preliminary Framework

Determining the viable and optimal non-interventional pregnancy studies to meet regulatory decision-making needs

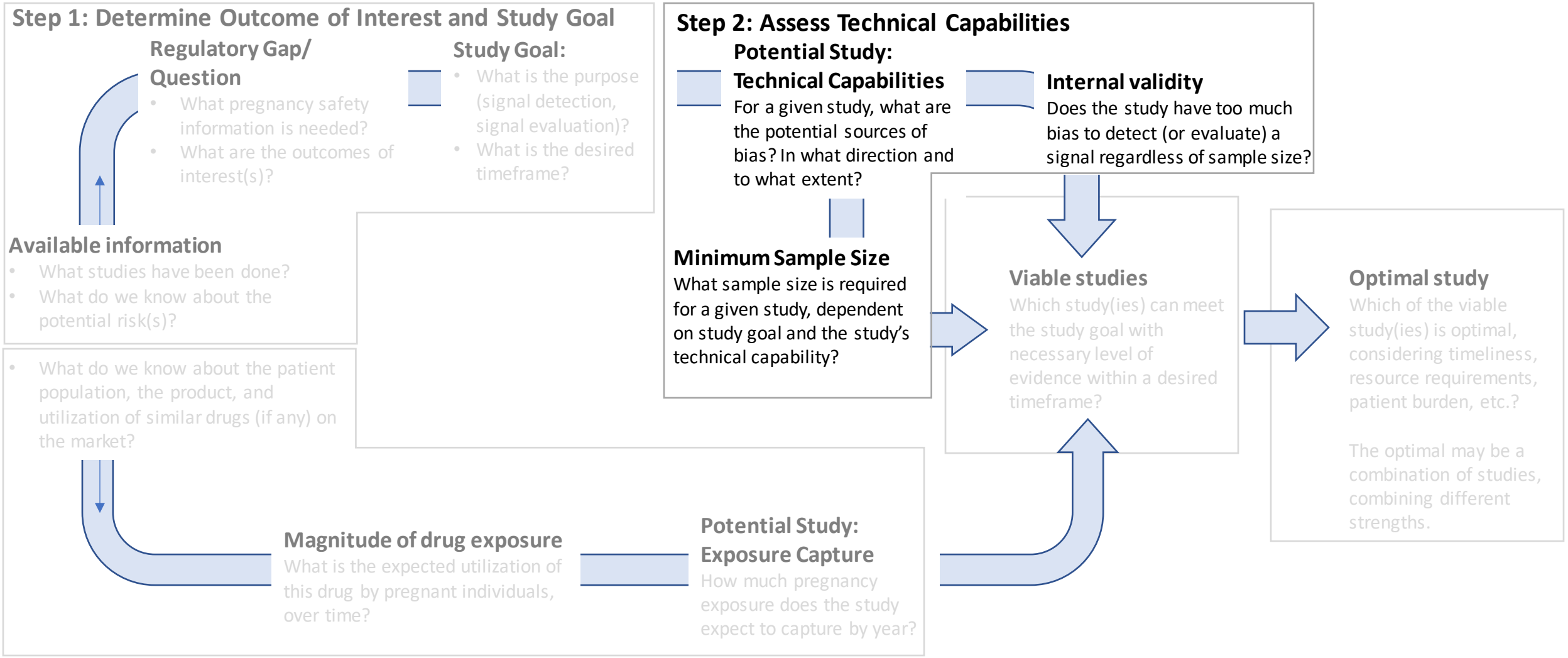


Determining Outcome of Interest and Study Goal

- 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



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?

Key Parameters		
Assumed true risk (product-outcome specific)		
Prevalence (outcome specific)		
Desired power		
Exposed vs. unexposed ratio		
Type I Error	→	When appropriate, may be less strict for signal detection to avoid missing a signal
Bias parameters, e.g., sensitivity and specificity of outcome ascertainment	→	Adjusted to estimate the projected RR and its sample size under various scenarios 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)

	Technical Capability				**Type I Error**	
	Outcome ascertainment				5%	20%
	Sensitivity (fixed)	Specificity in Exposed	Specificity in Unexposed	**Projected RR**	**Sample Size Exposed**	**Sample Size Exposed**
No bias	1.0	1.0	1.0	2.000	748	430
Examples of	0.8	0.9	0.6	0.345	808	464
outcome	0.8	0.8	0.6	0.573	2131	1222
misclassification	0.8	0.9	0.8	0.651	3826	2195
scenarios	0.8	0.6	0.8	1.945	842	483
	0.8	0.8	0.9	1.950	793	455
	0.8	0.6	0.9	3.504	175	100

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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	0.8	0.6	0.9	3.504	175	100

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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	0.8	0.8	0.9	1.950	793	455
	0.8	0.6	0.9	3.504	175	100

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

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

	Technical Capability				**Type I Error**	
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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)

	Technical Capability				**Type I Error**	
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→ 4) Missing a signal even with large sample size

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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	0.8	0.8	0.9	1.950	793	455
	0.8	0.6	0.9	3.504	175	100

4) Missing a signal even with large sample size

5) Inaccuracy acceptable for signal detection but concerning for signal evaluation if bias not accounted

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)

	Technical Capability				**Type I Error**	
	Outcome ascertainment				5%	20%
	Sensitivity (fixed)	Specificity in Exposed	Specificity in Unexposed	**Projected RR**	**Sample Size Exposed**	**Sample Size Exposed**
No bias	1.0	1.0	1.0	2.000	748	430
Examples of outcome misclassification scenarios	0.8	0.9	0.6	0.345	808	464
	0.8	0.8	0.6	0.573	2131	1222
	0.8	0.9	0.8	0.651	3826	2195
	0.8	0.6	0.8	1.945	842	483
	0.8	0.8	0.9	1.950	793	455
	0.8	0.6	0.9	3.504	175	100

4) Missing a signal even with large sample size

5) Inaccuracy acceptable for signal detection but concerning for signal evaluation if bias not accounted

1) Suboptimal outcome ascertainment introduces outcome misclassification

2) Risk estimate is biased in different directions to varying extents depending on the interplay of bias parameters

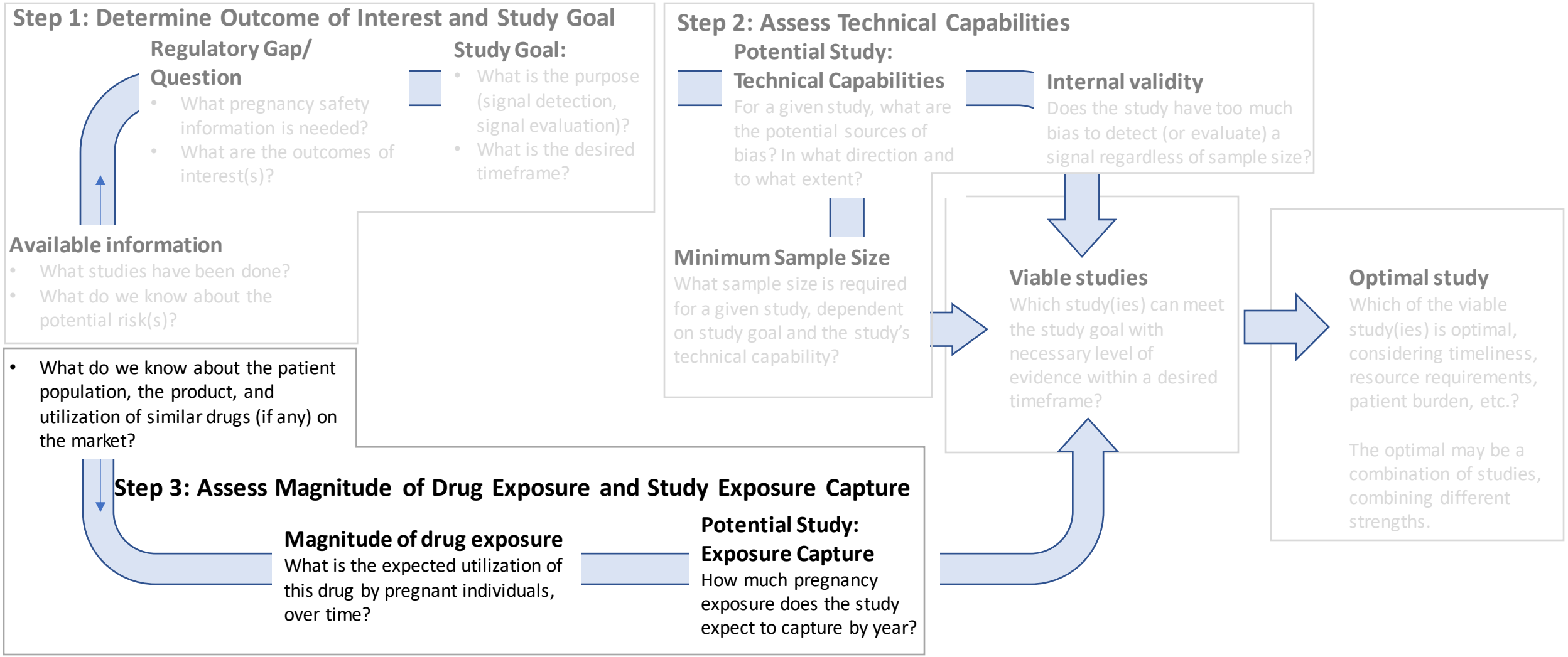
3) Minimum sample size could be larger (or smaller) than the true sample size in the presence of bias

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

Preliminary Framework

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



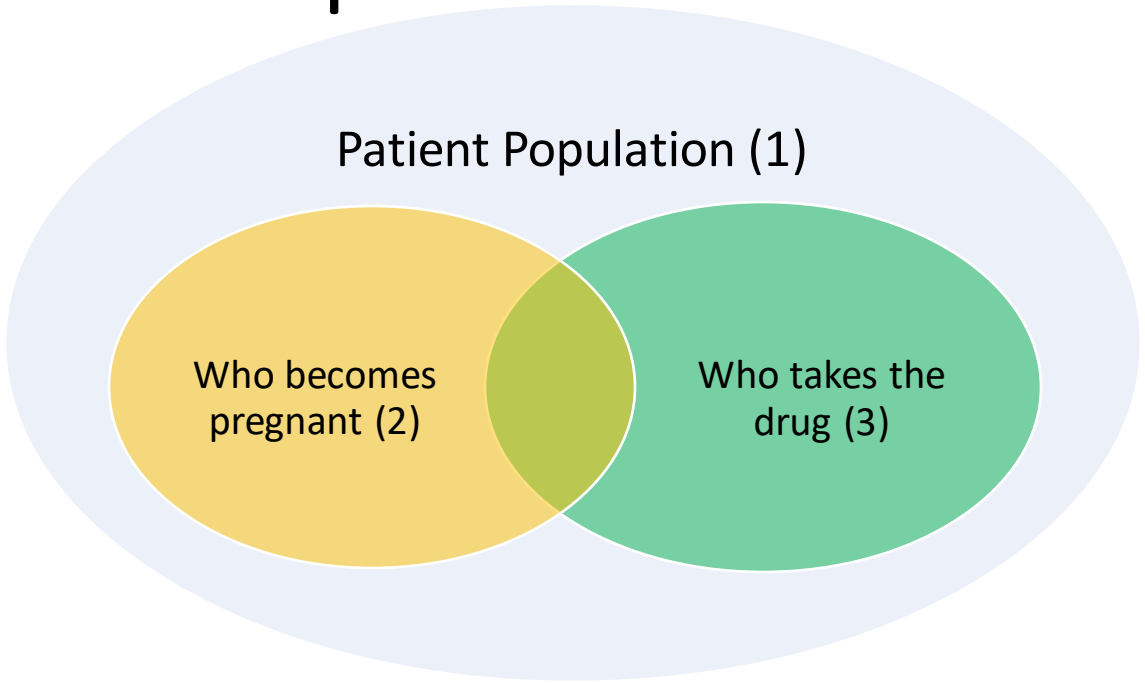
Magnitude of Drug Exposure among Pregnant Individuals Has an Impact on Study Suitability

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

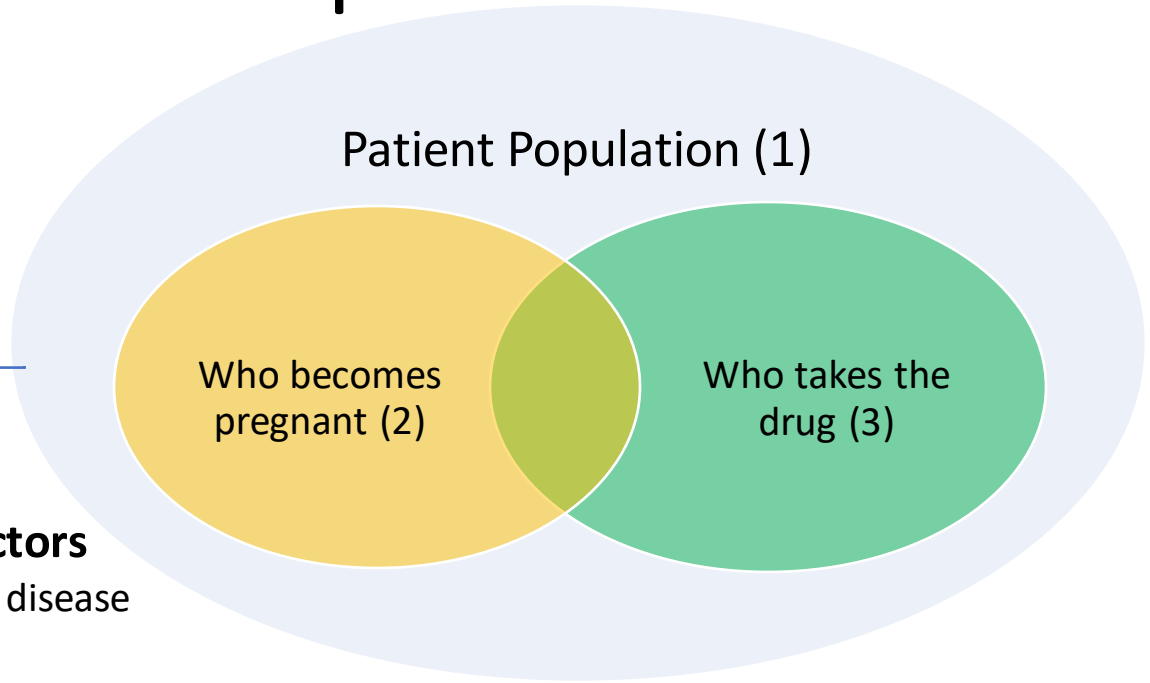
Hypothetical, for simple illustration		
Category	**Number of pregnant individuals exposed to drug, annual (range)***	**Impact on study suitability in the Framework**
1 (Very rare)	<10	Descriptive study may be the only option in this framework for signal detection; signal evaluation is likely not possible
2	10 - 100	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
3	100 – 1,000	
4	1,000 – 10,000	
5 (Very common)	10,000+	Many possible study options for signal detection and evaluation

*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



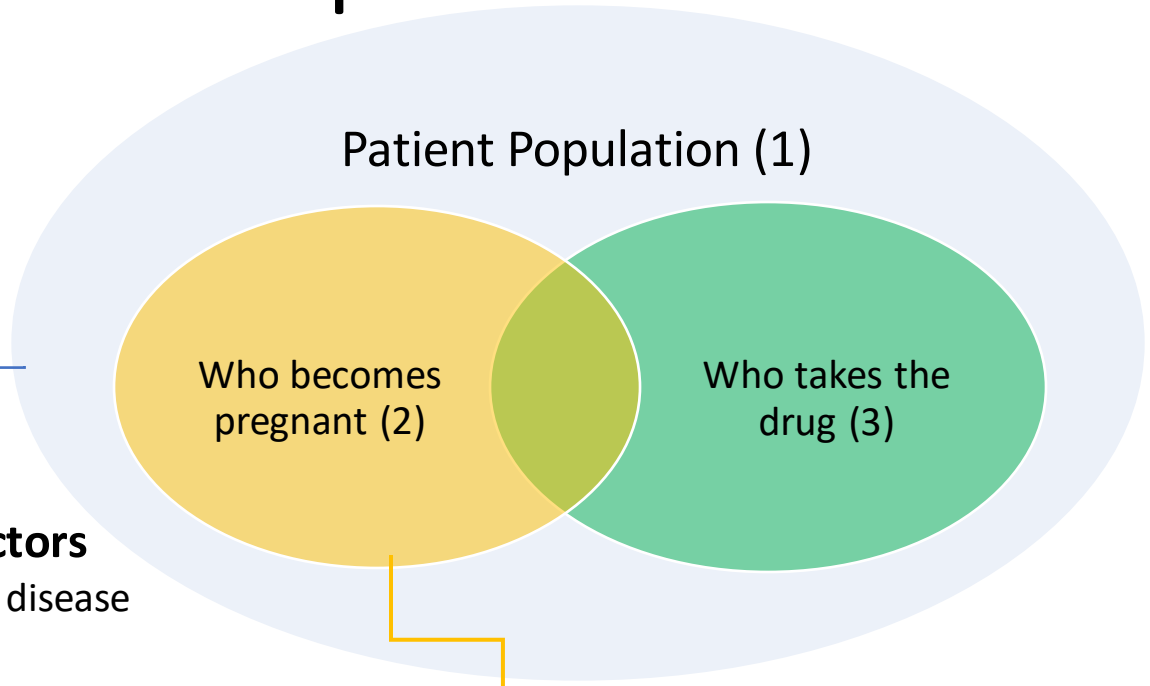
Estimating Magnitude of Drug Exposure by Year Integrates Multiple Patient and Treatment Factors



(1) Patient Factors

- Prevalence of disease or condition

Estimating Magnitude of Drug Exposure by Year Integrates Multiple Patient and Treatment Factors



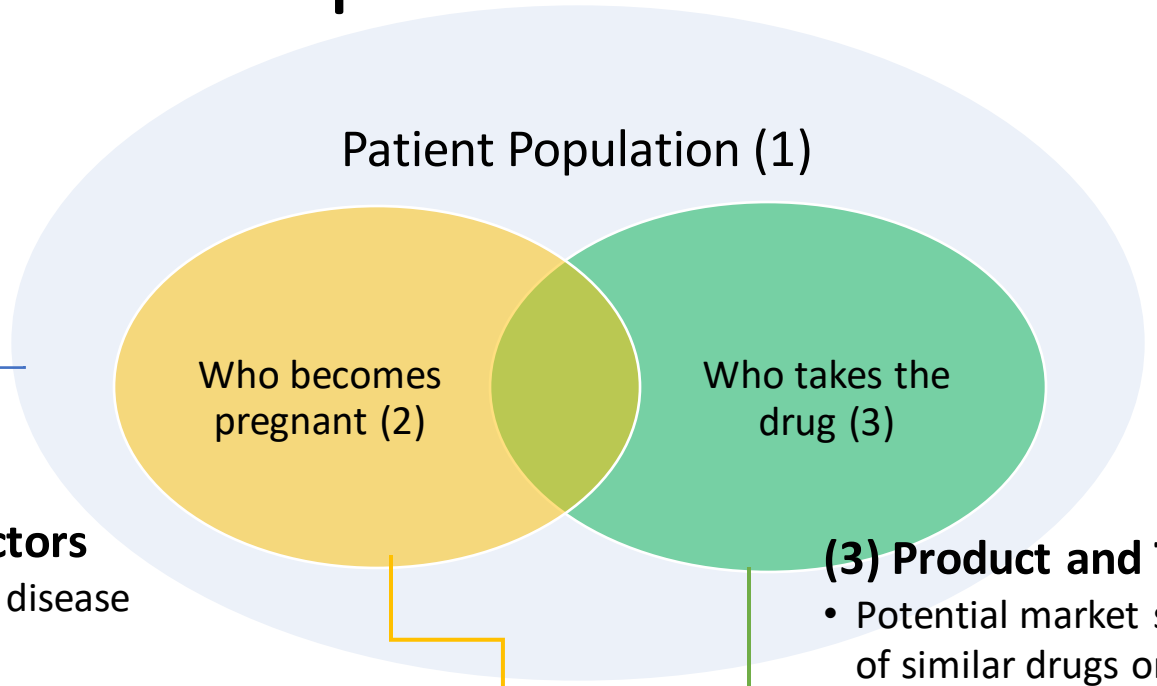
(1) Patient Factors

- Prevalence of disease or condition

(2) Patient Factors

- Characteristics of patient population, in particular: age, sex, and whether condition is common in pregnancy

Estimating Magnitude of Drug Exposure by Year Integrates Multiple Patient and Treatment Factors



(1) Patient Factors

- Prevalence of disease or condition

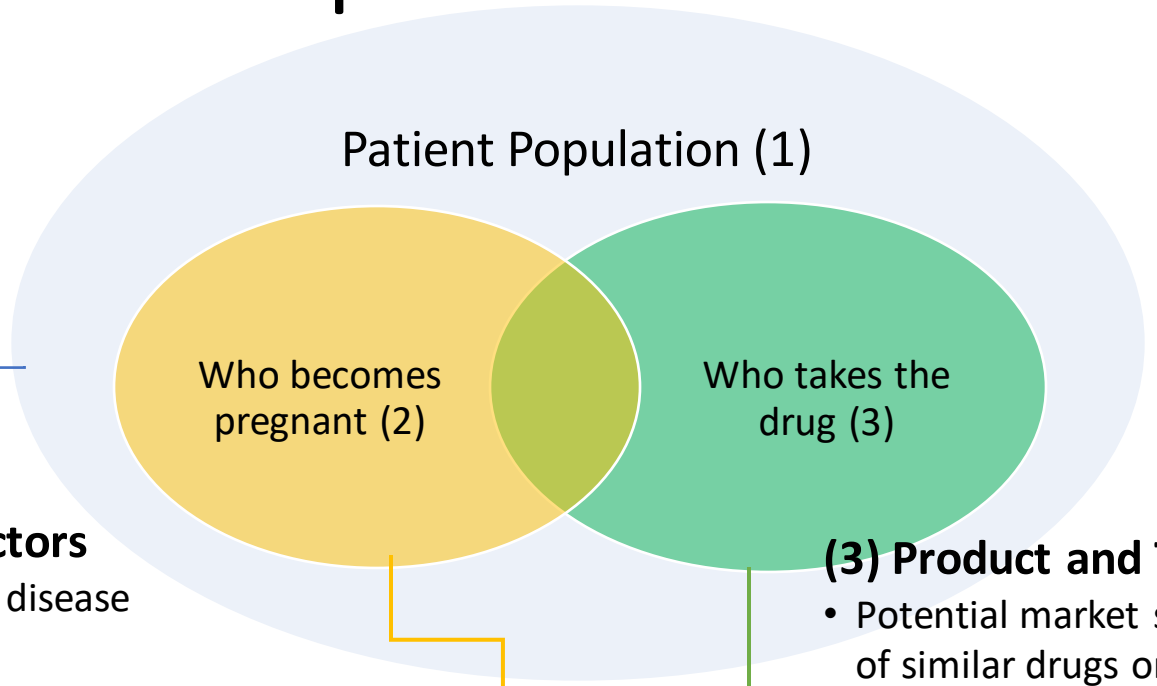
(2) Patient Factors

- 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., 1st vs. 9th 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



(4) Time factors

- Time since approval/Years on market

(1) Patient Factors

- Prevalence of disease or condition

(2) Patient Factors

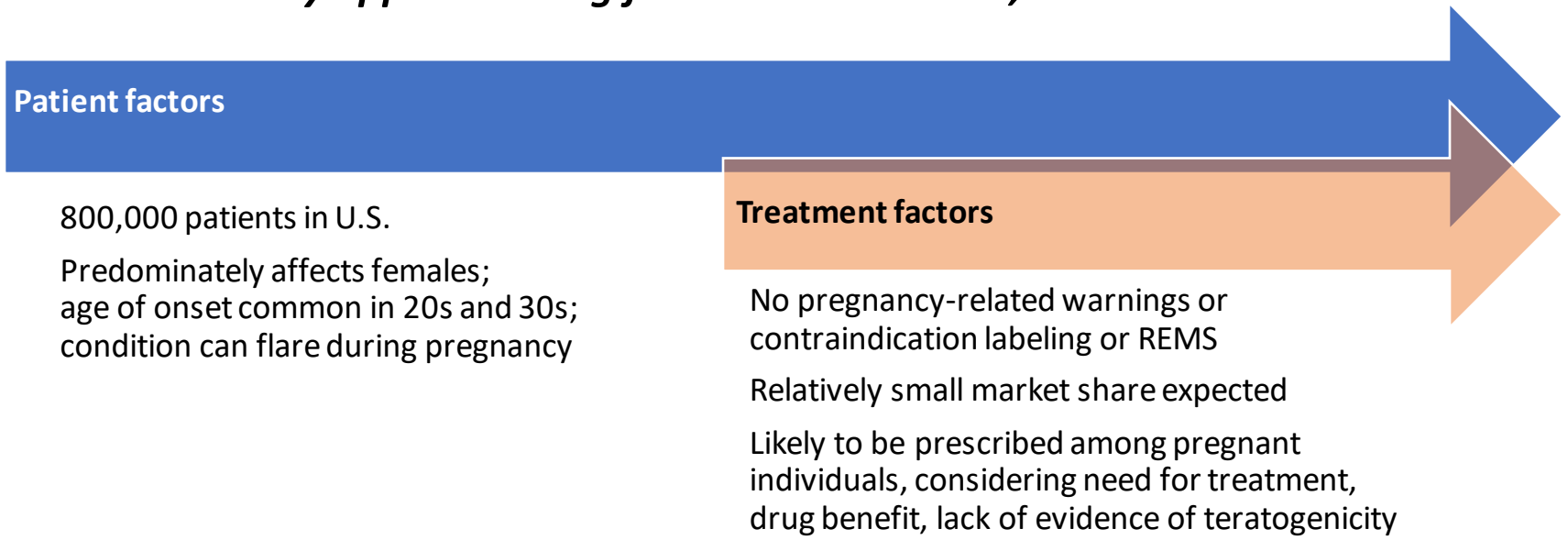
- Characteristics of patient population, in particular: age, sex, and whether condition is common in pregnancy

(3) Product and Treatment Factors

- Potential market share of product (e.g., 1st vs. 9th 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

Magnitude of Drug Exposure - Example of Hypothetical Scenario

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



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

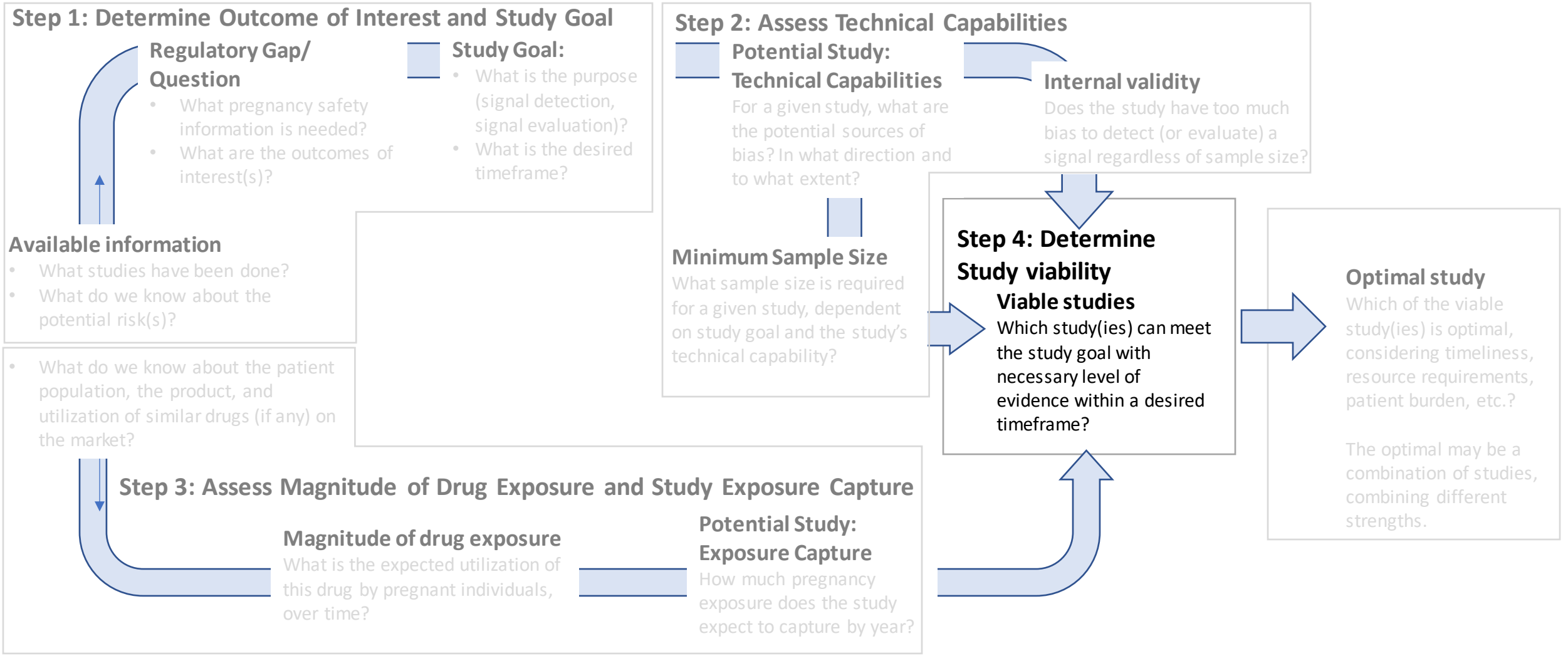
Integrating the Magnitude of Drug Exposure and the Study's Capture of Exposure

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



Hypothetical Look-up Table of Projected Risk Estimates and Possible Sample Sizes Based on Various Parameters

Assumed True Relative Risk (RR)	Outcome Ascertainment (Assuming outcome misclassification the only bias)				Desired power	Projected Relative Risk (RR)	Sample size for Exposed (1:1 Exposed to Unexposed ratio)	
	Sensitivity		Specificity				Type 1 error	Type 1 error
	Exposed	Unexposed	Exposed	Unexposed			5%	20%
2.0	100%	100%	100%	100%	80%	2.00	748	430
	90%	90%	100%	100%	80%	2.00	748	430
	90%	90%	90%	90%	80%	1.19	14,749	8,470
	80%	80%	90%	90%	80%	1.19	14,749	8,470
	80%	80%	80%	80%	80%	1.08	76,635	44,014
	80%	80%	60%	60%	80%	1.02	2,227,217	1,305,006
	80%	80%	90%	60%	80%	0.35	808	464
	80%	80%	80%	60%	80%	0.57	2,131	1,222
	…	…	…	…				
3.0	100%	100%	100%	100%	80%	3.00	245	140
	90%	90%	100%	100%	80%	3.00	245	140
	90%	90%	90%	90%	80%	1.39	4,019	2,308
	80%	80%	90%	90%	80%	1.39	4,019	2,308
	80%	80%	80%	80%	80%	1.17	20,219	11,500
	80%	80%	60%	60%	80%	1.06	155,115	89,087
	80%	80%	90%	60%	80%	0.40	979	562
	80%	80%	80%	60%	80%	0.62	2,813	1,615

Integrating Internal Validity, Minimum Sample Size, and Expected Exposure for a Given Signal Detection Study

Study Goal: Signal Detection for Outcome X (Hypothetical example)					
	Study Option 1	**Study Option 2**	**Study Option 3**	**Study Option 4**	**Study Option 5**
Potential Study	Pregnancy Registry *Case Report Form perfectly designed*	Pregnancy Registry *Case Report Form with less accuracy*	Healthcare Database Pre-specified outcome *Chart review*	Healthcare Database Pre-specified outcome *Claims-based algorithm*	Healthcare Database Non-Prespecified outcome *Singular codes, untargeted*
▪ **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

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	Study Option 1	Study Option 2	Study Option 3	Study Option 4	Study Option 5
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▪ **Internal validity**					
Non-differential Outcome misclassification	90% sensitivity 100% specificity	90% sensitivity 90% specificity	80% sensitivity 90% specificity	80% sensitivity 80% specificity	N/A
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**					
▪ **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)

	Study Option 1	Study Option 2	Study Option 3	Study Option 4	Study Option 5
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▪ **Internal validity**					
Non-differential Outcome misclassification	90% sensitivity 100% specificity	90% sensitivity 90% specificity	80% sensitivity 90% specificity	80% sensitivity 80% specificity	N/A
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	
Type I Error 5%	245	4,019	4,019	20,219	4,000 (hypothetical)
▪ **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

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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	
Type I Error 5%	245	4,019	4,019	20,219	4,000 (hypothetical)
▪ **Expected exposure**	Nationwide registry Capture at 10%	Regional registry Capture at 1%	Large database Capture at 40%	Large database Capture at 40%	Large database Capture at 40%
In U.S., 1,000-10,000 annual	100 – 1,000 annual	10 – 100 annual	400 – 4,000 annual	400 – 4,000 annual	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)

	Study Option 1	Study Option 2	Study Option 3	Study Option 4	Study Option 5
Potential Study	Pregnancy Registry *Case Report Form perfectly designed*	Pregnancy Registry *Case Report Form with less accuracy*	Healthcare Database Pre-specified outcome *Chart review*	Healthcare Database Pre-specified outcome *Claims-based algorithm*	Healthcare Database Non-Prespecified outcome *Singular codes, untargeted*
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In U.S., 1,000-10,000 annual	100 – 1,000 annual	10 – 100 annual	400 – 4,000 annual	400 – 4,000 annual	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	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

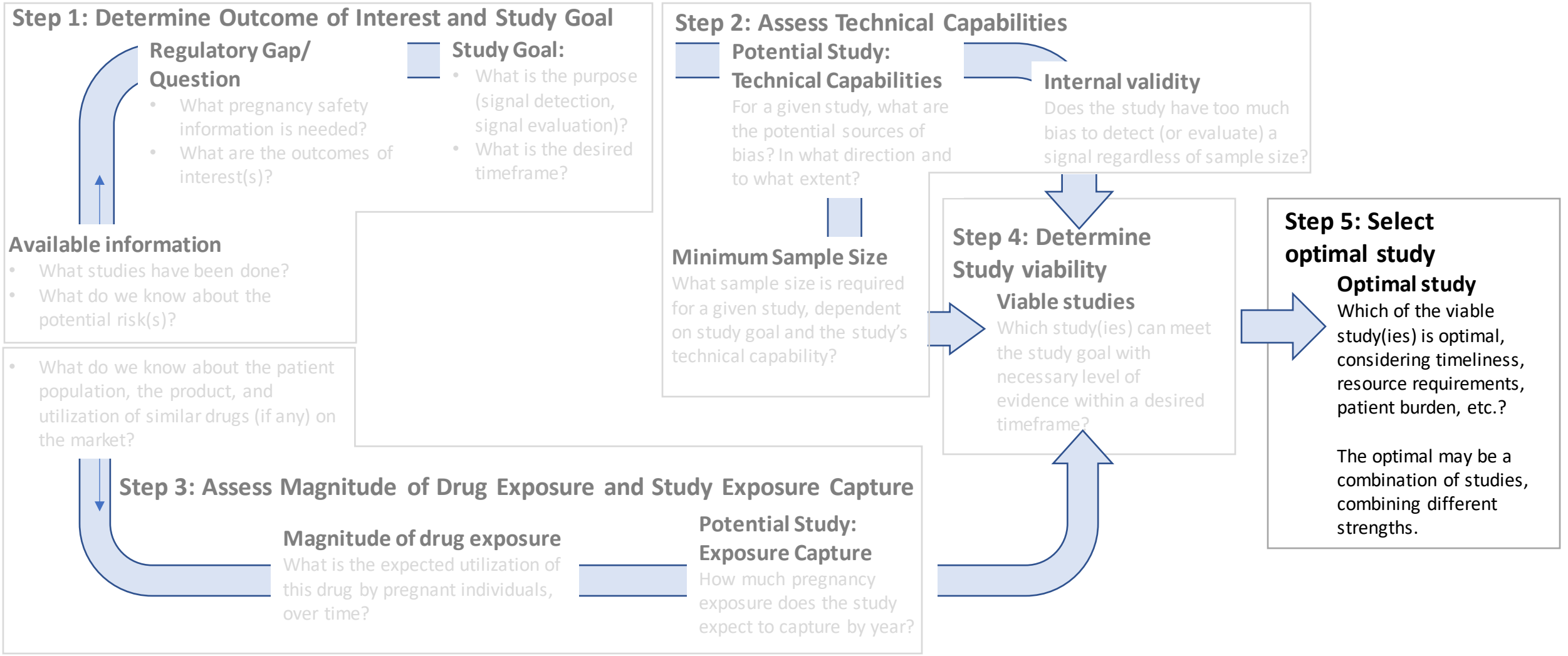
- The hypothetical example is a simple illustration of concepts. Real study scenarios involve a more complex interplay of outcome of interest, various sources of bias, necessary level of evidence, and the expected exposure
- Direction and magnitude of bias affects the accuracy of risk estimate and the 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



How Early Can a Signal be Detected?

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

	Study Option 1	Study Option 2	Study Option 3	Study Option 4	Study Option 5
Potential Study	Pregnancy Registry Nationwide *Case Report Form perfectly designed*	Pregnancy Registry Regional *Case Report Form with less accuracy*	Healthcare Database Pre-specified outcome *Chart review*	Healthcare Database Pre-specified outcome *Claims-based algorithm*	Healthcare Database Non-Prespecified outcome *Singular codes, untargeted*
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	
Type 1 Error 5%	245	4,019	4,019	20,219	4,000 (hypothetical)
Year since approval					
1-3	Slow market penetration in the initial years of approval and potential data lag				
4	100 – 1,000		400 – 4,000		400 -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

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

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 tech capabilities for more accuracy, sigal 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

U.S. FOOD & DRUG ADMINISTRATION

Questions

Closing Remarks

Marianne Hamilton Lopez

Senior Research Director, Duke-Margolis Center for Health Policy

Thank You!

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

September 18-19, 2023
Day 2

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

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

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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)

Background: PDUFA VII Commitment Letter

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.
   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 or MAPP/SOPP as appropriate to implement a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs.

Background: PDUFA VII Commitment Letter

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:

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

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.

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 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?

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

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?

What Does Each Design Provide?

Study design: **Database studies**		What do we know about the data this study design will provide?
Signal Detection	No prespecified outcome (like TreeScan)	Broad coverage, non-specific confounding control • Can be conducted at intervals as data accrues
	Prespecified outcomes (for example, sequential surveillance)	• Rather than "all outcomes," this approach involves a set of targeted outcomes • Power to detect is higher for targeted outcome than for all outcomes • Has targeted confounding control • Can be conducted at intervals as data accrues
Signal Evaluation	Prespecified outcome, active comparator, new users design	• High internal validity • 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

To be more fully described in the next presentation

Gaps in Knowledge

- What are we hoping to gain from the demonstration projects?
  - 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
  - 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

Pregnancy Safety Demonstration Projects

	Study Designs Being Compared	Approach	Exposure
Project "a"	Pregnancy registries versus electronic healthcare database studies	Signal Detection	Common
Project "c"		Signal Evaluation	

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

	Study Designs Being Compared	Approach	Exposure
Project "b"	Single arm safety study versus electronic healthcare database study	Signal Detection	Rare

This will help us to understand the strengths and limitations of these two study designs when the outcome is rare

Pregnancy Safety Demonstration Projects

	Assessment
Project “d”	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

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

Background: PDUFA VII Commitment Letter

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:

Allows for some modifications of these proposed projects as the protocols are developed to better address Pregnancy Safety Framework Gaps

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.
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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	
Likely sample size	Potential market share of the exposure (e.g., n^{th} product in class)
	Likely patterns of use during pregnancy (e.g., prevalence of disease, frequency of use, timing in gestation)
Toxicity Risk (e.g., requiring pregnancy-related warning or REMS)	
Severity of disease being treated	
Is outcome known (prespecified) or not?	
Likely capture: exposure, pregnancy-related outcome, covariates	

In what context should a registry study, a database study or both studies be required at approval?

Study Approach		
Non-database study	Registry	
	Safety study without comparator or sample-size	
Database study	Signal detection	No prespecified outcome (like TreeScan)
		Prespecified outcomes (sequential surveillance)
	Signal Evaluation	Inferential study

How Will the Demonstration Projects Inform the Proposed Framework?

Context	
Likely sample size	Potential market share of the exposure (e.g., n^{th} product in class)
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Toxicity Risk (e.g., requiring pregnancy-related warning or REMS)	
Severity of disease being treated	
Is outcome known (prespecified) or not?	
Likely capture in database of: exposure, pregnancy-related outcome, covariates	

Demonstration projects will consider frequency of exposure

Study Approach		
Non-database study	Registry	
	Safety study without comparator or sample-size	
Database study	Signal detection	No prespecified outcome (like TreeScan)
		Prespecified outcomes (sequential surveillance)
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How Will the Demonstration Projects Inform the Proposed Framework?

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Toxicity Risk (e.g., requiring pregnancy-related warning or REMS)	
Severity of disease being treated	
Is outcome known (prespecified) or not?	
Likely capture in database of: exposure, pregnancy-related outcome, covariates	

Demonstration projects will consider study design: non-database studies vs database studies

Study Approach		
Non-database study	Registry	
	Safety study without comparator or sample-size	
Database study	Signal detection	No prespecified outcome (like TreeScan)
		Prespecified outcomes (sequential surveillance)
	Signal Evaluation	Inferential study

How Will the Demonstration Projects Inform the Proposed Framework?

Context	
Likely sample size	Potential market share of the exposure (e.g., n^{th} product in class)
	Likely patterns of use during pregnancy (e.g., prevalence of disease, frequency of use, timing in gestation)
Toxicity Risk (e.g., requiring pregnancy-related warning or REMS)	
Severity of disease being treated	
Is outcome known (prespecified) or not?	
Likely capture in database of: exposure, pregnancy-related outcome, covariates	

Demonstration projects will consider Signal Detection vs Signal Evaluation

Study Approach		
Non-database study	Registry	
	Safety study without comparator or sample-size	
Database study	Signal detection	No prespecified outcome (like TreeScan)
		Prespecified outcomes (sequential surveillance)
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How Will the Demonstration Projects Inform the Proposed Framework?

Context	
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Toxicity Risk (e.g., requiring pregnancy-related warning or REMS)	
Severity of disease being treated	
Is outcome known (prespecified) or not?	
Likely capture in database of: exposure, pregnancy-related outcome, covariates	

Demonstration projects will consider whether MCM is an appropriate outcomes

Study Approach		
Non-database study	Registry	
	Safety study without comparator or sample-size	
Database study	Signal detection	No prespecified outcome (like TreeScan)
		Prespecified outcomes (sequential surveillance)
	Signal Evaluation	Inferential study

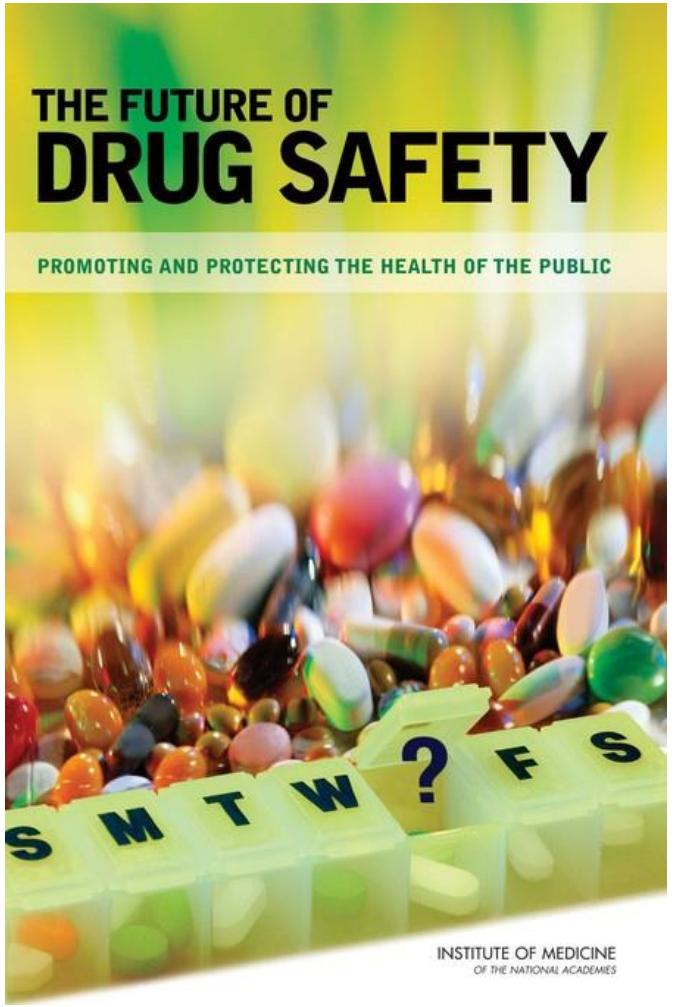
Gaps in Knowledge

- What else are we doing to address knowledge gaps?
  - Drug utilization information is still coming in and will include data on products not included in the current analysis.
  - Data may also include further analyses, such as based on year of approval and number of drugs in class.
  - 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



Guidance for Industry

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

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)

April 2011
Drug Safety

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

STATUTORY PROVISIONS

Under section 505(o)(3)(D)(i), before requiring a *postmarketing study*, FDA must find that adverse event reporting under section 505(k)(1) of the Act and the new pharmacovigilance system that will be established under section 505(k)(3) of the Act will not be sufficient to meet the purposes described in section 505(o)(3)(B).

Under section 505(o)(3)(D)(ii), before requiring a *postmarketing clinical trial*, FDA must find that a postmarketing study will not be sufficient to meet the purposes described in section 505(o)(3)(B).

Guidance for Industry

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

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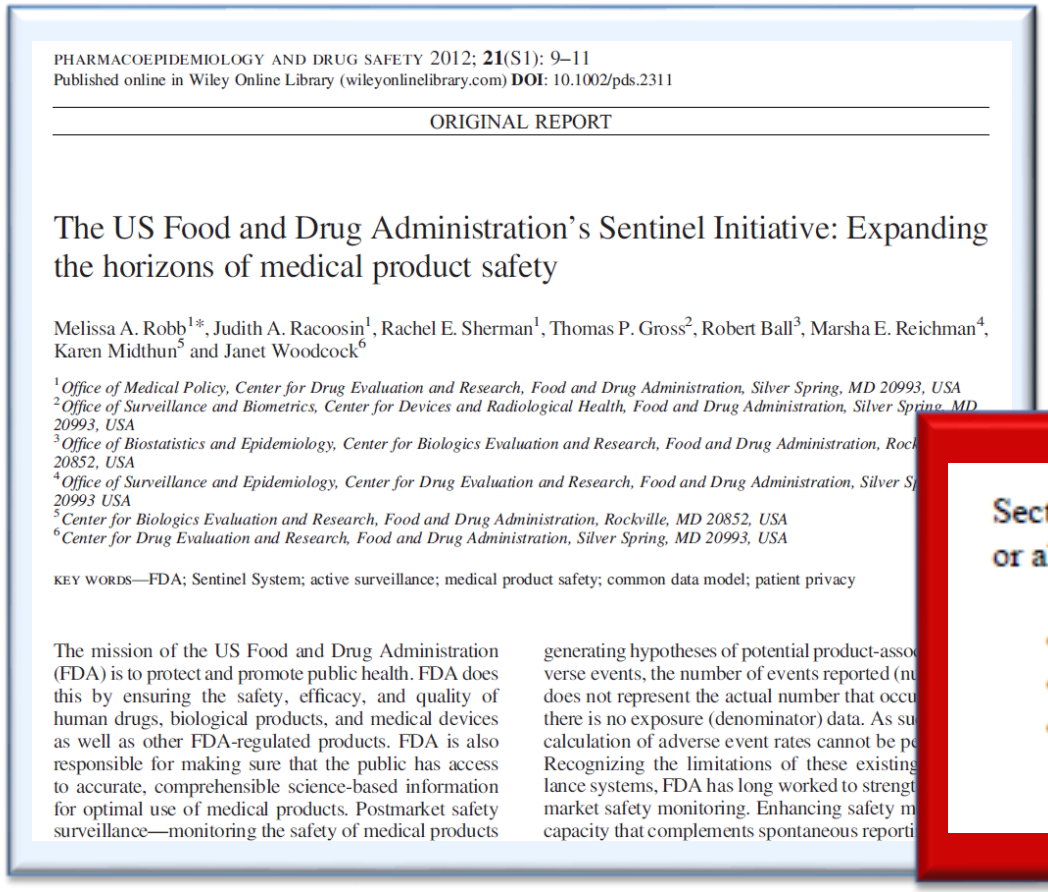
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2011
Drug Safety

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

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,[3] through the processes of signal generation, signal refinement, and signal evaluation.



PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; **21**(S1): 9–11
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2311

ORIGINAL REPORT

The US Food and Drug Administration's Sentinel Initiative: Expanding the horizons of medical product safety

Melissa A. Robb[1]*, Judith A. Racoosin[1], Rachel E. Sherman[1], Thomas P. Gross[2], Robert Ball[3], Marsha E. Reichman[4], Karen Midthun[5] and Janet Woodcock[6]

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[2] *Office of Surveillance and Biometrics, Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD 20993, USA*
[3] *Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Roc 20852, USA*
[4] *Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver S 20993 USA*
[5] *Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD 20852, USA*
[6] *Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993, USA*

KEY WORDS—FDA; Sentinel System; active surveillance; medical product safety; common data model; patient privacy

The mission of the US Food and Drug Administration (FDA) is to protect and promote public health. FDA does this by ensuring the safety, efficacy, and quality of human drugs, biological products, and medical devices as well as other FDA-regulated products. FDA is also responsible for making sure that the public has access to accurate, comprehensible science-based information for optimal use of medical products. Postmarket safety surveillance—monitoring the safety of medical products

generating hypotheses of potential product-asso
verse events, the number of events reported (nu
does not represent the actual number that occu
there is no exposure (denominator) data. As su
calculation of adverse event rates cannot be pe
Recognizing the limitations of these existing
lance systems, FDA has long worked to strengt
market safety monitoring. Enhancing safety m
capacity that complements spontaneous reporti

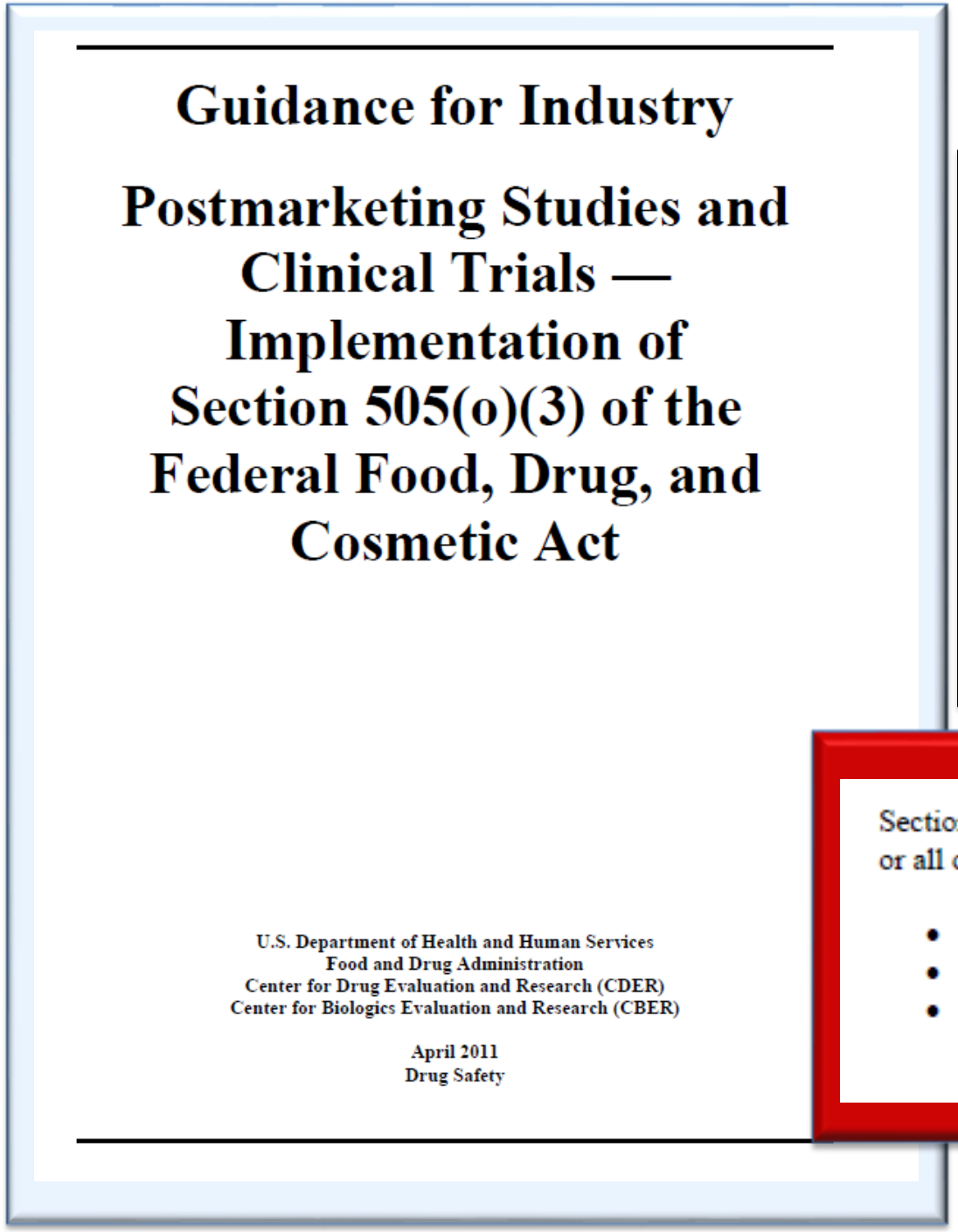
Signal evaluation consists of the implementation of a full epidemiological analysis to more thoroughly evaluate the causal relationship between exposure to the medical product and the adverse outcome of interest.

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.

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

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)

April 2011
Drug Safety

Data Gaps about Risk Determines Study Goal

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

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

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

Part of the concern is whether ARIA can appropriately capture MCM

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

[1] *A recording of "Other" indicates that an appropriate MedDRA code was not identified for a given health outcome of interest.*

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:
  - 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:
  - 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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Using the Sentinel System to Respond to FDA Regulatory Needs in Monitoring Medication Safety in Pregnancy

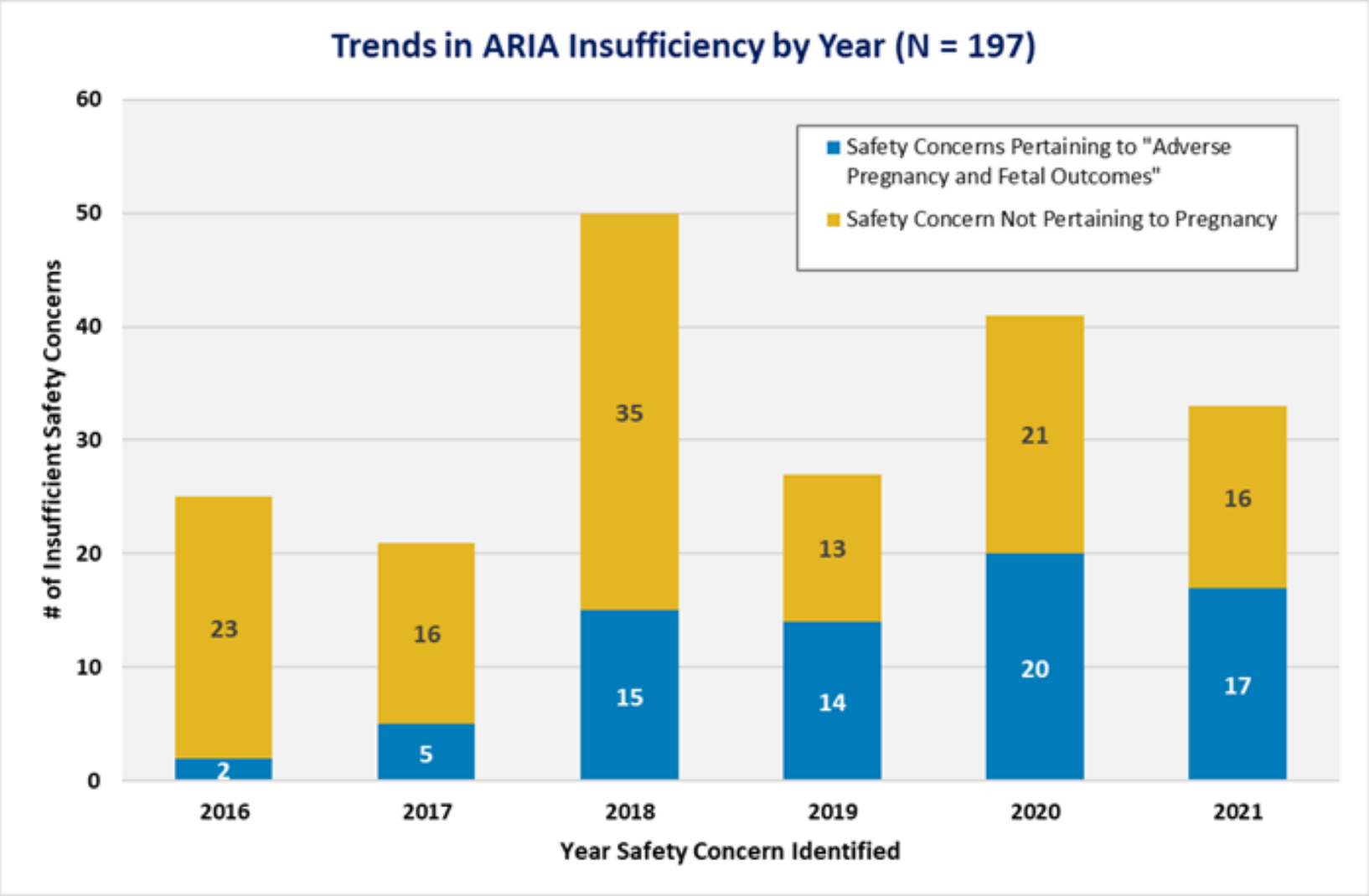
Judith C. Maro, PhD

Sentinel Operations Center

September 19, 2023

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



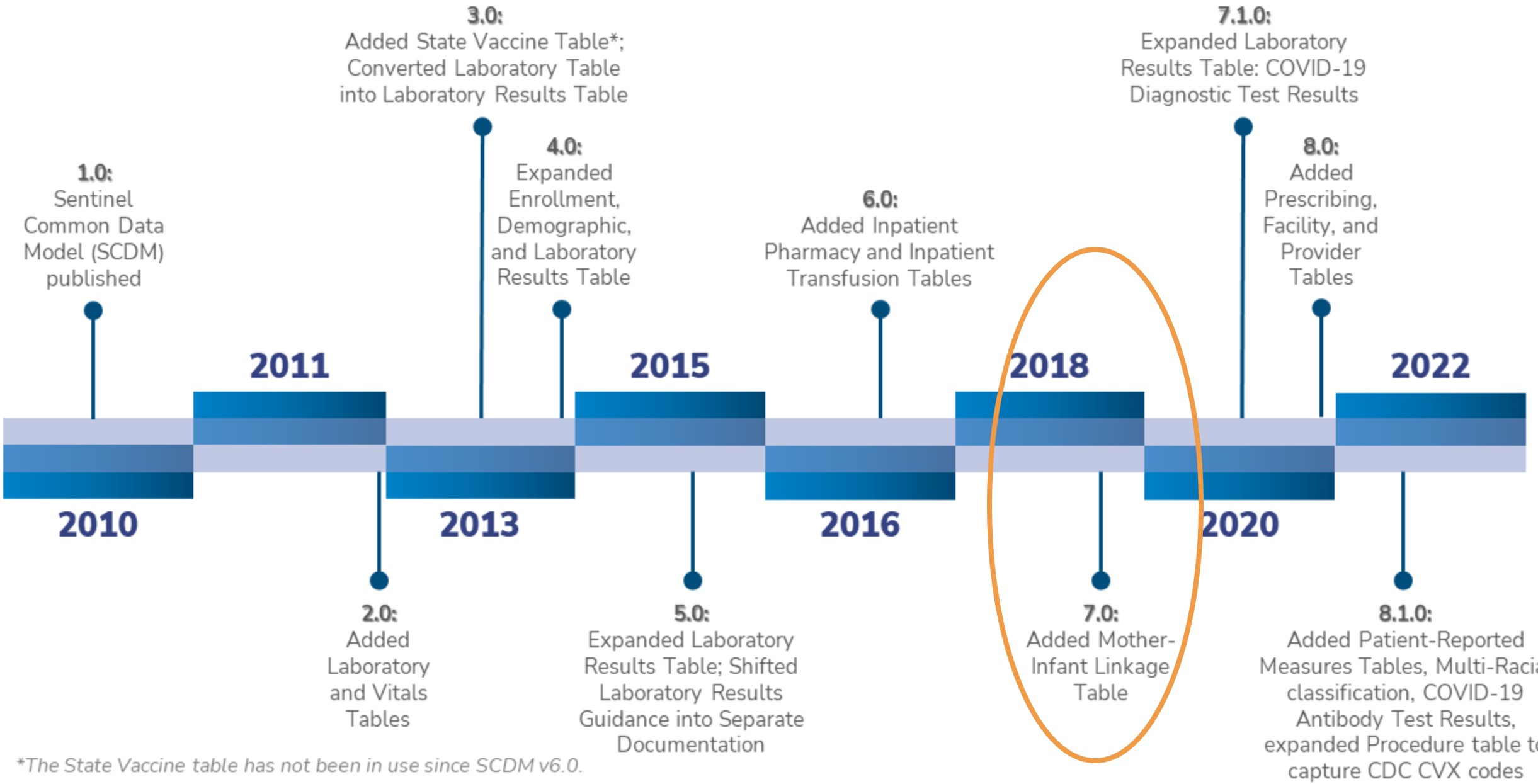
ARIA = Reusable and Parameterizable Tools + Electronic Data

* 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)



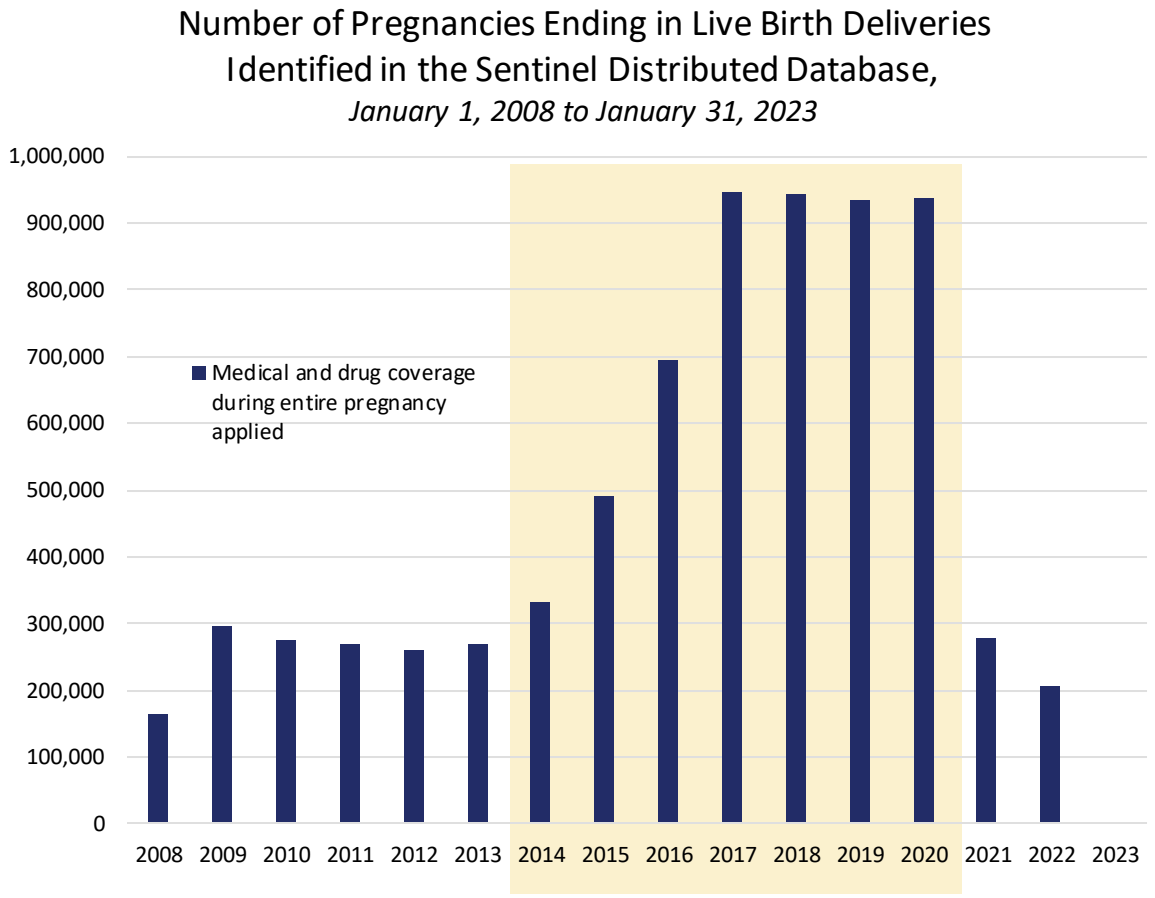
**The State Vaccine table has not been in use since SCDM v6.0.*

Live Birth Deliveries Available in Sentinel

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

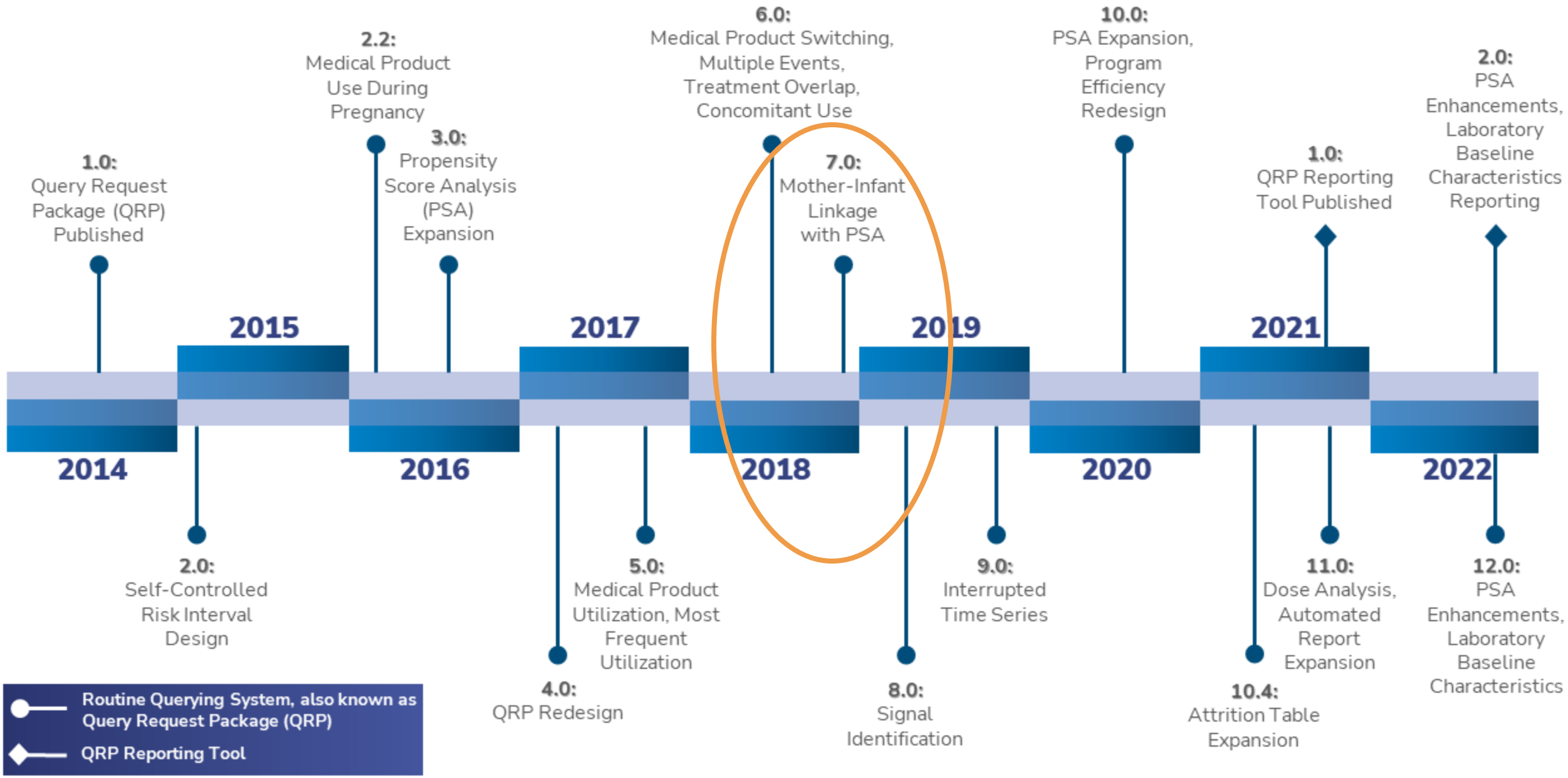
- Applying standard enrollment requirements (medical and drug coverage during entire pregnancy): ~7.3 million total pregnancies

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



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

https://www.sentinelinitiative.org/active-risk-identification-and-analysis-aria

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 > PDF TOOLS SHARE

https://pubmed.ncbi.nlm.nih.gov/36351880/

Public Training on Signal Validation Studies in Pregnancy

Meetings, Workshops, & Trainings

Sentinel Public Training on Maternal Health and Pregnancy

Details | **Additional Information**

Date: Monday, November 2, 2020

Time: 9:00am - 12:00pm EST

Event Type: Training

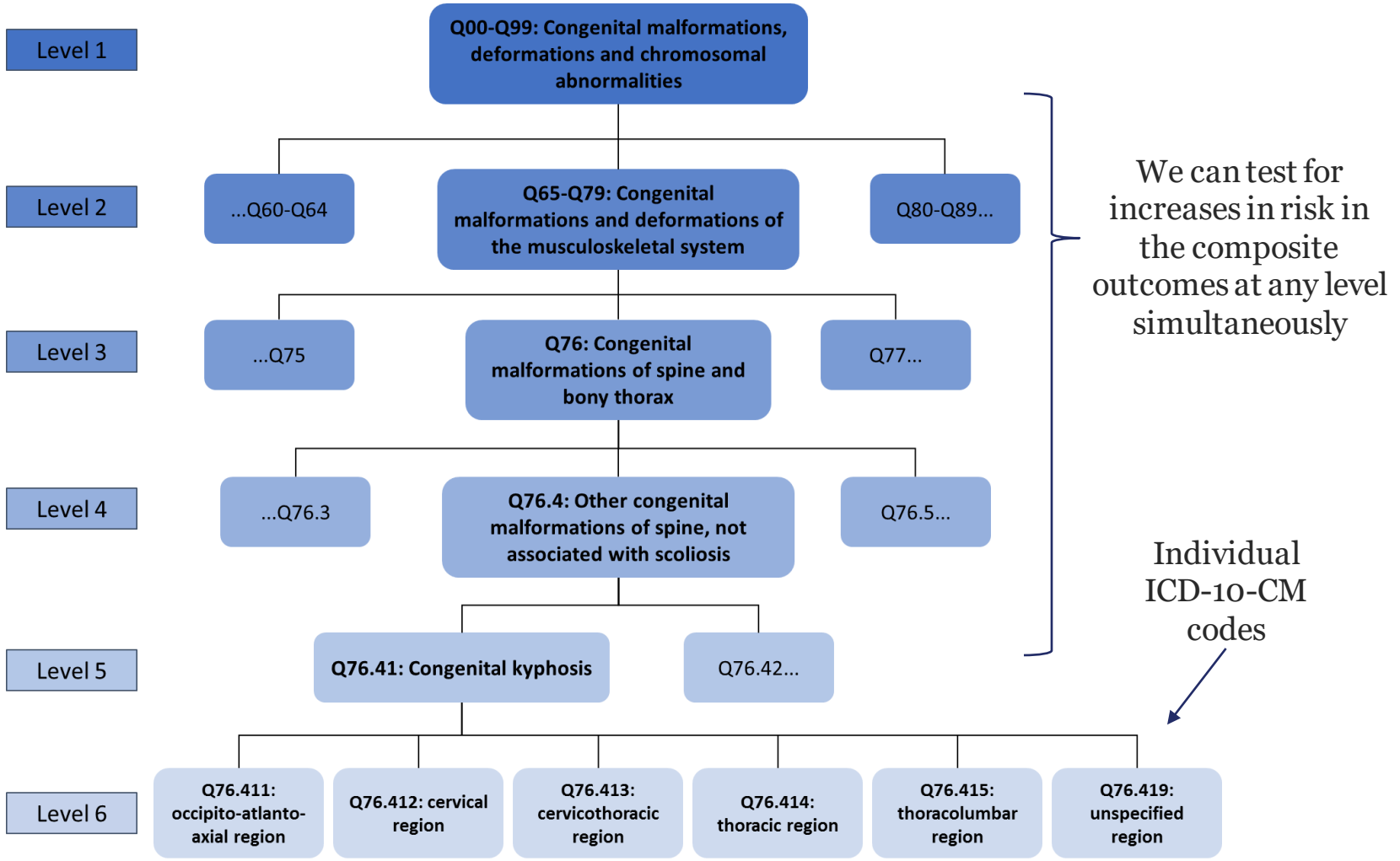
Description:

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

Sentinel Public Training on Maternal Health and Pregnancy

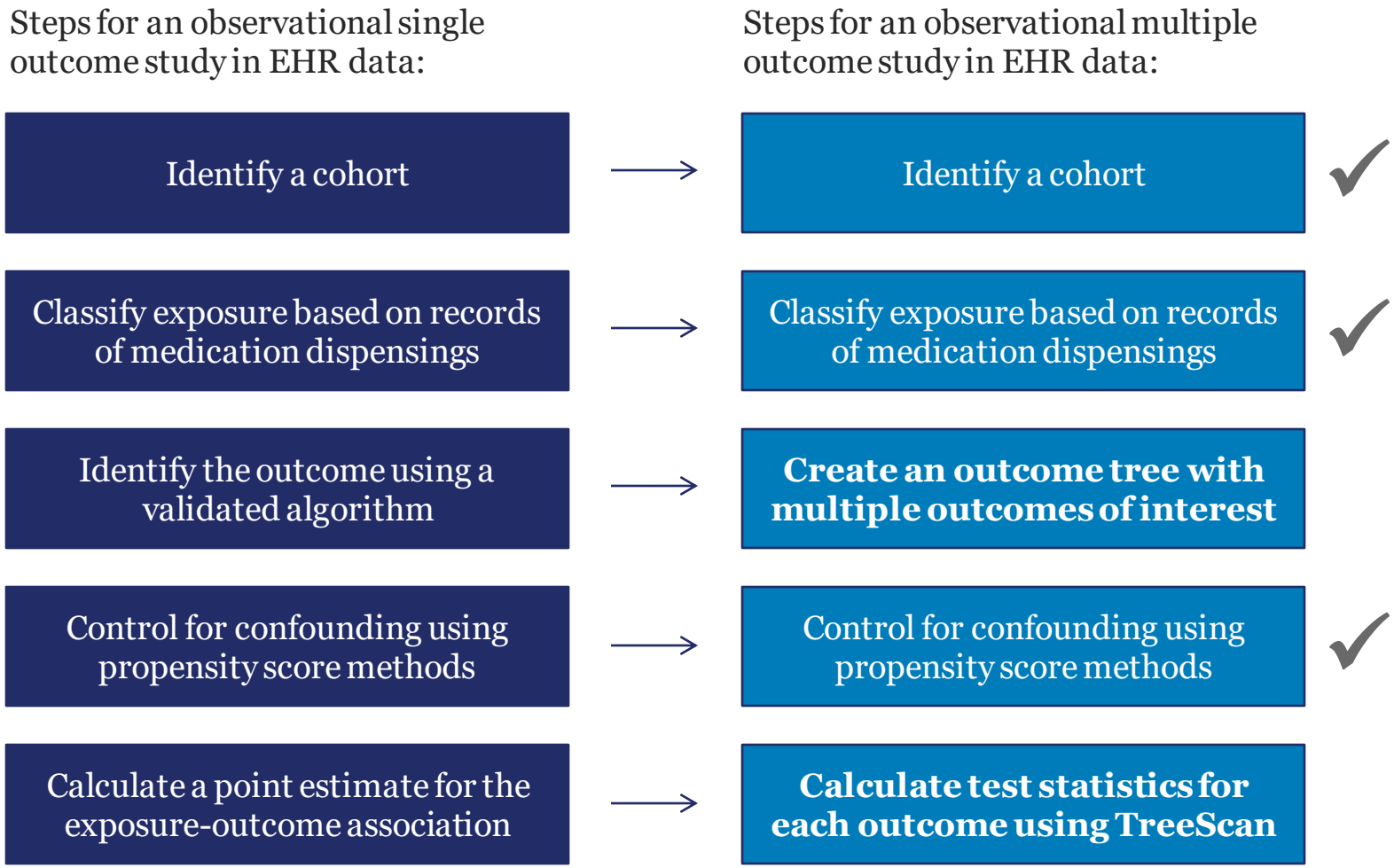
https://www.youtube.com/watch?v=BpdrFTXco2g

Signal Identification – Use of Untargeted Methods



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



EHR = Electronic Health Record

Validation of Signal Identification in Pregnancy Using Empirical and Simulated Data

https://pubmed.ncbi.nlm.nih.gov/36252086/
https://pubmed.ncbi.nlm.nih.gov/35871766/

Public Training on Signal Identification Studies in Pregnancy

2023 Sentinel Public Training Day I 11th April, 2023

Sentinel Initiative
221 subscribers
Subscribe
4
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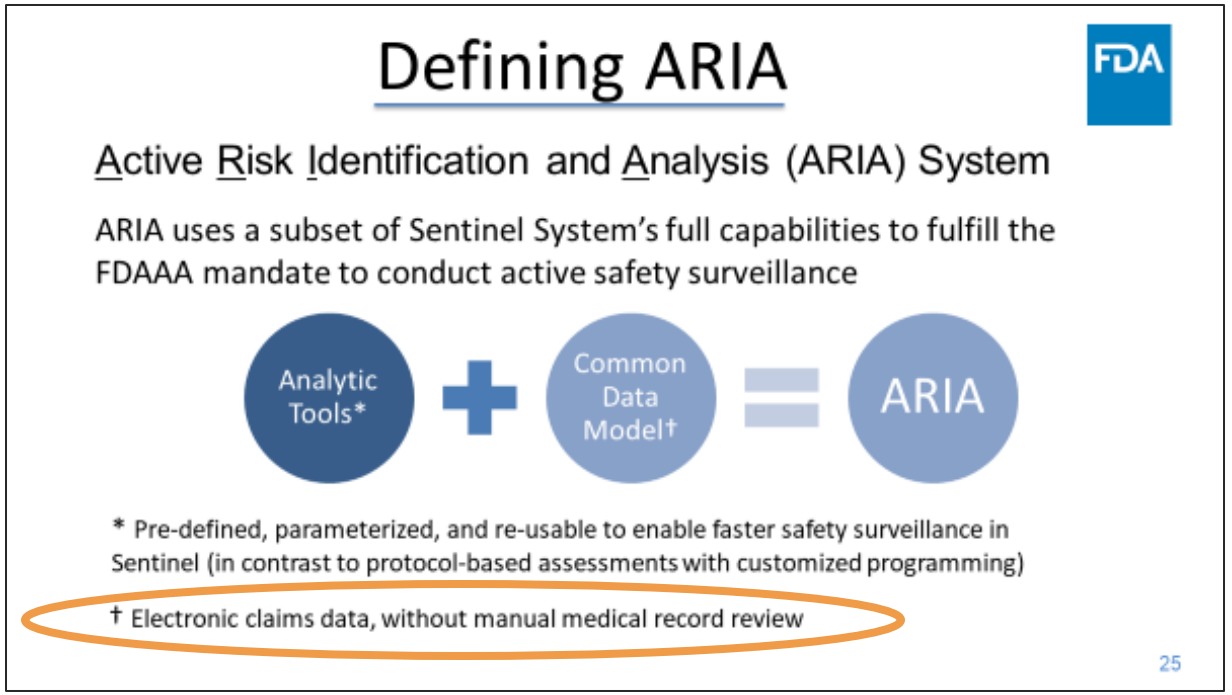
Save

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:
  - Andrade SE et al. **Validation of an ICD-10-based algorithm to identify stillbirth in the Sentinel System**. Pharmacoepidemiol Drug Saf. 2021 Sep;30(9):1175-1183. doi: 10.1002/pds.5300. Epub 2021 Jun 11. PMID: 34089206.
  - Moll K et al. **Validating Claims-Based Algorithms Determining Pregnancy Outcomes and Gestational Age Using a Linked Claims-Electronic Medical Record Database.** Drug Saf. 2021 Nov;44(11):1151-1164. doi: 10.1007/s40264-021-01113-8. Epub 2021 Sep 30. PMID: 34591264; PMCID: PMC8481319.

- 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

FY 23	FY 24	FY 25	FY 26	FY 27
Oct 1, 2022 – Sep 30, 2023	Oct 1, 2023 – Sep 30, 2024	Oct 1, 2024 – Sep 30, 2025	Oct 1, 2025 – Sep 30, 2026	Oct 1, 2026 – Sep 30, 2027
By September 30, 2023, FDA will hold a public workshop postapproval safety studies in pregnant individuals By September 30, 2023, FDA will hold a public workshop on the use of negative controls 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.) ♺ *Recurring annually*	By September 30, 2024, FDA will publish a pregnancy workshop report describing the proposed framework By September 30, 2024, FDA will initiate 5 pregnancy demonstration projects (may be modified as needed): 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 By September 30, 2024, FDA will initiate methods projects: 1. Negative control automation in Sentinel tools 2. Double negative control adjustment	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 By September 30, 2025, FDA will analyze, and report on the use of Sentinel for regulatory purposes (e.g., labeling changes, PMRs, PMCs)		By September 30, 2027, FDA will publish a report on the results of the negative control and pregnancy development projects

PDUFA = Prescription Drug User Fee Act, PMRs = Postmarket Requirements, PMCs = Postmarket Commitments, MCM = Major Congenital Malformations, EHR = Electronic Health Record

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

Birth Defects Research

Society for Birth Defects Research & Prevention
EST. 1960 AS THE TERATOLOGY SOCIETY

ORIGINAL ARTICLE

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 Badalamenti, 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

Read the full text > PDF TOOLS SHARE

- 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).

https://onlinelibrary.wiley.com/doi/abs/10.1002/bdr2.1526, MCM = Major Congenital Malformation

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.

ORIGINAL ARTICLE

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 DeLuccia, Muthalagu Ramanathan, Tejaswini Dhawale, Sonali Harchandani ... See all authors

First published: 26 April 2021 | 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

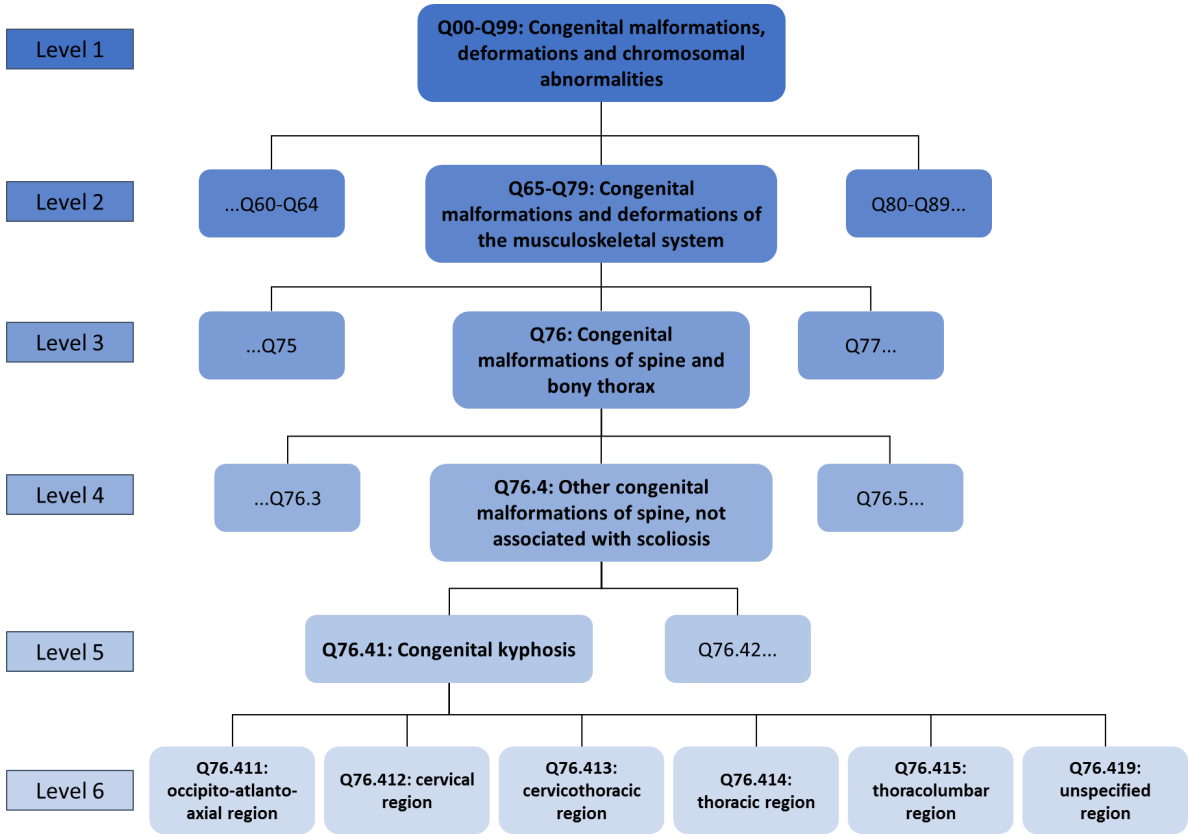
"We examined the ability of the **clinician adjudicators** to classify lymphoma case status for algorithm-identified cases based on these de-identified, patient-level claims profiles, and ultimately compared these results to the chart review results."

"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. "

https://onlinelibrary.wiley.com/doi/10.1002/pds.5256

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
demonstration
September 30,

(a) Assess
electro
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(b) Assess
signal
data to
pregna

(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.

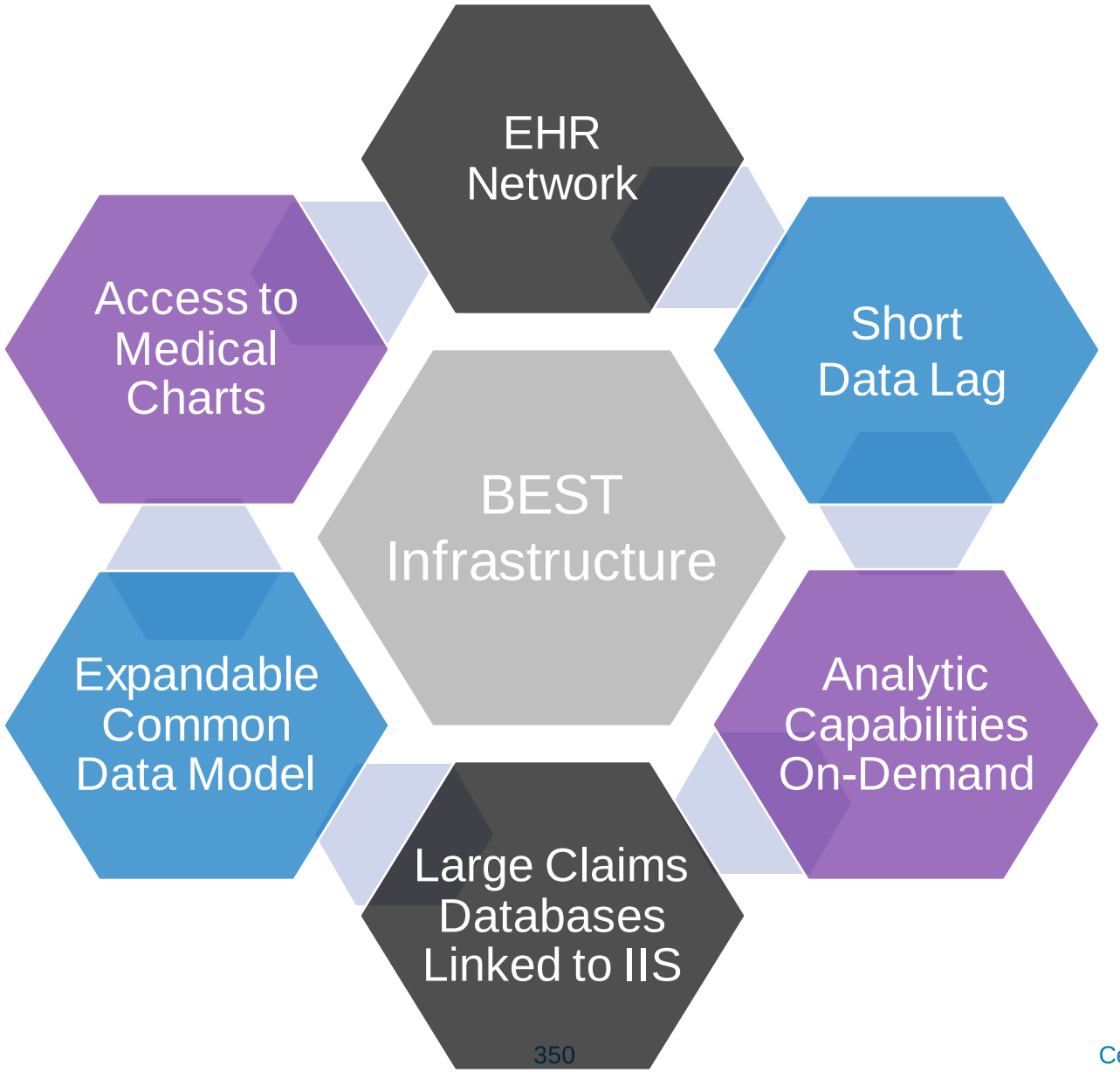
Introduction to the Biologics Effectiveness and Safety (BEST) Initiative

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

Biologics Effectiveness and Safety (BEST) Infrastructure



BEST Data Sources

Data Source*	Database Type	No. Patients Covered (Millions)	Time Period Covered
CMS–Medicare	Claims	105	2005 - present
MarketScan Commercial and Medicare Supplemental	Claims	254	1999 - 2019
MarketScan Medicaid	Claims	48	1999 - 2019
Blue Health Intelligence	Claims	33.6	2012 - present
Optum–Adjudicated	Claims	66	1993 - present
Optum–Pre adjudicated	Claims	22	2017 - present
Carelon Research	Claims	76	2006 - present
CVS Health	Claims	26	2018 - present
OneFlorida Clinical Research Consortium–Medicaid	Claims	6.7	2012 - present
OneFlorida Clinical Research Consortium–EHR	EHR	5.6	2012 – present
Optum EHR	EHR	102	2007 - 2020
MedStar Health Research Institute	EHR	6.0	2009 - present
PEDSnet	EHR	6.2	2009 - present
IBM CED	Linked EHR Claims	5.4	2000 - present
Optum Integrated Claims–EHR	Linked EHR Claims	25	2007 - 2020
OneFlorida Clinical Research Consortium–Linked EHR Claims	Linked EHR Claims	1.5	2012 - present

*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

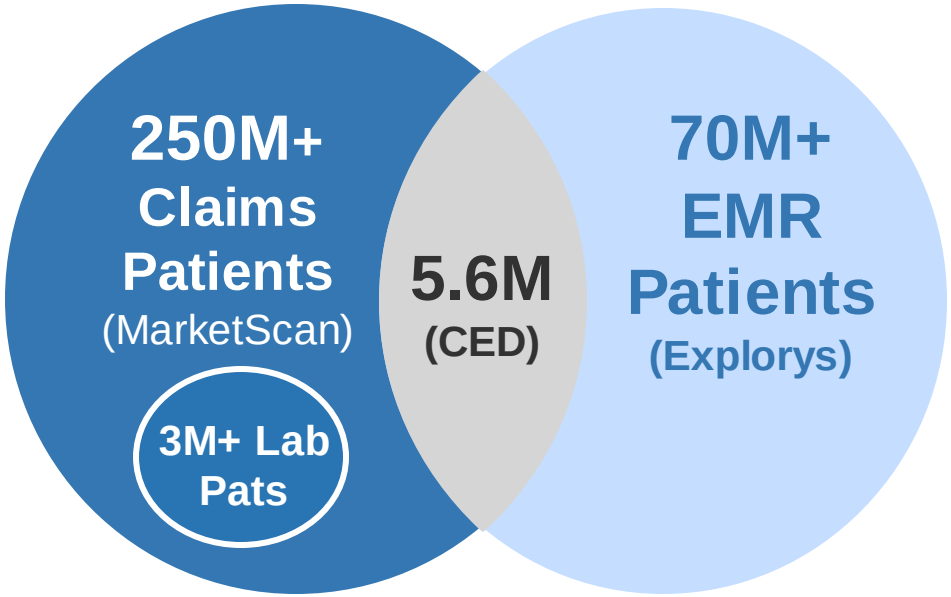
Study Aims

- 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)



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

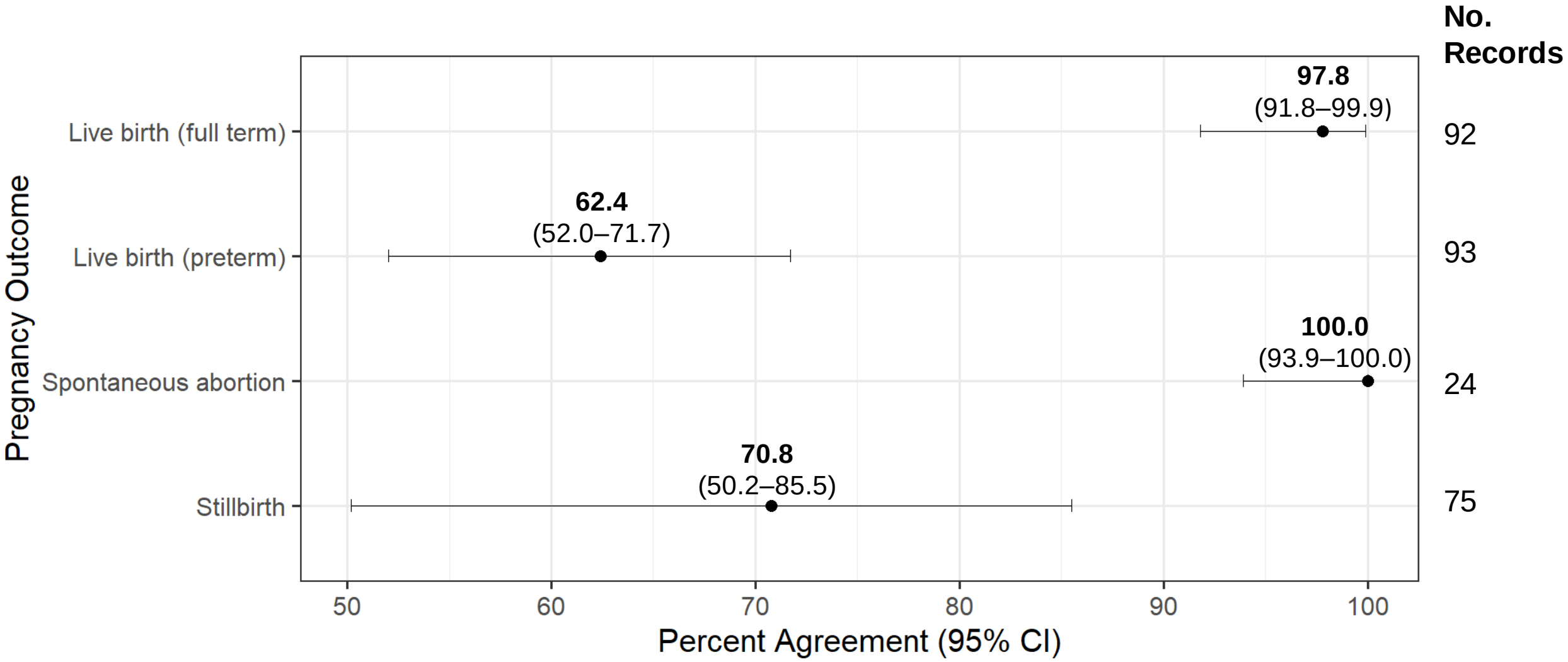
Algorithms: Outcomes of Interest (Aim 1)

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

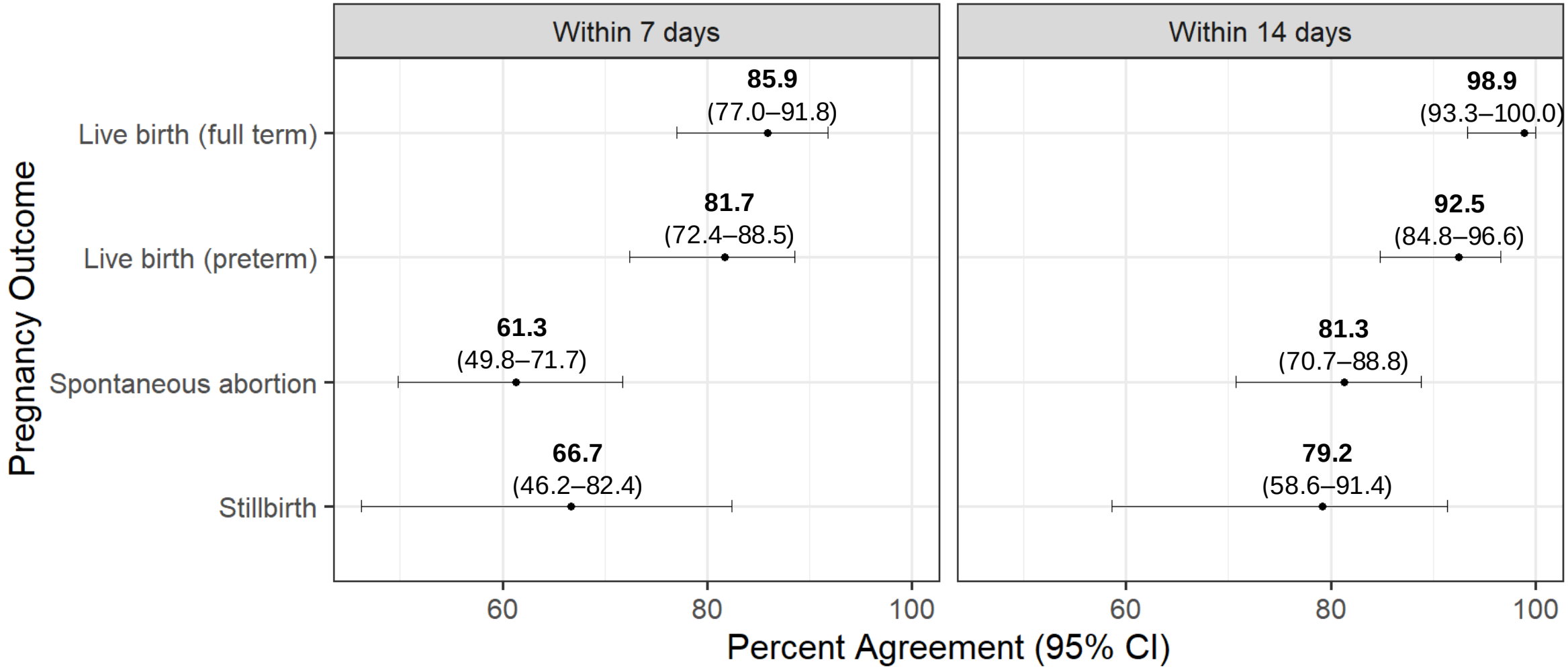
Validation: Use of Structured EHR to Evaluate Algorithms (Aim 2)

- 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

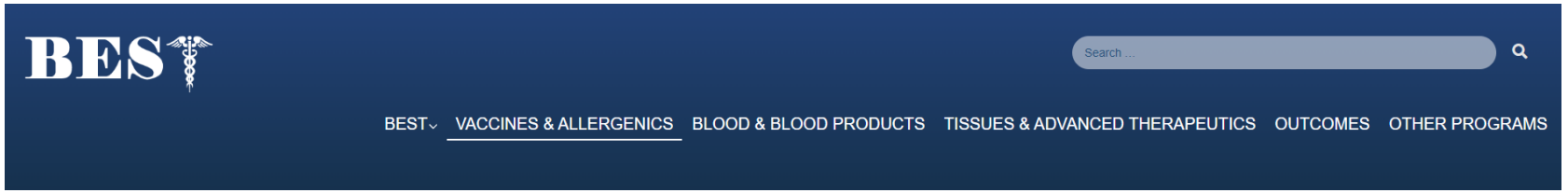
Algorithm Performance: Pregnancy Outcomes



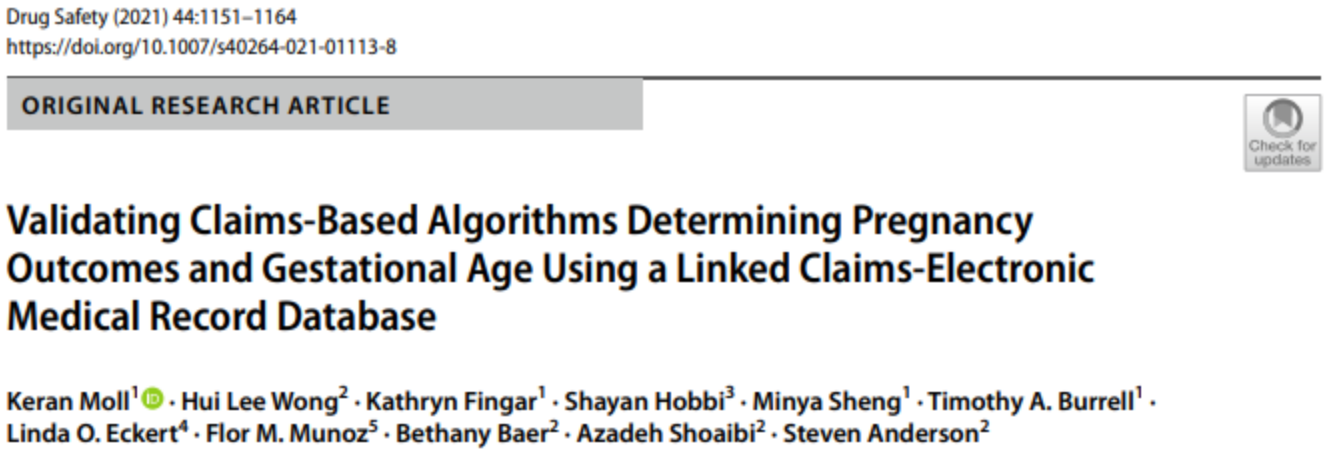
Algorithm Performance: Gestational Age by Pregnancy Outcome



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



Drug Safety (2021) 44:1151–1164
https://doi.org/10.1007/s40264-021-01113-8

ORIGINAL RESEARCH ARTICLE

Check for updates

Validating Claims-Based Algorithms Determining Pregnancy Outcomes and Gestational Age Using a Linked Claims-Electronic Medical Record Database

Keran Moll[1] · Hui Lee Wong[2] · Kathryn Fingar[1] · Shayan Hobbi[3] · Minya Sheng[1] · Timothy A. Burrell[1] · Linda O. Eckert[4] · Flor M. Munoz[5] · Bethany Baer[2] · Azadeh Shoaibi[2] · Steven Anderson[2]

Additional Information: Vaccine Exposures in Pregnancy

Vaccine 39 (2021) 6095–6103

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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

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[c] Acumen LLC, 500 Airport Blvd, Suite 100, Burlingame, CA 94010, USA
[d] IBM Global Business Services, 6710 Rockledge Dr, Bethesda, MD 20817-1834, USA
[e] Stanford University, Department of Epidemiology and Population Health at Stanford School of Medicine, 291 Campus Drive, Stanford, CA 94305, USA
[f] Stanford University, Department of Economics, 579 Jane Stanford Way, Stanford, CA 94305, USA

Linkage of Mothers and Infants in Claims Databases

Background and Motivation

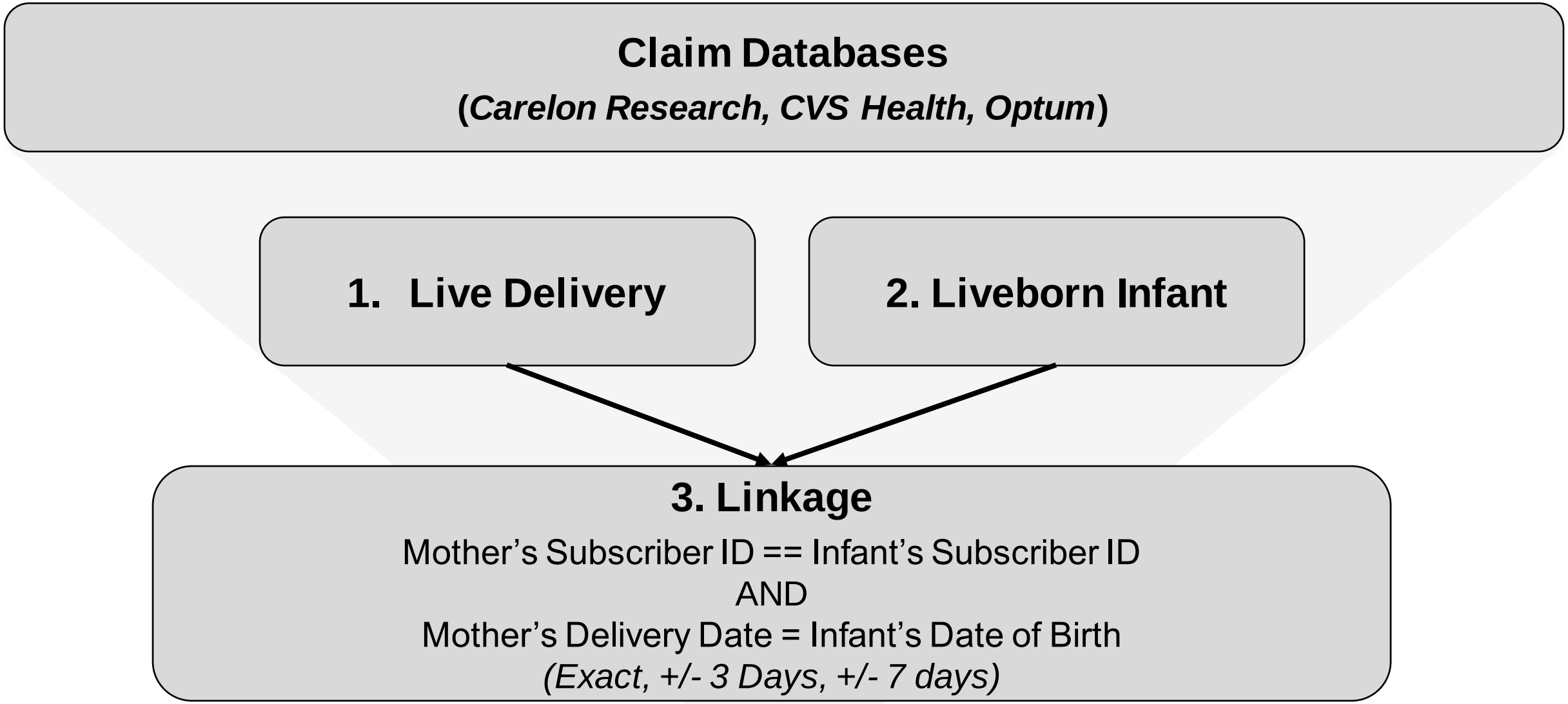
To conduct safety surveillance of biologics in pregnancy and on the health of infants, BEST needs the capability to:

- Link pregnant individuals to infants

Study Aim

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

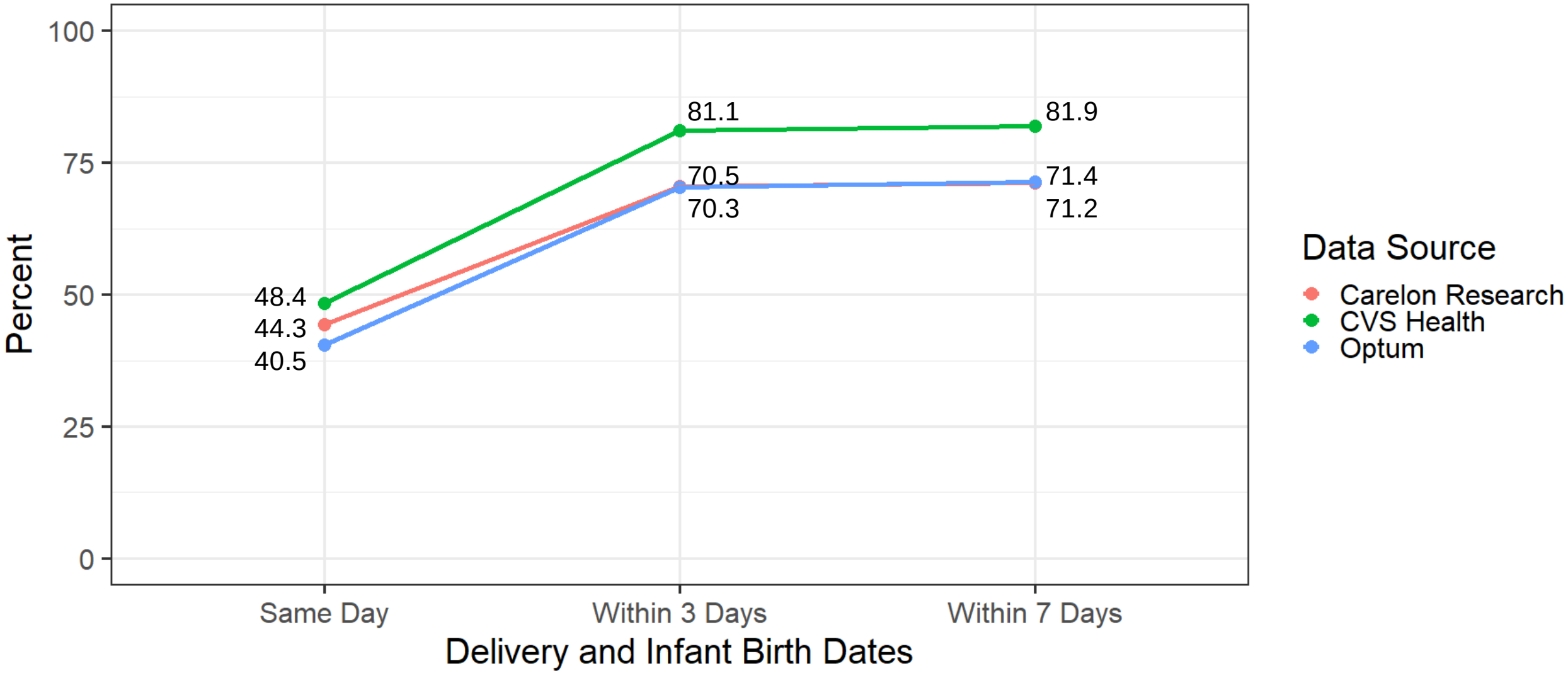
Methods


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

Data Source	Data Start (Year)	Data End (Year)	Total Live Deliveries
Carelon Research	2016	2022	1,269,762
CVS Health	2019	2023	646,573
Optum	2020	2023	347,583

Mother-Infant Linkage Rates



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?

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?

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.

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

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

healthpolicy.duke.edu

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