
Optimizing
Pregnancy Registries
Public Workshop
MAY 7-8, 2026
Virtual & In-Person
FDA

U.S. FOOD & DRUG ADMINISTRATION

Welcome and Opening Remarks

U.S. FOOD & DRUG ADMINISTRATION

Session 1: Current State of Pregnancy Registries

Pregnancy Registries:
Current Status and FDA Observations

Optimizing Pregnancy Registries Workshop 2026

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Food and Drug Administration (FDA)
May 7-8, 2026

Disclosure

- I have no financial relationships to disclose related to this presentation.

- The views expressed in this talk represent my opinion and not necessarily the views of FDA.

Outline of Presentation

- Background
- Efforts to Advance Safety Data Collection in Pregnant Women
- Current Status of Postapproval Pregnancy Safety Studies
- Incorporation of Pregnancy Registry Data in Labeling

BACKGROUND

Background

- There are approximately 5.5 million women who become pregnant in the U.S./year
- Pregnant women may need treatment for chronic or acute conditions
- Pregnant women have historically been excluded from drug development trials

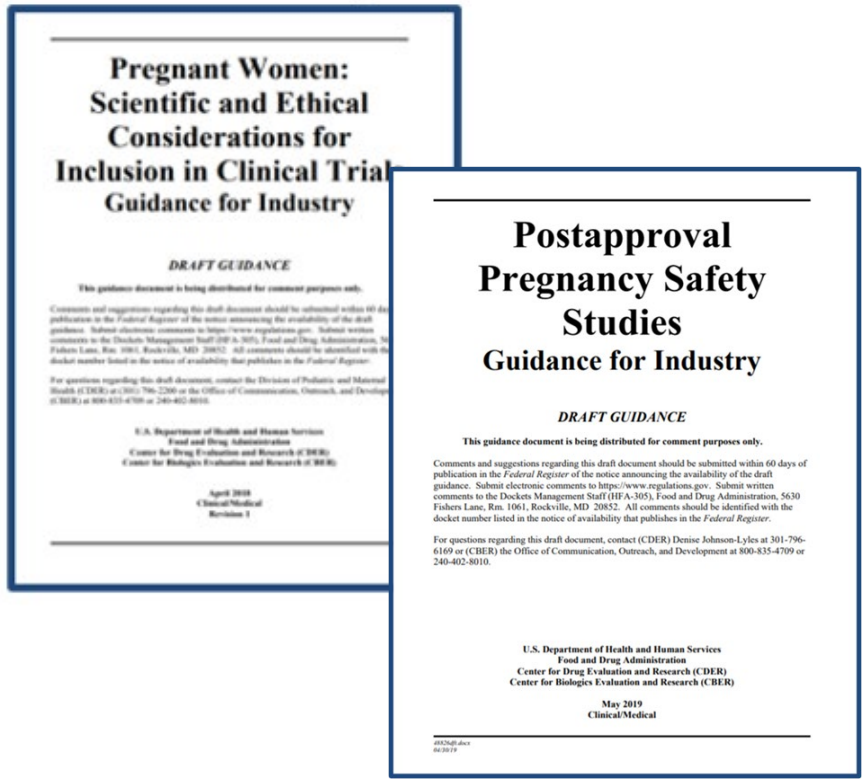
Background

- Drugs are often approved with only nonclinical reproductive toxicology data.
- Lack of a safety signal in nonclinical reproductive toxicology data does not confirm that a drug is safe to use in pregnancy
- Limited pregnancy safety data in labeling poses challenges for pregnant women and their healthcare providers. Lack of human pregnancy safety data is a public health issue.

EFFORTS TO ADVANCE SAFETY DATA COLLECTION IN PREGNANT WOMEN

Efforts to Advance Safety Data Collection in Pregnant Women

- **FDA Guidances**
  - Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials (Draft 2018)
  - Postapproval Pregnancy Safety Studies (Draft 2019)- currently being revised
  - International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) E21 guidance on the inclusion of pregnant and breastfeeding women in clinical trials published in July 2025



E21 Inclusion of Pregnant and Breastfeeding Women in Clinical Trials | FDA

Task Force on Research Specific to Pregnant 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
- The Task Force submitted 15 recommendations regarding research and the development of safe and effective therapies specific in pregnant women and lactating women to the Secretary of Health and Human Services (completed September 2018; implementation report completed August 2020)
- PRGLAC Implementation Working Group of Council published a status report in July 2024

*https://www.nichd.nih.gov/about/advisory/PRGLAC

PRGLAC Recommendations on Collection of Safety Data in Pregnant Women

- Recommendation #2: Increase the quantity, quality, and timeliness of research involving therapeutic products used by pregnant women
- Recommendation #10: 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
- Recommendation #11: Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women
  - Provide financial support and incentives to established and develop new multicenter infrastructures that capitalize on standard of care procedures (opportunistic studies), innovative designs, and methodologies.
  - Broaden focus of ongoing research networks to include research on therapeutic products in pregnant women and lactating women
  - Encourage networks/collaborations to engage in public-private partnerships to facilitate research

PRGLAC Recommendations on Collection of Safety Data in Pregnant Women

- Recommendation #12: 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
- Recommendation #13: Optimize pregnancy registries
  - Expand the use of disease-based pregnancy registries
  - Facilitate access to data and transparency of information in registries
  - Develop disease/condition-focused registries
    - Move toward a single registry for all therapeutic products with input from stakeholders

FDA-Duke Margolis Public Workshop

- FDA-Duke Margolis Public Workshop September 18 & 19, 2023: Optimizing the Use of Postapproval Pregnancy Safety Studies
- Workshop goal: to seek input from interested parties on:
  - The development of a framework to optimize postapproval pregnancy safety studies
  - Review of proposed demonstration PDUFA VII projects to address data gaps
- A workshop report was published in 2024

*https://www.fda.gov/media/151712/download

CURRENT STATUS OF POSTAPPROVAL PREGNANCY SAFETY STUDIES

Food and Drug Administration Amendments Act of 2007 (FDAAA)

- Section 505(o)(3) of the FD&C Act

"The Secretary may require a postapproval study or studies (including observational studies) or a postapproval clinical trial or trials for the purpose of—

(i) assessing a known serious risk related to the use of the drug involved;

(ii) assessing signals of serious risk related to the use of the drug; or

(iii) identifying an unexpected serious risk when available data indicates the potential for a serious risk."

Pregnancy PMRs

- Pregnancy Postmarketing Requirements (PMRs)
  - Pregnancy Registry
  - Complementary Study (i.e., database study)
  - Descriptive Pregnancy Safety Study (DPSS)

Pregnancy Safety Studies

- **Pregnancy Registries**
  - Prospective observational study usually comparing an exposed cohort with one or more disease matched comparator cohorts unexposed to the drug of interest
  - Actively collect information on product exposures during pregnancy and associated pregnancy outcomes by enabling voluntary participation of women who have been exposed to a specific drug of interest
  - Typically powered to detect a 2-3-fold risk for major birth defects
  - While it is useful to collect data on the effects of rare exposures during pregnancy, it alone may not be sufficient to assess the safety of products, due to challenges of achieving sufficient enrollment.
- **Complementary Studies**
  - Additional studies with different study designs complement data obtained from pregnancy registries and other sources and can be implemented to better understand the safety of a product during pregnancy, and to more precisely quantify the magnitude of an association between a pregnancy exposure and a specific outcome
  - Has the potential to be powered to detect up to 2-fold risk for major birth defects
- **Descriptive Pregnancy Safety Studies (DPSS)**
  - Observational, often global surveillance programs designed to collect prospective and retrospective data on product exposure during pregnancy

Pregnancy Registry

Strengths

- Collection of data prospectively, in real time
- Collection of detailed patient level data
  - The patient confirms that she took the medication, dose, duration
  - Covariates, clinical information
- Collection of miscarriage, termination, and stillbirth information
- Adjudication of outcomes, especially major birth defects, by experts
- Pregnancy registries may support assessment of multiple maternal, obstetrical, fetal, and infant outcomes

Limitations

- Requires recruitment/awareness efforts
- Smaller sample size compared to database study
- Longer to conduct compared to a database study
- Selection bias due to self selection

Database Study

Strengths	Limitations
• Does not require recruitment/awareness efforts • Potentially larger sample size compared to registry study • May take less time to conduct compared to a registry study	• Uncertainty regarding exposure: based on dispensing • Potential exposure misclassification (estimates based on algorithms) • Potential outcomes misclassification (based on ICD codes) • Non-live birth outcomes may be underestimated • Some covariates not well captured which may hamper data interpretation

Descriptive Pregnancy Safety Study (DPSS)

- Considered when the drug will be used in a small population (e.g. rare disease, contraindication for use in pregnancy), and it is unlikely that a pregnancy registry or the complementary study would provide an adequately powered comparative analysis.

PREGNANCY REGISTRY DATA IN LABELING

FDA Review of Postapproval Safety Studies

Postapproval Safety Studies Issued

	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 Attrition

	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.

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

FDA Review of Postapproval Safety Studies

- **65 completed studies**
- Average time from study requirement to labeling update: 11 years (range 6-18 years)

Types of Completed Postapproval Safety Studies

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

Pregnancy Registry Data in Labeling

- Pregnancy registries are the most common source of drug safety data collected during pregnancy and incorporated into prescription drug labeling.
- Antiretroviral Pregnancy Registry (APR) (n=38)

Examples of Pregnancy Registry Data in Labeling

- EPIVIR-HBV (lamivudine) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection
- **Source:** Antiretroviral Pregnancy Registry (APR)

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

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

*The Metropolitan Atlanta Congenital Defects Program (MACDP) is a population-based tracking system for birth defects.

Examples of Pregnancy Registry Data in Labeling

- Gardasil 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) injection is indicated for the prevention of genital and certain head and neck cancers (including oropharyngeal) caused by HPV types 16, 18, 31, 33, 45, 52 and genital warts caused by type 6 and 11.
- **Source:** Gardasil Pregnancy Registry

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

…A five-year pregnancy registry enrolled 2,942 women who were exposed to GARDASIL within one month prior to the LMP or at any time during pregnancy, 2,566 of whom were prospectively followed. After excluding elective terminations (n=107), ectopic pregnancies (n=5) and those lost to follow-up (n=814), there were 1,640 pregnancies with known outcomes. Rates of miscarriage and major birth defects were 6.8% of pregnancies (111/1,640) and 2.4% of live born infants (37/1,527), respectively. These rates of assessed outcomes in the prospective population were consistent with estimated background rates…

Examples of Pregnancy Registry in Labeling

- Humira (adalimumab) is indicated for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, and non-infectious intermediate, posterior, panuveitis
- **Source:** The Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Studies

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

A prospective cohort pregnancy exposure registry conducted by OTIS/MotherToBaby in the U.S. and Canada between 2004 and 2016 compared the risk of major birth defects in live-born infants of 221 women (69 RA, 152 CD) treated with adalimumab during the first trimester and 106 women (74 RA, 32 CD) not treated with adalimumab.

The proportion of major birth defects among live-born infants in the adalimumab-treated and untreated cohorts was 10% (8.7% RA, 10.5% CD) and 7.5% (6.8% RA, 9.4% CD), respectively. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects. This study cannot reliably establish whether there is an association between adalimumab and major birth defects because of methodological limitations of the registry, including small sample size, the voluntary nature of the study, and the non-randomized design.

Key Takeaways

- Pregnancy registries are an important study method that provides high quality safety data.
- There are challenges with conducting single product pregnancy registry studies.
- We need to consider more efficient models for collecting pregnancy registry data.
- Continued collaboration between regulatory agencies, industry, academia, healthcare providers, and patients is crucial to determine the optimal approach for the collection of pregnancy registry data.

Thank you for your attention...

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Update on FDA PDUFA VII activities

PDUFA VII Pregnancy Safety Study Demonstration Projects

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May 7, 2026

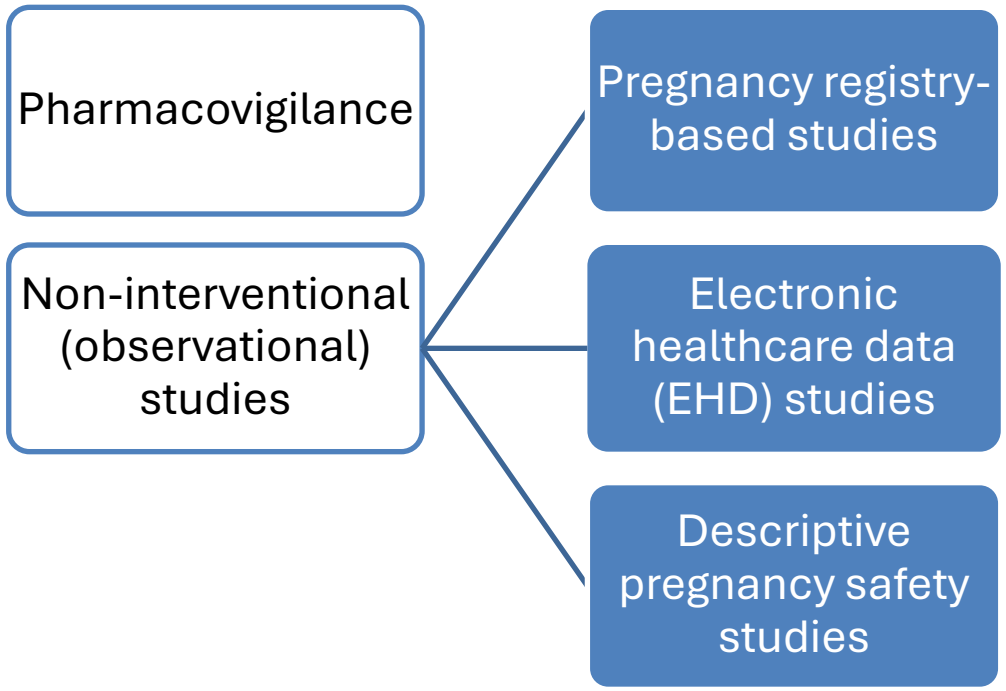
This presentation was created with the assistance of Gen AI tools (Elsa and Gemini Enterprise). Elsa and Gemini Enterprise were used for brainstorming and editing. The content has been reviewed, verified, and edited by Youjin Wang.

Objectives

- Recap of the PDUFA VII Pregnancy Safety Study Framework and Demonstration Projects
- Sentinel System for Pregnancy Medication Safety Surveillance
- PDUFA VII Pregnancy Safety Study Demonstration Project Updates

Recap of the PDUFA VII Pregnancy Safety Study Framework and Demonstration Projects

Post-market Pregnancy Safety Evaluation



- **Pregnancy registry-based studies** are an important post-market safety evaluation approach due to the prospective design and detailed patient-level data collection
- However, pregnancy registry-based studies alone are often insufficient for safety assessment due to low enrollment
- Use of complementary approaches (i.e., **electronic healthcare data (EHD) studies**) may help address the limitations
- **Descriptive pregnancy safety studies (DPSS)** are considered when exposure in pregnancy is expected to be low

FDA Commitment under the PDUFA VII Reauthorization - Pregnancy Safety Study Framework

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 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

PDUFA: Prescription Drug User Fee Act

Pregnancy Safety Study Framework

Purpose

The purpose of the framework is to develop a consistent and transparent approach to help decide when and what post-approval 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.

Slide adapted from Dr. Wei Hua's presentation "FDA's Current Thinking on the Pregnancy Safety Study Framework" at the Margolis-FDA Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies, September 18-19, 2023

Pregnancy Safety Study Framework
Goals

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

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PDUFA VII Commitment Letter

PDUFA VII Commitment Letter
Demonstration Projects to Address Gaps in Knowledge

(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.

Conduct **5 demonstration projects** to address gaps in knowledge about **performance characteristics of different study designs**

This presentation will focus on **four projects (a-d)** related to the **safety of medications in pregnancy**

PDUFA: Prescription Drug User Fee Act

PDUFA VII Pregnancy Safety Study Demonstration Projects

Goals

- To provide **data** that will **inform and challenge** our understanding of the strengths and limitations of various **types of pregnancy safety studies**, such as pregnancy registry-based studies and electronic healthcare database studies
- To provide **insights** from the use-cases that will inform **refinements** to the proposed draft **Pregnancy Safety Framework**

PDUFA: Prescription Drug User Fee Act

Slide adapted from Dr. Patricia Bright's presentation "Informing the Pregnancy Safety Framework by Addressing Knowledge Gaps " at the Margolis-FDA Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies, September 18-19, 2023

PDUFA VII Pregnancy Safety Study Demonstration Projects

Study Types to Evaluate

Types of Study	Signal Detection	Signal Evaluation
Pregnancy Registry-Based Study • Primary data collection • With comparator and sample size requirements	Project a (**common** exposure)	Project c (**common** exposure)
Single Arm Safety Study (DPSS) • Single arm study (no comparator) • No sample size requirements • Primary data collection, EHR with medical record review, or other data sources or data collection methods • Considered when exposure is expected to be low	Project b (**low** exposure)	
Electronic Healthcare Database Study with prespecified outcomes • Existing large scale electronic health care data • Pre-specified outcomes	Projects a and b (**common** & **low** exposure)	Project c (**common** exposure)
Electronic Healthcare Database Study without prespecified outcomes, e.g., TreeScan™ • Existing large scale electronic health care data • Non-prespecified outcomes	Projects a and b (**common** & **low** exposure)	

Slide adapted from Dr. Wei Hua's presentation "FDA's Current Thinking on the Pregnancy Safety Study Framework" at the Margolis-FDA Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies, September 18-19, 2023

PDUFA: Prescription Drug User Fee Act
EHR: Electronic Health Record

PDUFA VII Pregnancy Safety Study Demonstration Projects

Study Goal

Signal Detection	Signal Evaluation
• 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)	• Hypothesis testing to confirm or quantify a risk • Prespecified, signaled outcomes • Higher level of certainty needed, strong internal validity

Slide adapted from Dr. Wei Hua's presentation "FDA's Current Thinking on the Pregnancy Safety Study Framework" at the Margolis-FDA Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies, September 18-19, 2023

The Demonstration Projects Will Inform the Proposed Framework

(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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(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.

Projects a-c

Demonstration projects evaluate **different study types**

Slide adapted from Dr. Patricia Bright's presentation "Informing the Pregnancy Safety Framework by Addressing Knowledge Gaps " at the Margolis-FDA Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies, September 18-19, 2023

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Projects a-c

Demonstration projects consider **frequency of exposure**

Slide adapted from Dr. Patricia Bright's presentation "Informing the Pregnancy Safety Framework by Addressing Knowledge Gaps " at the Margolis-FDA Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies, September 18-19, 2023

The Demonstration Projects Will Inform the Proposed Framework

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Projects a-c

Demonstration projects evaluate **signal detection *vs.* signal evaluation**

Slide adapted from Dr. Patricia Bright's presentation "Informing the Pregnancy Safety Framework by Addressing Knowledge Gaps " at the Margolis-FDA Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies, September 18-19, 2023

The Demonstration Projects Will Inform the Proposed Framework

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(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.

Project d

Demonstration projects will help understand the performance of **MCM** as a composite outcome

Slide adapted from Dr. Patricia Bright's presentation "Informing the Pregnancy Safety Framework by Addressing Knowledge Gaps " at the Margolis-FDA Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies, September 18-19, 2023

PDUFA VII Pregnancy Safety Study Demonstration Projects
FDA Commitments and Timeline

Hold a **public workshop** on post-approval pregnancy safety studies

- Review types of post-approval pregnancy data included in pregnancy labeling
- Develop a framework: possibilities for optimal use of data from different types of post-approval pregnancy safety studies

Publish a **workshop report** describing the proposed framework

Initiate **demonstration projects** that may be modified as needed

Today

Based on results of demonstration projects:

- Refine the proposed **framework**
- Develop a **guidance or MAPP/SOPP** as appropriate to implement a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs

9/30/2023 9/30/2024 9/30/2027

FY23 FY24 FY25 FY26 FY27

MAPP: Manual of Policies and Procedure
SOPP: Standard Operating Policy and Procedure
PMRs: Post-marketing Requirements

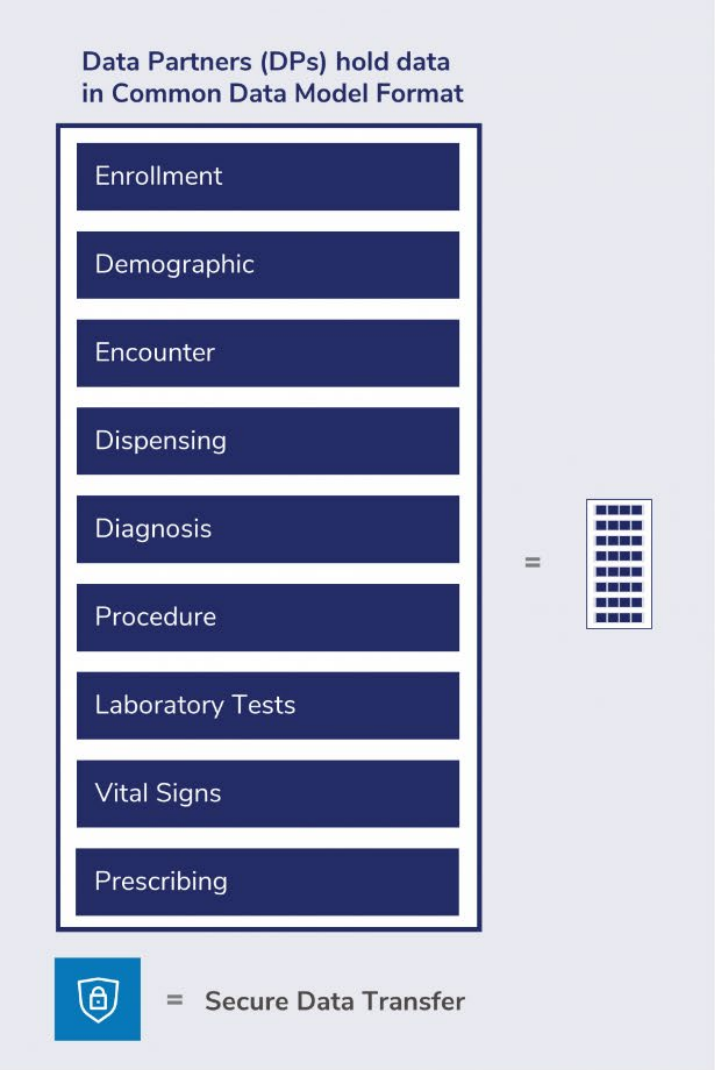
Sentinel System for Pregnancy Medication Safety Surveillance

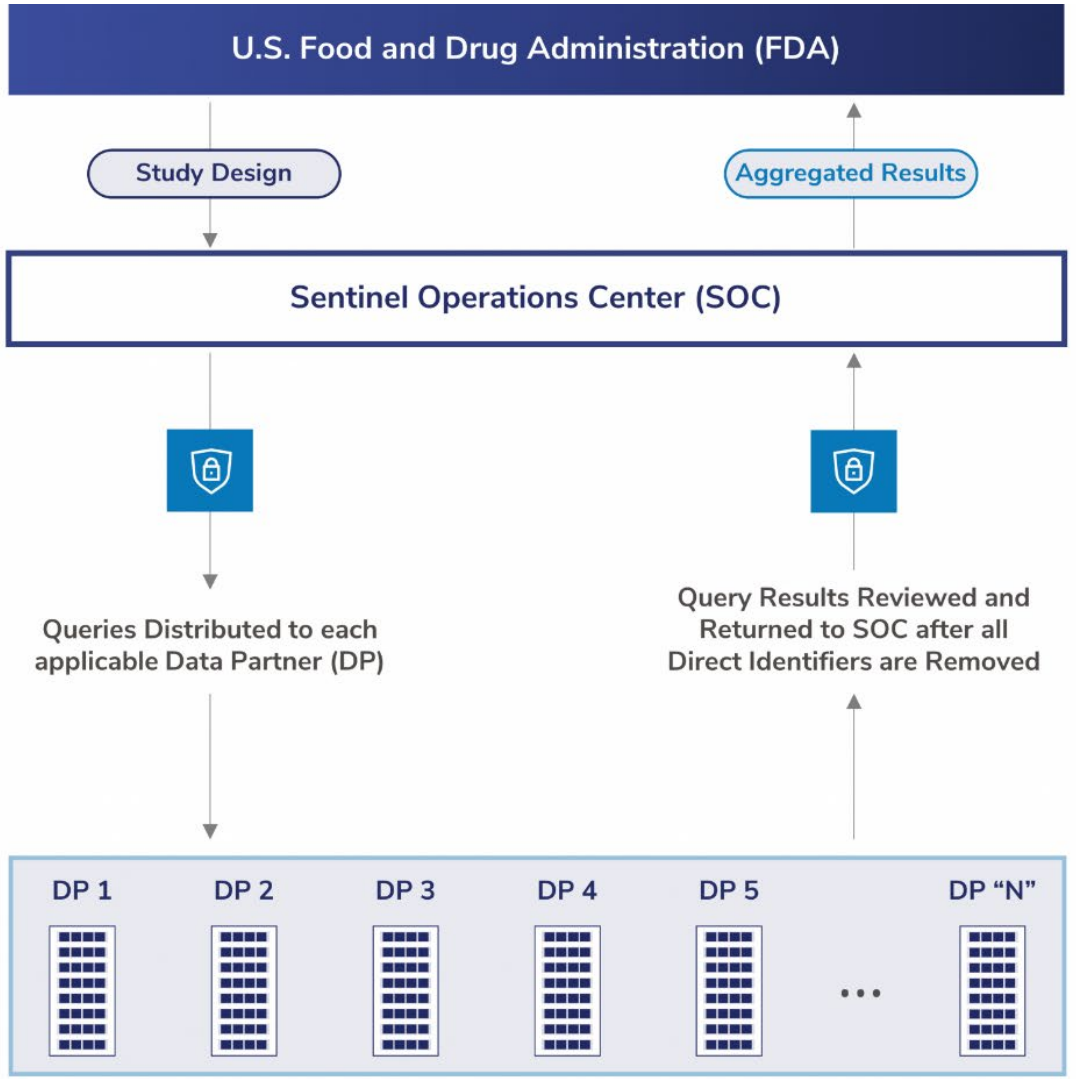
What is Sentinel System?

- The **Sentinel Initiative** was launched in May 2008 in response to the Food and Drug Administration Amendments Act of 2007, which mandated the establishment of an active postmarket risk identification and analysis system
- A core component of the Sentinel Initiative is the **Sentinel System**, a national medical product safety surveillance system
- The Sentinel System includes one of the largest multisite distributed **electronic healthcare databases in the world**, primarily from insurance claims data

The Sentinel Distributed Database

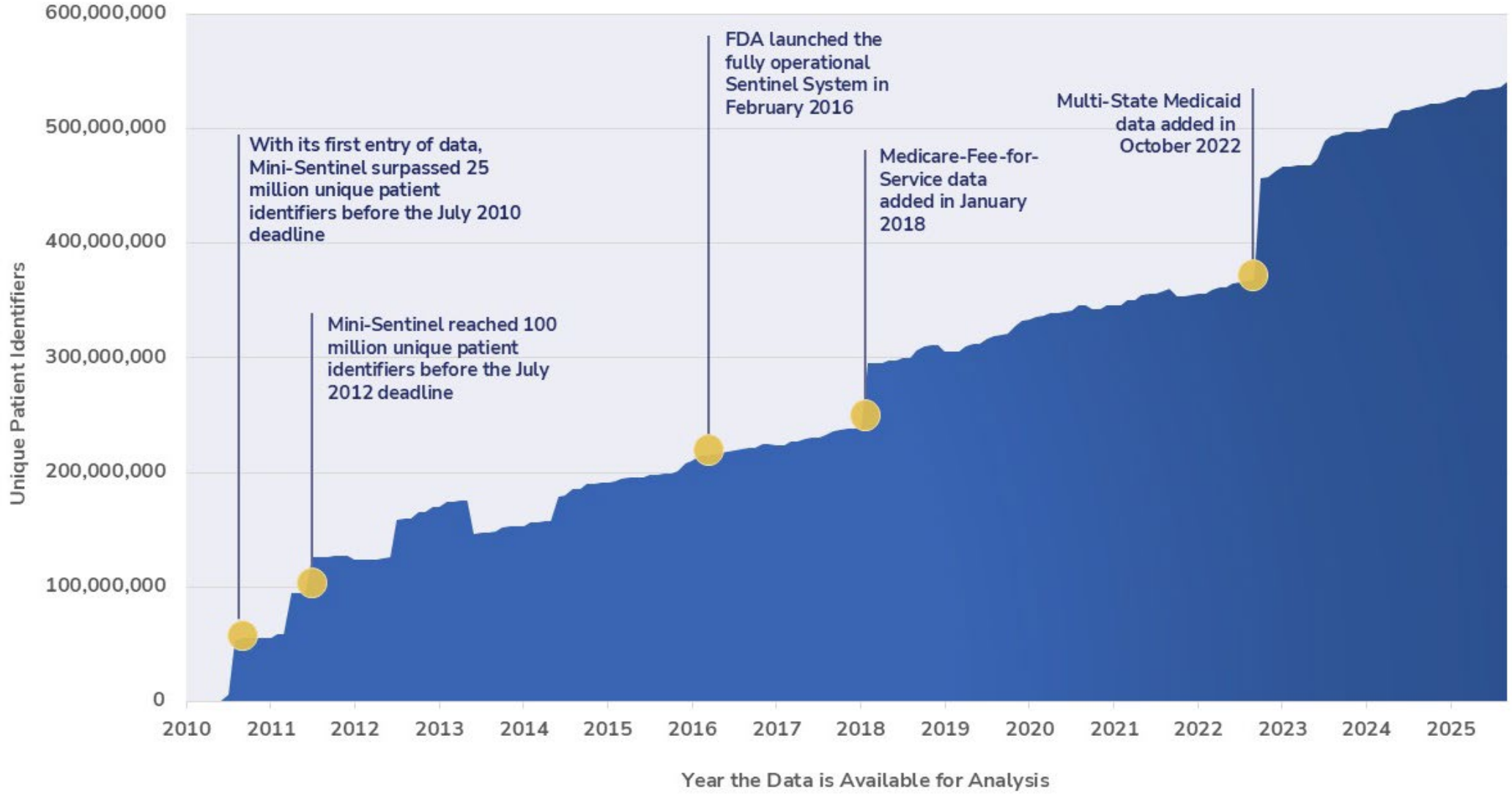
The Sentinel Distributed Database is the collection of harmonized datasets from **many different Data Partners**





https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data

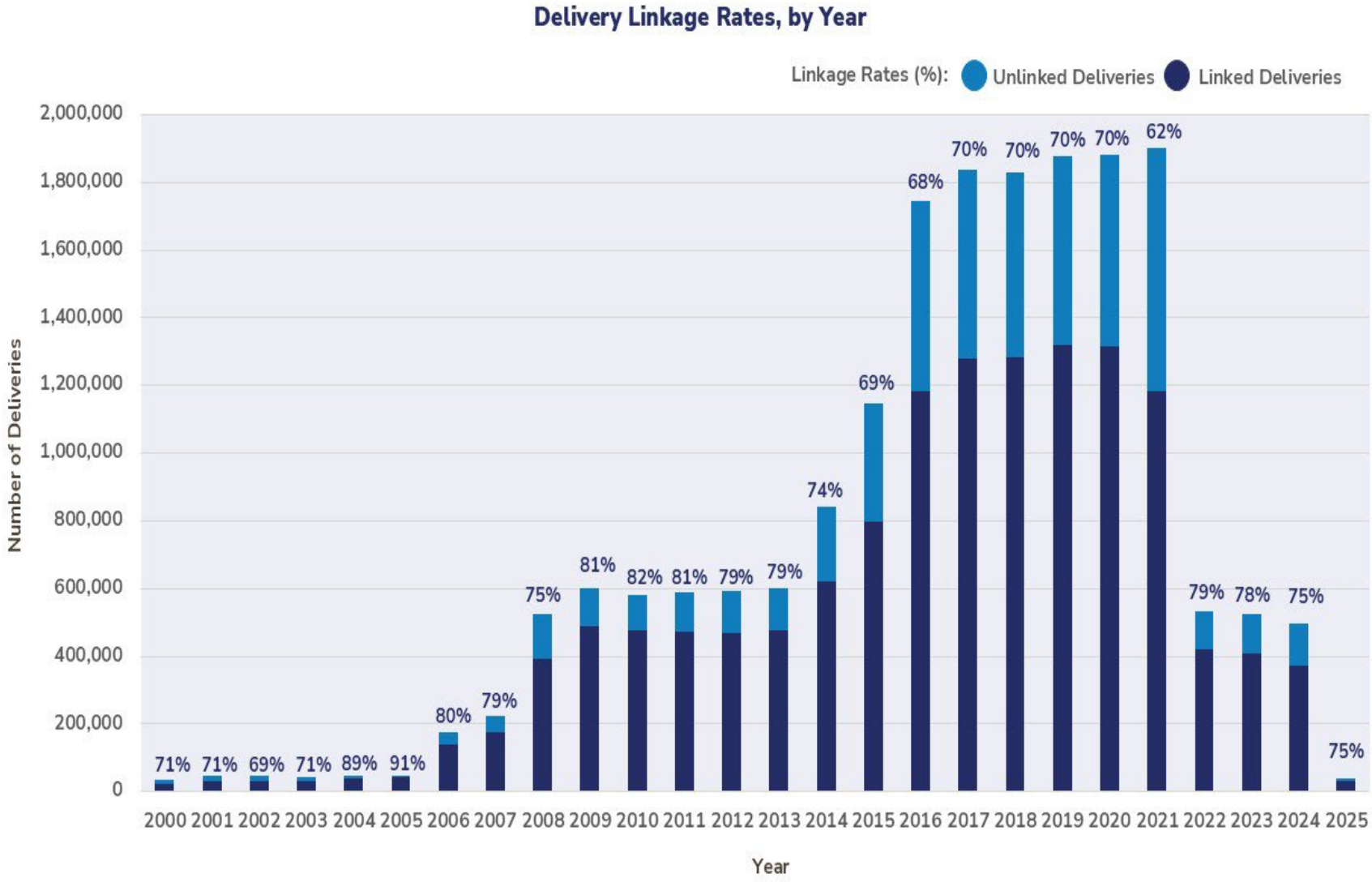
Growth of the Sentinel Distributed Database



https://www.sentinelinitiative.org/about/key-database-statistics

Mother-Infant Linkage in Sentinel

- Enables evaluation of infant outcomes following maternal medication exposure during pregnancy
- **As of October 2025**
  - **13.5 million** linked mother-infant pairs
  - 6 Data Partners with 71.8% linkage rate



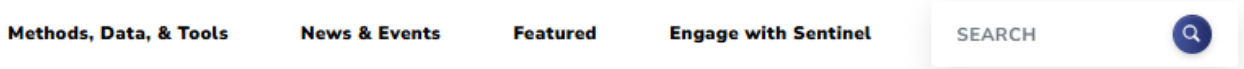
https://www.sentinelinitiative.org/about/key-database-statistics

Select Sentinel Pregnancy Safety Studies*

Study	Study Impacts
Gilenya (Fingolimod hydrochloride) & Cardiac Congenital Malformations, Urinary Congenital Malformations, Other Non-Cardiac and Non-Urinary Congenital Malformations, and All Congenital Malformations	• Contributed to a Newly Identified Safety Signal (NISS) evaluation • Informed feasibility or utility of an ongoing Postmarket Requirement (PMR)
Provigil (Modafinil) and Nuvigil (Armodafinil) & Congenital Cardiac and Non-Cardiac Malformations	• Contributed to a NISS evaluation
Taltz (Ixekizumab) & Use in Pregnancy	• Informed feasibility or utility of an ongoing PMR
Women with Heart Failure & Pregnancy	• Informed New Drug Application (NDA) or Biologics License Application (BLA) review
COVID-19 in Pregnancy & Drug Utilization, Disease Severity, Adverse Neonatal Outcomes, and Adverse Maternal Outcomes	• Impact to FDA's public health initiatives • Informed other agency request

An Assessment of the Sentinel System (2022 to 2024)
Appendix D: Comprehensive List of Sentinel System Studies (2022 to 2024)

Sentinel System advances pregnancy safety assessment by using its analytic and data capacity



Pregnancy

Developing and refining methods to assess medical product utilization, safety, and effectiveness during pregnancy is a focus of FDA's Sentinel System. The Sentinel Common Data Model (SCDM) includes a Mother-Infant Linkage (MIL) table that enables routine evaluation of the effects of medical product exposures during pregnancy on infant outcomes. Descriptions of efforts led by the Center for Drug Evaluation and Research are shown below. Please visit the links to learn more about each area of activity.

‹ Card View

https://www.sentinelinitiative.org/featured-topics/pregnancy#

Title	Date
Products with Converted Labeling Reference Studies for the Pregnancy and Lactation Rule for the Development of the Pregnancy Safety Study Framework	12/10/2025
Syphilis Diagnosis Algorithm Defined in "Characterization of Syphilis Testing and Treatment in Pregnant Women: A Descriptive Analysis"	09/12/2025
Characterization of Syphilis Testing and Treatment in Pregnant Women: A Descriptive Analysis	09/12/2025
Characterization of Syphilis Testing and Treatment in Infants in the Mother-Infant Linkage Table in the Sentinel Distributed Database: A Descriptive Analysis	09/12/2025
Improving the Identification of Pregnancies in Claims Data: A Descriptive Analysis	08/26/2025
Pregnancy Algorithms	08/26/2025
Mayzent (siponimod)	07/31/2025
Mother-Infant Linkage Table	07/31/2025
Products for the Development of the Pregnancy Safety Study Framework	07/24/2025
Comparison of Signal Detection and Evaluation Study Designs to Inform Development of the Pregnancy Safety Framework	06/13/2025

‹ 1 2 3 4 5 ›

PDUFA VII Pregnancy Safety Study Demonstration Project Updates

PDUFA VII Pregnancy Safety Study Demonstration Projects a, b, c

Drug and Outcome Selection

Drug selection criteria

- Quality evidence on teratogenicity
- The availability of a pregnancy registry and data in Sentinel
- Varying exposure levels (common *vs*. low)

Selected drugs

Exposure level	Drugs	Drug class
Common (Projects a & c)	valproate, topiramate	Anticonvulsant agents*
Low (Project b)	mycophenolate, leflunomide	Immunosuppressive agents**

*Common exposure: Most patients with a diagnosis of epilepsy continue treatment during pregnancy to prevent fatal seizures

**Low exposure: Risk management strategies minimize fetal exposure

Pregnancy-related maternal, fetal, and infant outcomes of interest

- Composite outcome of major congenital malformations
- Specific malformations (e.g., neural tube defects, oral clefts, microcephaly, cardiovascular malformations, hypospadias, limb malformations, and microtia/anotia)
- Fetal growth restriction
- Low birth weight
- Small for gestational age
- Spontaneous abortion (SA), SA in the first trimester
- Induced abortion
- Stillbirth
- Preterm birth
- Cesarean section
- Preeclampsia
- Gestational diabetes
- Maternal death

Projects a and c

Signal detection and evaluation for relatively **common exposures**

- Association between valproate exposure during pregnancy and various maternal, fetal, and infant outcomes in electronic healthcare and registry databases
- Association between topiramate exposure during pregnancy and various maternal, fetal, and infant outcomes in electronic healthcare and registry databases

Sentinel Operations Center (SOC) working with FDA and the North American Antiepileptic Drug (NAAED) Pregnancy Registry

Generated common protocol, aligned on definitions of eligible population, exposure, outcome, comparator, and covariates

Project b

Signal detection for relatively **low** **exposures**

- Association between mycophenolate exposure during pregnancy and various maternal, fetal, and infant outcomes in electronic healthcare and registry databases
- Association between leflunomide exposure during pregnancy and various maternal, fetal, and infant outcomes in electronic healthcare and registry databases

Mycophenolate:

SOC working with FDA and Transplant Pregnancy Registry International (TPRI)

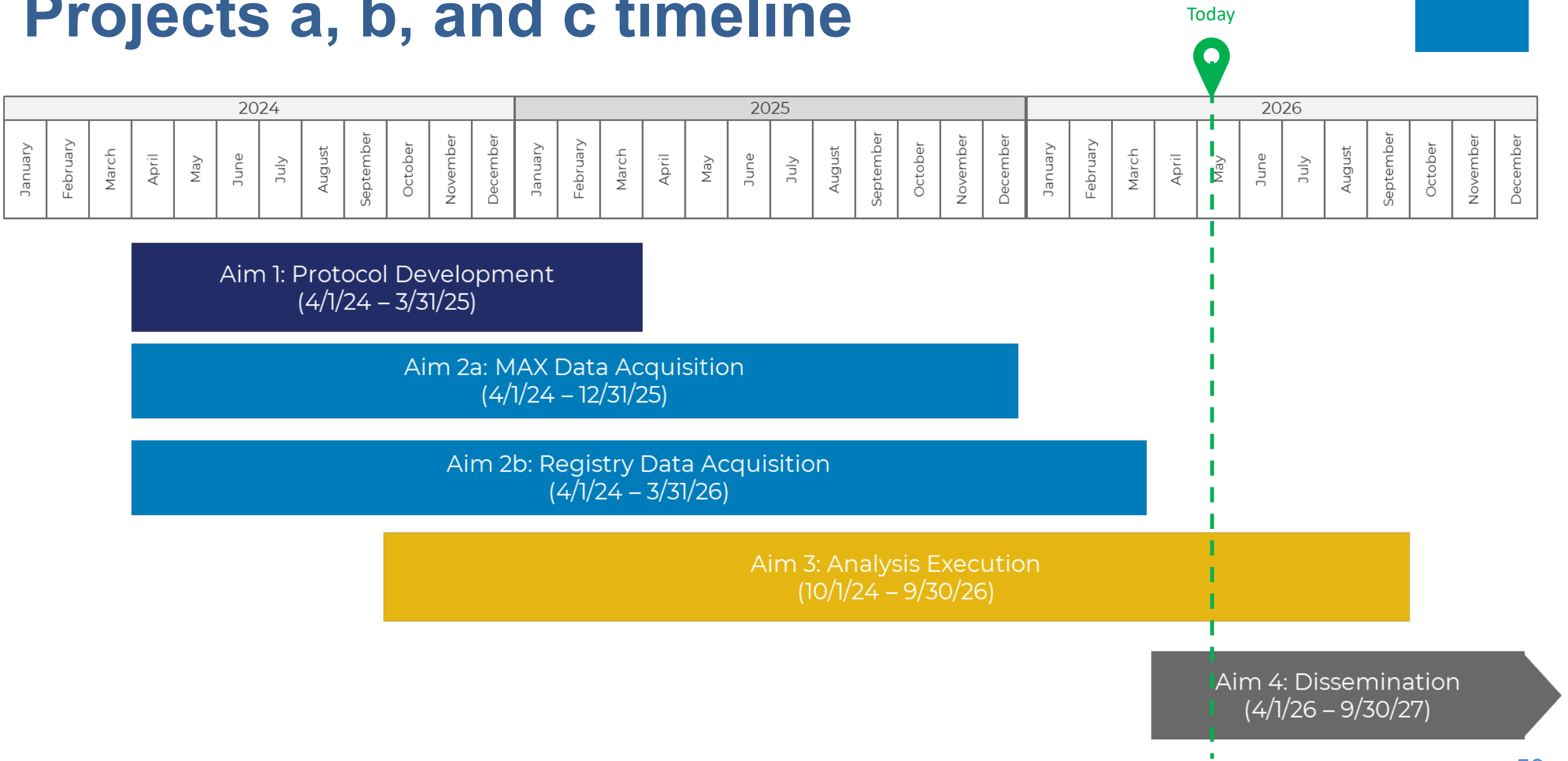
Leflunomide:

SOC working with FDA and registry data through the Organization of Teratology Information Specialists (OTIS)

Generated common protocol, aligned on definitions of eligible population, exposure, outcome, comparator, and covariates

REMS: Risk Evaluation and Mitigation Strategy

Projects a, b, and c timeline



Planned timeline as of April 2026

MAX: Medicaid Analytic eXtract

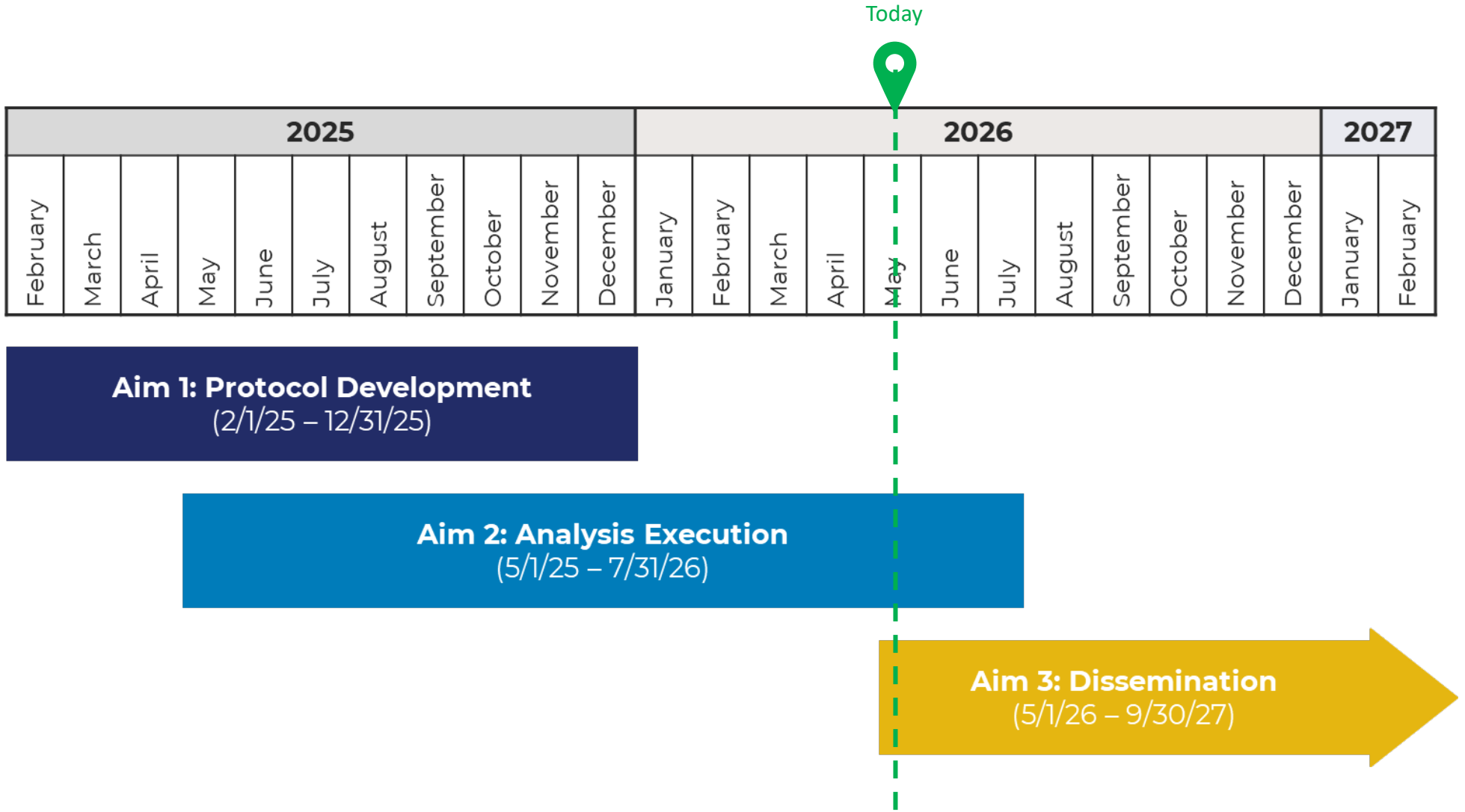
Project d

Project Summary: Assessing 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

This assessment will evaluate **the targeted outcome analyses using composite** and **the untargeted outcome Tree-based scan statistics (TBSS)** under varying parameters that influence statistical power:

- Size of the exposed population
- Background incidence of the outcome
- Magnitude of the effect size
- Potential biases
  - Outcome misclassification (non-differential and differential)
  - Exposure misclassification
  - Confounding (assuming using an active comparator design could address most of potential confounders)
- Multiplicity control (TBSS only)

Project d timeline



Planned timeline as of April 2026

Additional Projects to Support Pregnancy Safety Study Framework

- Developing a prediction model to estimate the magnitude of exposure
- Chart review for major congenital malformations

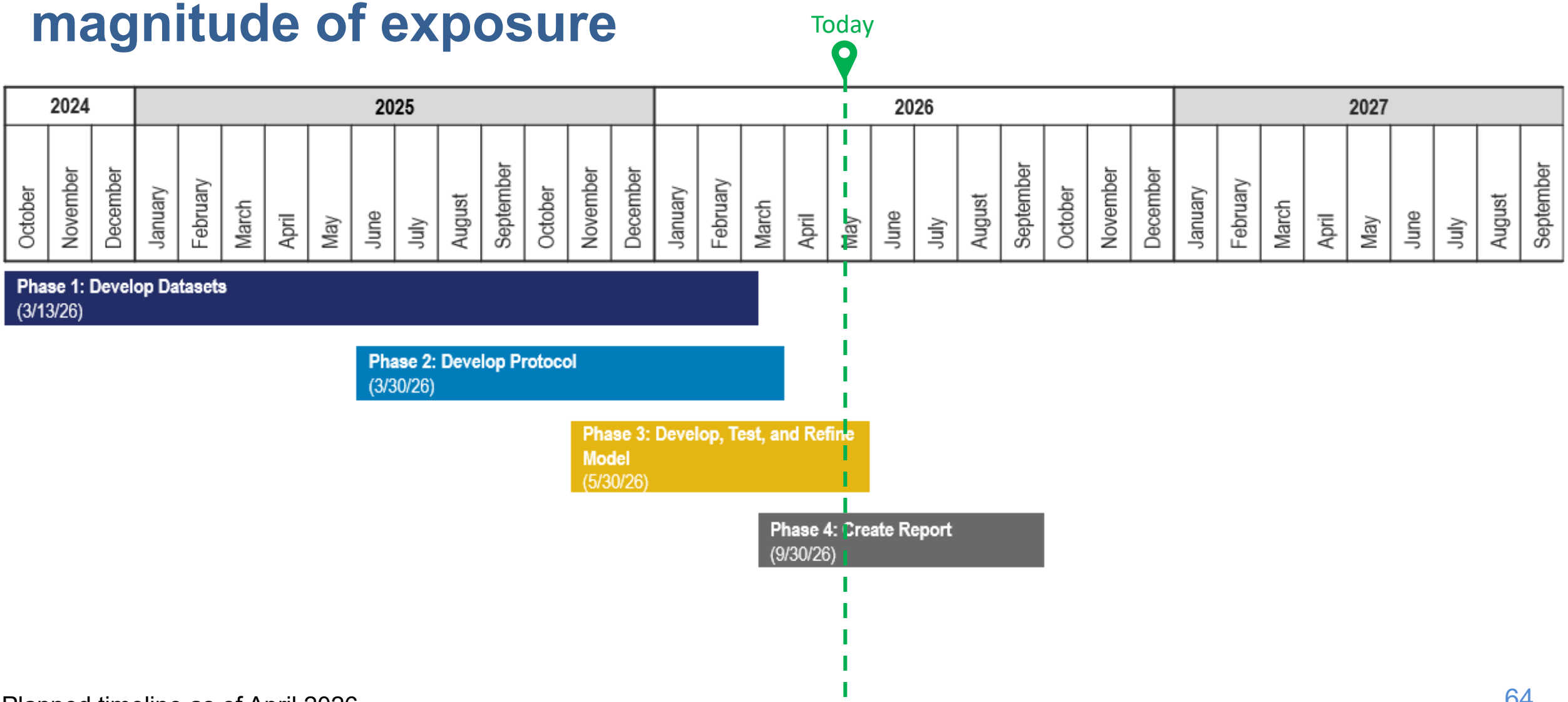
Developing a prediction model to estimate the magnitude of exposure

Project Goal: To develop a model to estimate the magnitude of future exposure in pregnancy of products of interest at the time of regulatory decision-making

- Model development incorporating multiple estimation variables to solve for known product utilization in pregnancy
  - Directly measured characteristics (e.g., prevalence of indication)
  - Coded qualitative characteristics (e.g., first-in-class status, breakthrough therapy designation)
  - Regression analysis
- Leveraging multiple data sources to populate datasets, including multiple queries distributed to the Sentinel Distributed Database (SDD)

Additional Projects to Support Pregnancy Safety Study Framework

Developing a prediction model to estimate the magnitude of exposure



Planned timeline as of April 2026

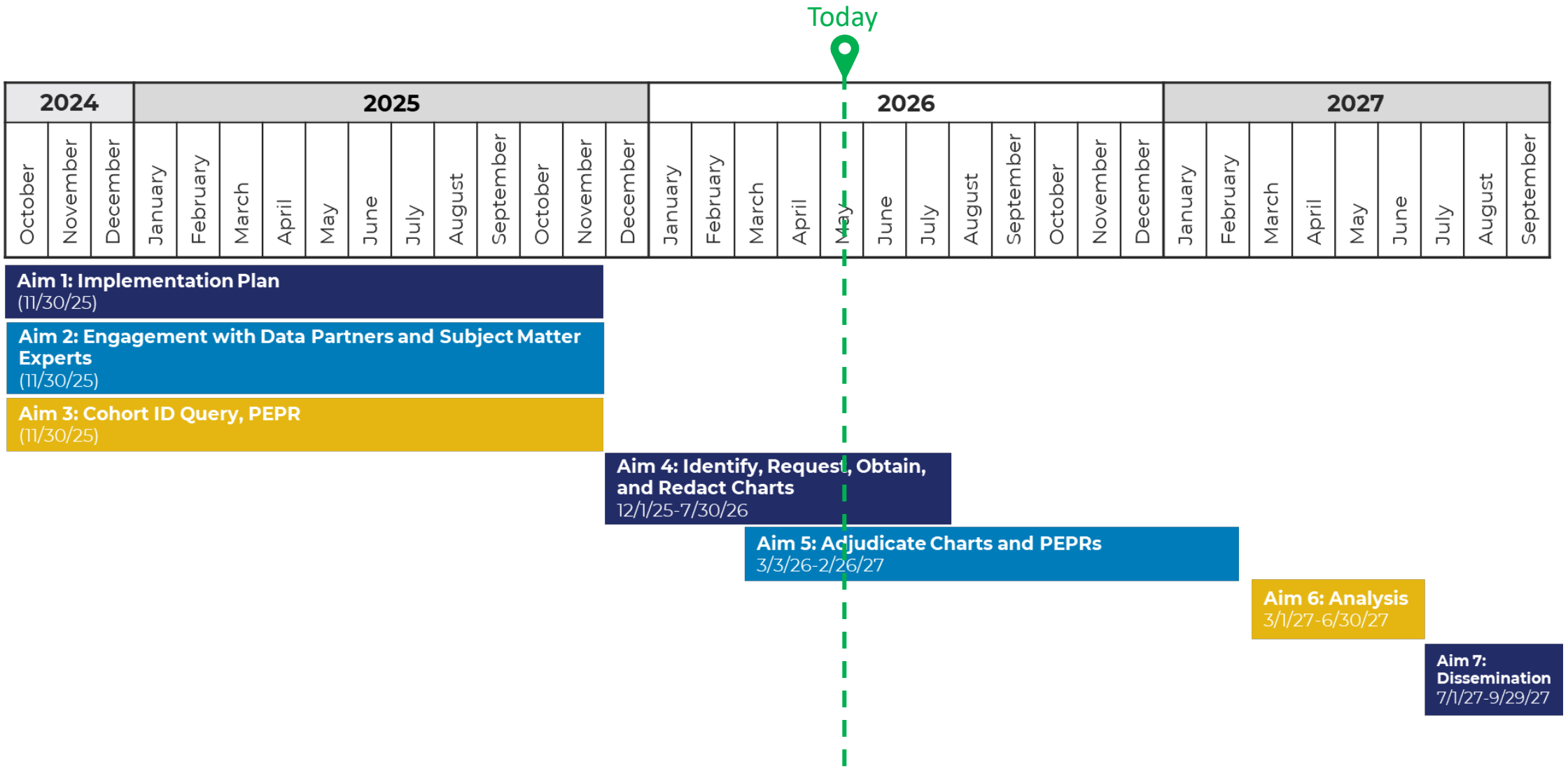
Chart review for major congenital malformations

Project Goal: Assess the performance of the composite major congenital malformations (MCM) algorithm using ICD-10-CM diagnoses codes in administrative claims data by

- Conducting a chart review
- Patient Episode Profile Retrieval (PEPR) review

Additional Projects to Support Pregnancy Safety Study Framework

Chart review for major congenital malformations



Planned timeline as of April 2026

Conclusion and Next Steps

- The PDUFA VII Pregnancy Safety Study Demonstration Projects are ongoing
- Sentinel System has been supporting the demonstration projects with its analytic and data capacity
- This work will inform refinement to the proposed Pregnancy Safety Study Framework to obtain timely evidence for regulatory decision making
- The results from the demonstration projects can provide valuable contributions to the current discussion on optimizing pregnancy registries
- They can also help explore how the integration of registries with other data sources, such as electronic health databases, can advance and complement them to improve post-market safety surveillance

PDUFA: Prescription Drug User Fee Act

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Registries

North American Antiepileptic Drug (NAAED) Pregnancy Registry
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Transplant Pregnancy Registry International (TPRI)
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Dorothy Kliniewski
Stephen Tornone

The Organization of Teratology Information Specialists (OTIS)
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Patricia Armour
Martina Cotton
Diana Johnson
Yunjun Luo
Maria Mann
Neeraja Ramesh


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Back Up

BEST PDUFA VII Pregnancy Demonstration Project e

(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.

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

BEST PDUFA VII Pregnancy Demonstration Project e - Overview

- Developed a validation study to assess performance of claims-based algorithms using healthcare data to identify preterm birth with maternal vaccination* in pregnant women ages 12-55 years.
- Identified preterm births in administrative claims data using 5 claims-based algorithm options.
- Performed medical record review on maternal records.
- Conducted adjudication for a sample of claims-based preterm birth records to assess positive predictive value (PPV) of each algorithm.
- 2 Commercial Claims Data Sources:
  - Carelon Research: >37 million female** & 4.4 million infant*** enrollees
  - CVS Health: >26 million female** & 1.9 million infant*** enrollees
- Of 215,631 eligible pregnancy episodes observed between 11/1/23 – 11/1/24, there were 10,063 mother and/or infant claims-identified pre-term births.

**Tdap, Influenza, RSV, Covid-19*
***All ages*
****Infants 0-1 years old*

BEST PDUFA VII Pregnancy Demonstration Project e (Update as of January 2026)

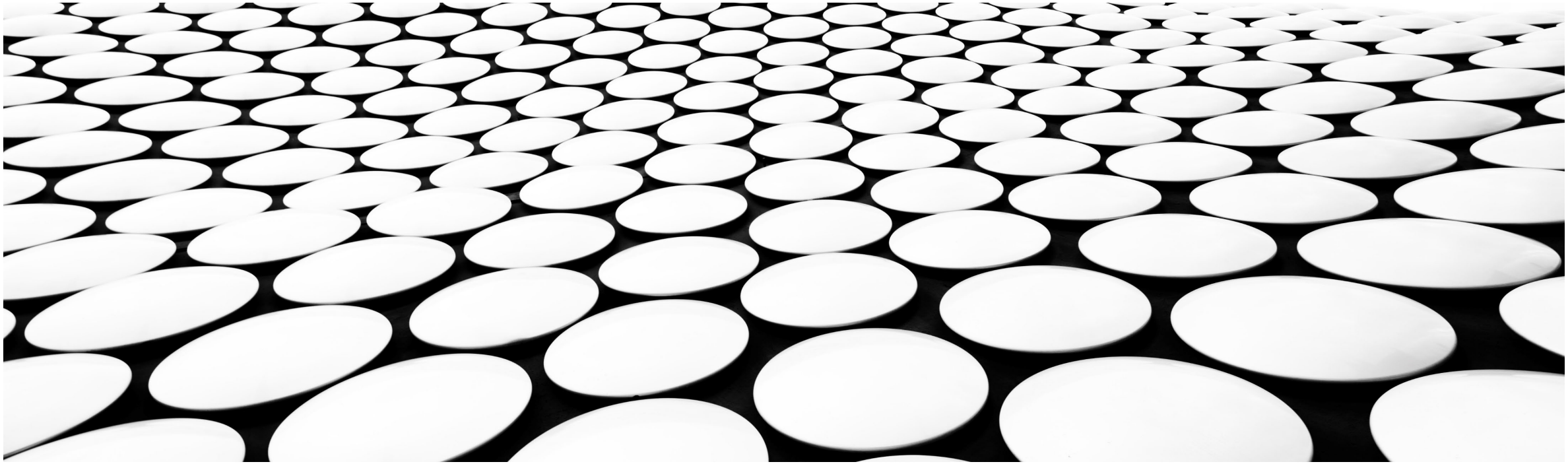
- Of the 105 records randomly sampled for medical record review, 84 had delivery records available.
- Results from 5 algorithm options examining presence of preterm births:

Algorithm Identifying Pre-Term Births	Preterm Births / # of Reviewed Cases	Positive Predictive Value (PPV), (95% CI)
Maternal claims only	54 / 63	85.7% (74.6-93.3)
Infant claims only	48 / 50	96.0% (86.3–99.5)
Maternal linked-claims	38 / 44	86.3% (72.6-94.8)
Both maternal and infant claims	29 / 29	100% (88.1-100)
Either maternal or infant claims	73 / 84	86.9% (77.8-93.3)

- Linking mother to infant claims improved PPV but resulted in smaller samples. Potential misclassification of outcome and sample size are important factors to consider when using linked data in future studies.

THE PHYSICIAN'S PERSPECTIVE: *PRESCRIBING MEDICATIONS IN PREGNANCY*

Megan E. B. Clowse, MD, MPH
Professor of Medicine, OB/GYN, and Population Health Sciences
Chief, Division of Rheumatology & Immunology
Duke University



DISCLOSURES

- Grants: GSK, UCB, NIH: NIAMS
- Consulting: GSK, UCB, AZ, MotherToBaby

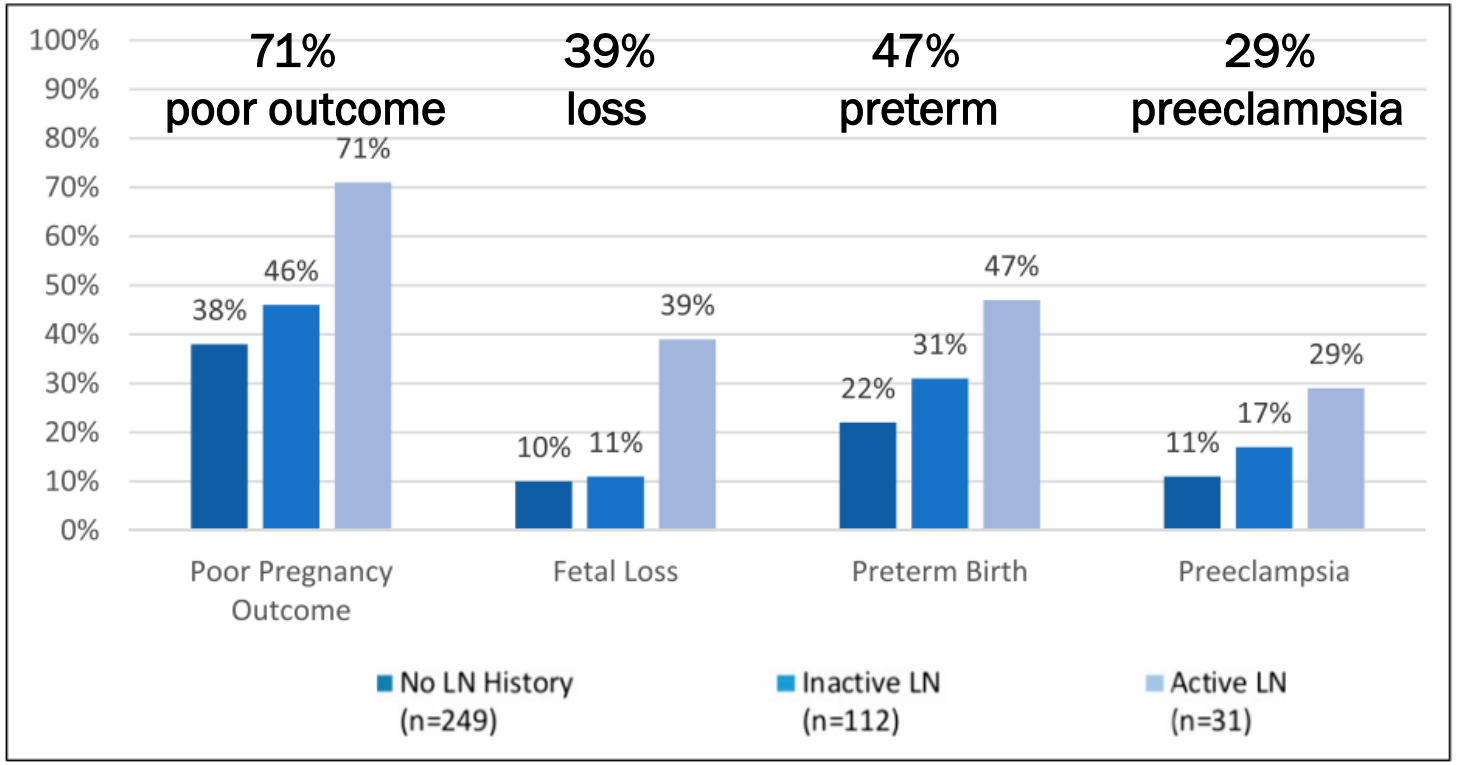
- Discussing some treatments for lupus that are not FDA approved for lupus

OUTLINE

- A case
- Challenges of the current system
- What data do doctors and patients want?
- A few thoughts about what's next

A 26 YEAR OLD WOMAN WITH A 5 YEAR HISTORY OF SYSTEMIC LUPUS ERYTHEMATOSUS (LUPUS) PRESENTS TO THE RHEUMATOLOGIST 8 WEEKS PREGNANT.

- Her Lupus
  - Positive ANA, dsDNA, and low complement
  - History of arthritis and rash
  - *Active lupus nephritis with 3 grams of protein in her urine*



Incremental increase in adverse outcomes based on lupus nephritis diagnosis and disease activity.

Lucas 2022

HER CURRENT MEDICATIONS

Hydroxychloroquine

Mycophenolate

HYDROXYCHLOROQUINE:

Prescribed for malaria, lupus, and other rheumatic diseases in pregnancy x 30 years

FDA LABEL:

- Prolonged clinical experience over **decades of use and available data** from published epidemiologic and clinical studies with hydroxychloroquine sulfate use in pregnant women **have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal, or fetal outcomes.**

AMERICAN COLLEGE OF RHEUMATOLOGY:

Reproductive Health Guidelines (2020)

- **We recommend that all women with SLE take hydroxychloroquine during pregnancy if possible.**

Sammaritano, 2020

MYCOPHENOLATE:

Immunosuppressant prescribed for solid-organ transplants, lupus, and other severe autoimmune diseases.

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES and SERIOUS INFECTIONS

See full prescribing information for complete boxed warning

- **Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available. Females of reproductive potential must be counseled regarding pregnancy prevention and planning *[see Warnings and Precautions (5.1)]*.**

FDA Label, Mycophenolate

Mycophenolate mofetil and mycophenolic acid	XX Stop >6 weeks prior to conception to assess disease stability

Sammaritano 2020

Perez-Aytes. European Journal of Medical Genetics. 2017

WHAT'S A DOCTOR & PREGNANT PATIENT TO DO?

- Don't add medication and allow nephritis to run its course in pregnancy
- Try older medications with lower efficacy for nephritis but established pregnancy safety profile *(Azathioprine, Tacrolimus)*
- Try new medications with higher efficacy for nephritis but very limited pregnancy data *(Voclosporin, Obinutuzumab, Belimumab)*

What is the medication(s) that will give her and her developing fetus the greatest chance at survival and good health?

We have no idea!!

Pregnancy outcomes are impacted by MANY factors

Accurately measuring all of these is challenging but important.

- Maternal diagnosis
- Disease activity
- Medications
- Comorbidities
- Social Determinants of Health
- Genetics

CHALLENGES OF PUBLICLY COLLECTED MEDICAL DATABASES

PROS

- Large numbers of pregnancies
- Less biased enrollment

CONS

- Inaccurate diagnoses
- Unmeasured disease activity
- Unclear medication use
  - Adherence in pregnancy is a challenge!
- Inaccurate social determinants of health

CURRENT CHALLENGES IN PARTICIPATING IN RESEARCH

LOCAL STUDIES

Benefits:

- Providers are motivated
- Patient enroll in-person

Challenges:

- Under-powered to find important problems
- Variable rigor in data collection
- Funding

NATIONAL REGISTRIES

Benefits:

- Potential for improved power to find rare and important problems
- Enhanced pregnancy and infant outcome evaluation

Challenges:

- Providers forget – patients are spread thinly across a lot of doctors
- Gap between referral and enrollment

WHAT DATA DO PHYSICIANS NEED TO MAKE INFORMED DECISIONS?

BABY HAZARDS:

- Major birth defects
- Pregnancy loss
- Preterm delivery
- Health in early month

MATERNAL HAZARDS:

- Health of the mother
- Efficacy of the drug to avoid maternal harm

WHAT DO PATIENTS WANT TO KNOW?

- Will my baby be OK?
  - Longer-term infant and child outcomes
  - Infections & hospitalizations
  - School performance

THE IDEAL: BALANCE EASE WITH RIGOR

- EASY
  - Recruitment – few exclusions
    - Providers enroll a lot of patients so it remains top-of-mind
    - Simple ‘screening’
  - Enrollment – fast and simple
- RIGOROUS & RELIABLE
  - Facts, when possible
    - Pull labs, pregnancy outcomes from EMR
  - Focus on common tests & data
    - Limit missingness
  - Medication adherence checks
    - Prescription refill data
    - Patient-reported adherence
    - Blood levels, when possible

GATHERING ESSENTIAL DATA FROM PROVIDERS & PATIENTS

- PHYSICIAN REPORTING
  - Integrate within usual care
  - Quick
  - Clinically applicable & within their knowledge-base
  - Compensated for their time & effort
- PATIENT REPORTING
  - Integrate within usual care
  - Quick
  - Clinically applicable & known by the patient
  - Compensated for their time & effort

HOW DO WE ANSWER THE ESSENTIAL QUESTIONS ABOUT MEDICATIONS IN PREGNANCY EFFICIENTLY, QUICKLY, AND ACCURATELY?

- *I look forward to learning from all of you!*

Optimizing Pregnancy Registries: National Pregnancy Registry for Psychiatric Medications: Lessons Learned and a Look to the Future

Lee S. Cohen, MD
Director, Ammon-Pinizzotto Center for Women's Mental Health, Perinatal and Reproductive Psychiatry,
Massachusetts General Hospital
Harvard Medical School

May 8, 2026

HARVARD MEDICAL SCHOOL | Massachusetts General Hospital
Founding Member, Mass General Brigham

Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

12-Month Disclosure

Research Support for the National Pregnancy Registry for Atypical Antipsychotics: Alkermes Biopharmaceuticals; Janssen Pharmaceutica; Otsuka Pharmaceuticals; Teva Pharmaceuticals; Sage Therapeutics, Inc.; Sunovion Pharmaceuticals, Inc; Supernus Pharmaceuticals; Bristol-Myers Squibb

Other research support: National Institutes of Health; Sage Therapeutics, The Marriott Foundation, NEDA

Advisory/Consulting: JDS Therapeutics LLC; Luminous Minds LLC; As an employee of MGH, Dr. Cohen works with the MGH CTNI, which has had research funding from multiple pharmaceutical companies, including Praxis Precision Medicines, Inc., and the NIMH.

Honoraria: None

Royalty/patent, other income: None

National Pregnancy Registry for Psychiatric Medications: Introduction

- History of National Pregnancy Registry for Psychiatric Medications (NPRPM)
- Lessons learned across a decade
- Look to the future : model of integration of real-world evidence with Registry data – challenges and opportunity

National Pregnancy Registry for Atypical Antipsychotics

The **National Pregnancy Registry for Atypical Antipsychotics** is dedicated to evaluating the safety of atypical antipsychotic medications that may be taken during pregnancy to treat a wide range of mood, anxiety, or psychiatric disorders. The goal of this Registry is to gather information on the safety of these medications during pregnancy, as current data is limited.

TO PARTICIPATE CALL TOLL-FREE: 1-866-961-2388

All pregnant people 45 and younger with a history of psychiatric illness are eligible to enroll in the registry. If you are interested in participating in the National Pregnancy Registry, please call the toll-free number above or fill out this **Participant Interest Form** to be contacted by a member of our research team. All information is kept strictly confidential.

More Information and Enrollment

FOR PARTICIPANTS

FOR CLINICIANS

Sponsorship of NPRPM

The National Pregnancy Registry for Atypical Antipsychotics

The National Pregnancy Registry for Antidepressants

The National Pregnancy Registry for ADHD Medications

The National Pregnancy Registry for Sedative-Hypnotics and Other Sleep Medications

Required Sponsorship Disclosures:

Current Sponsors: Alkermes, Inc. (2016-Present); Bristol-Myers Squibb Company (2025-Present); Eisai Inc. (2022-Present); Otsuka America Pharmaceutical, Inc. (2008-Present); Sage Therapeutics (2019-2023, 2024-Present); Supernus Pharmaceuticals (2021-Present).

Past Sponsors: Forest/Actavis/Allergan (2016-2018, declined to sponsor: 2018-Present); Aurobindo Pharma (2020-2022, declined to sponsor: 2022-Present); AstraZeneca Pharmaceuticals (2009-2014, declined to sponsor: 2014-Present); AuroMedics Pharma LLC (2021-2022, declined to sponsor: 2022-Present); Johnson & Johnson/Janssen Pharmaceuticals, Inc (2019-2023, declined to sponsor: 2024-Present) ; Ortho-McNeil-Janssen Pharmaceuticals, Inc (2009-2014, declined to sponsor: 2015-Present); Pfizer, Inc. (2009-2011, declined to sponsor: 2012-Present); Sunovion Pharmaceuticals, Inc. (2011-2023, declined to sponsor: 2024-Present); Teva Pharmaceutical Industries Ltd. (2018-2025; declined to sponsor 2026-Present); Dr. Reddy's Laboratories, Inc. (2023-2025, declined to sponsor 2026-Present).

Declined to sponsor: AbbVie Inc.; Ajanta Pharma USA Inc.; Apotex Inc.; Arcolab Private Limited; Eli Lilly and Company; Intra-Cellular Therapies, Inc.; Novartis Pharmaceuticals; Qilu Pharmaceutical Co., Ltd.; Vanda Pharmaceuticals Inc; Axsome Therapeutics, Inc.

Funding Information: Manufacturers of psychiatric medications have been approached regarding funding of the National Pregnancy Registry. Regardless of which entities have supported this initiative, all medications in this class are studied. For more information on how to sponsor the Registry, please see the contact information below.

National Pregnancy Registry Methods Overview

Scientific Objectives

Primary Aim:

- To prospectively evaluate rates of major malformations among infants exposed to newer psychiatric medications in utero relative to unexposed infants

Secondary Aims:

- To evaluate obstetrical outcomes associated with use of atypical antipsychotics in utero relative to unexposed infants
- To evaluate neonatal outcomes of infants with prenatal exposure to atypical antipsychotics relative to unexposed infants
- To evaluate maternal health outcomes of mothers exposed to atypical antipsychotics during pregnancy compared to unexposed mothers
- To evaluate neurobehavioral development of children (1 month and older) with prenatal exposure to atypical antipsychotics

- **Parallel aims for other classes of medications.*

Subject Selection

Exposed Group:

- Pregnant women
- Age 45 years or younger*
- Has taken an atypical antipsychotic during first trimester
- Willing to participate over the phone and able to provide informed consent

Control Group:

- Pregnant women
- Age 45 years or younger*
- Has not taken an atypical antipsychotic at any point during pregnancy or a history of psychiatric illness without taking medication
- Willing to participate over the phone and able to provide informed consent

*participants under the age of 18 or > 45 years old enrolled per PI review

Overview of Study Design: Interviews and Medical Record Review

Baseline:

consent, enrollment interview

(45 minutes)

7 months' gestation:

second interview

(15 minutes)

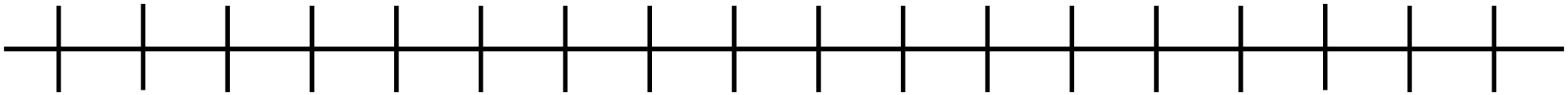
3 months postpartum:

postpartum interview, request for medical record release forms

(20 minutes)

7 months postpartum:

labor and delivery and pediatric medical records requested



Once all records are obtained:

records reviewed by trained RA and principal investigator

potential malformations sent to exposure-blinded dysmorphologist

Recruitment Methods

Internal Sources:

- Referrals from Center for Women's Mental Health (CWMH) psychiatric consultations
- Registry of MGH patients who consent to be contacted about participation in MGH research studies
- Virtual Rounds at CWMH https://womensmentalhealth.org/virtual-rounds-at-the-cwmh/

Center for Women's Mental Health Research Interest Form

Thank you for your interest in research at the Center for Women's Mental Health! Our research interest form will add your information to a database that we search periodically to recruit potential participants for some of our studies. Your information may be helpful in better understanding women's mental health and psychiatric health, as well as for matching you to future research studies that you may be eligible to participate in depending on your psychiatric history and other health factors.

You may have found our research interest form on our website, womensmentalhealth.org, or have been directed to this page after speaking with a member of our research team or making a consultation appointment with one of our psychiatrists.

This database is a research study in the form of a data repository. It is funded by internal funding at the Perinatal and Reproductive Psychiatry Program at Massachusetts General Hospital. You will not be compensated for adding your contact information to our database, but you may be compensated if you choose to participate in future studies at our Center.

External Sources:

- Study updates and announcements disseminated through established listservs of multiple professional organizations
- Distribution of NPRPM materials at relevant continuing medical education conferences
- Presentation of preliminary findings at nationwide conferences
- Social Media Recruitment – Scaled effort in 2025/2026 ; enhanced ability to disseminate information regarding NPRPM

FDA Postapproval Pregnancy Safety Studies Guidance for Industry

Guidance Document - May 2019

Docket Number: FDA-2018-D-4693

Issued by: Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research

The purpose of this guidance is to provide sponsors and investigators with recommendations on how to design investigations to assess the outcomes of pregnancies in women exposed to drugs and biological products regulated by FDA (i.e., pregnancy safety studies). The goal of postapproval pregnancy safety studies is to provide clinically relevant human safety data that can inform health care providers treating or counseling patients who are pregnant or anticipating pregnancy about the safety of drugs and biological products through inclusion of the information in a product's labeling.

U.S. Food and Drug Administration. Postapproval Pregnancy Safety Studies: Guidance for Industry. May 2019.https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry

To Fund or Not to Fund a Registry

1. When a Sponsor Must Fund a Pregnancy Registry

The FDA does **not require a sponsor to create a pregnancy registry for every drug**.

A sponsor is generally required to establish a registry **only if the FDA issues a Postmarketing Requirement (PMR) or Postmarketing Commitment (PMC)** specifically calling for it.

Without a PMR or formal commitment, there is **no legal requirement** for a sponsor to fund a registry.

2. When a Medication Manufacturer May Choose to Fund a Registry Voluntarily

Manufacturers often establish registries voluntarily for:

- Safety monitoring to support labeling updates.
- Marketing or risk management purposes.
- Responding to professional guidelines or public interest.

Industry Engagement in Pregnancy Registries (or not)

Industry engagement in pregnancy registries is typically limited in the absence of a Postmarketing Requirement (PMR)

"[*Company*] is committed to the advancement of medical and scientific knowledge and appreciates receiving sponsorship opportunities. [*Company*] has reviewed your sponsorship request and we are unfortunately **unable to commit to sponsoring the National Pregnancy Registry of Atypical Antipsychotics at this time.** Though we are unable to fund this particular sponsorship request, [*Company*] remains committed to closely monitoring all reports of potential adverse events in the post-marketing period and to timely reporting those to regulatory authorities to ensure the safe and appropriate use of our products."

Industry Engagement in Pregnancy Registries

"Thank you submitting your request for sponsorship of the National Pregnancy Registry for Psychiatric Medications. [*company*] **cannot provide sponsorship support** for this initiative at this time.

Thank you for bringing this initiative to our attention, and we will be in touch in the future if our ability to sponsor changes."

"Unfortunately, we **were not able to obtain agreement from our colleagues to proceed with sponsorship at this time.** I would note that this doesn't preclude sponsorship at a later date and I will plan to be in touch should specific pregnancy-related evidence needs arise in this or other programs."

SKYRIZI Pregnancy Registry

Before using SKYRIZI, tell your healthcare provider about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section **"What is the most important information I should know about SKYRIZI?"**
- have an infection that does not go away or that keeps coming back.
- have TB or have been in close contact with someone with TB.
- have recently received or are scheduled to receive an immunization (vaccine). Medicines that interact with the immune system may increase your risk of getting an infection after receiving live vaccines. You should avoid receiving live vaccines right before, during, or right after treatment with SKYRIZI. Tell your healthcare provider that you are taking SKYRIZI before receiving a vaccine.
- are pregnant or plan to become pregnant. It is not known if SKYRIZI can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SKYRIZI passes into your breast milk.
- become pregnant while taking SKYRIZI. You are encouraged to enroll in the Pregnancy Registry, which is used to collect information about the health of you and your baby. Talk to your healthcare provider or call 1-877-302-2161 to enroll in this registry.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Vraylar (cariprazine) FDA Medication Guide

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 VRAYLAR during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Zurzuvae (Zuranolone) FDA Medication Guide

8 USE IN SPECIFIC POPULATIONS

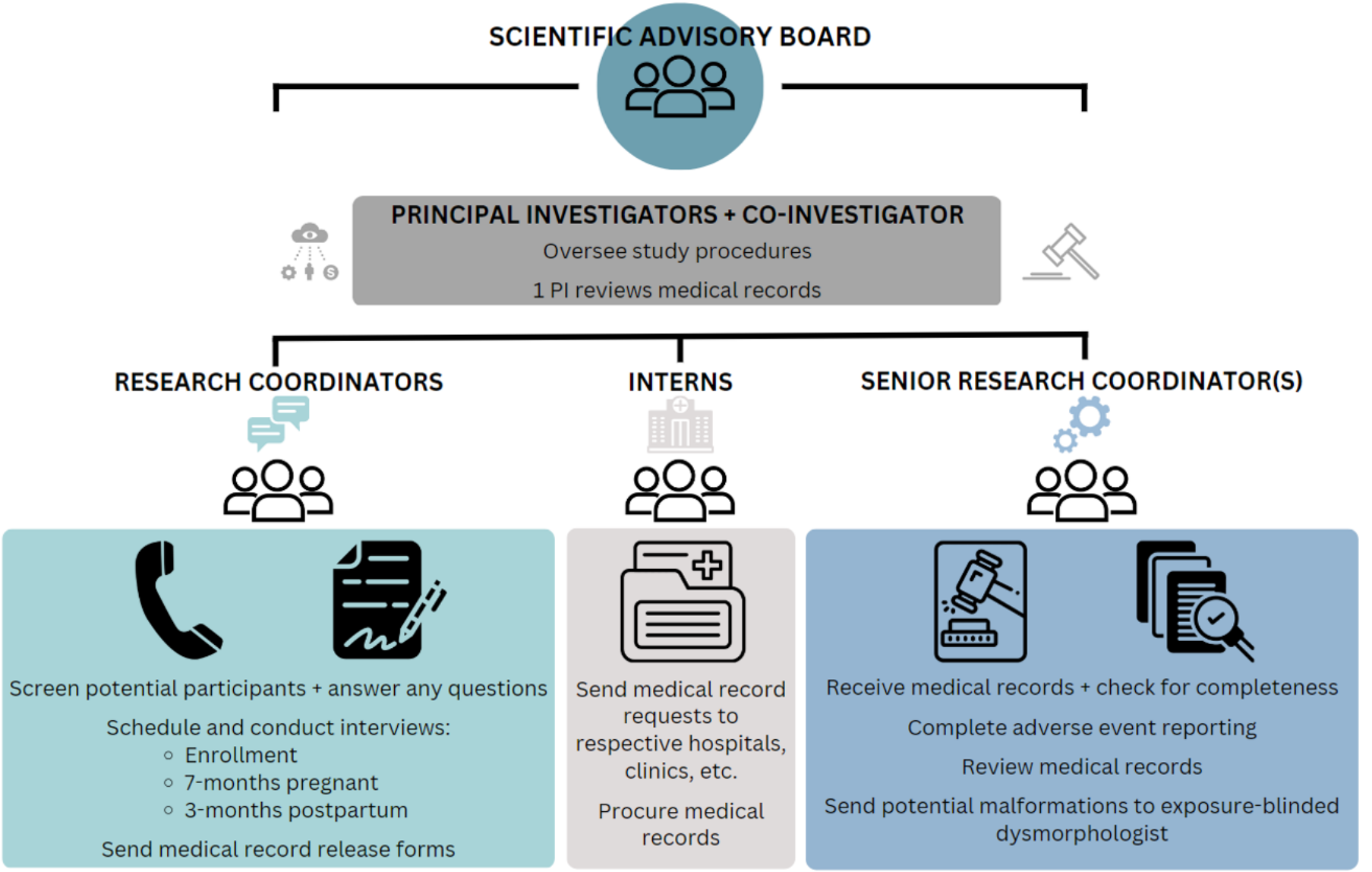
8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including ZURZUVAE, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/

Registry Sponsorship

Overview of Registry Infrastructure



Case Identification and Adjudication for Primary Outcome

- Labor and delivery, and pediatric (birth-6 months) medical records are requested
  - ➢ Medical record procurement rate = **75%***
- Records are reviewed by a trained research assistant, then reviewed again by one principal/co-investigator (ACV, ERR)
- Potential cases of malformations are identified by the research assistant and confirmed by principal investigator, then sent to dysmorphologist blinded to exposure for adjudication

  Note: Maternal reports of apparent major malformations are also sent to dysmorphologist for adjudication if medical records cannot be obtained.

**Calculated by dividing the number of participants for whom we have complete medical records, by all participants who completed their final study interview and their participation in the Registry (excludes participants whose records are actively being requested).*

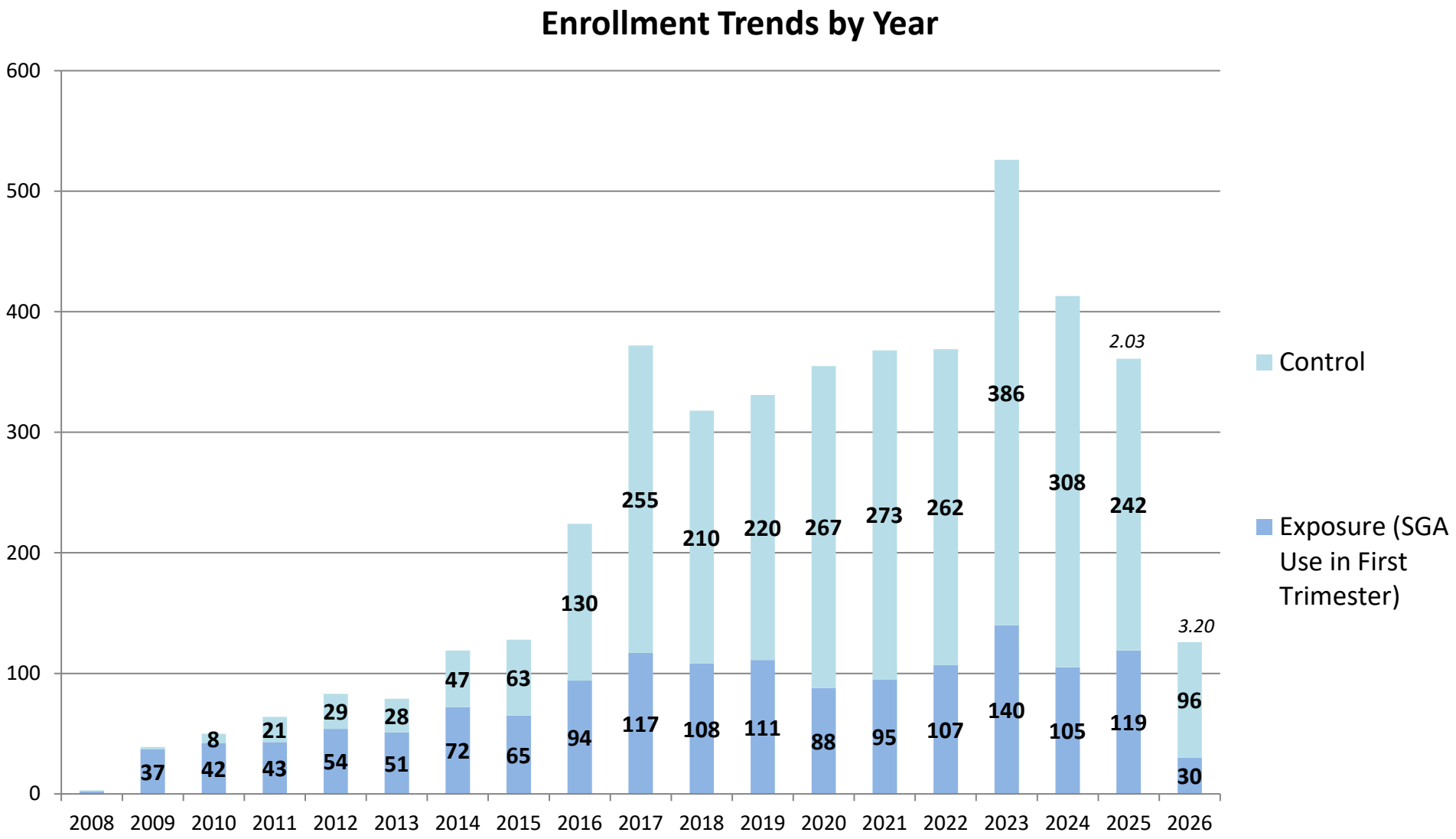
Atypical Antipsychotic Exposure

Exposure Stratified by Medication

Atypical Antipsychotic	First Trimester Exposure
quetiapine (Seroquel)	33.2%
aripiprazole (Abilify)	27.1%
lurasidone (Latuda)	21%
cariprazine (Vraylar)	6.5%
olanzapine (Zyprexa)	5.7%
ziprasidone (Geodon)	5.4%
risperdone (Risperdal)	3.6%
brexpiprazole (Rexulti)	2.1%
lumateperone (Caplyta)	1.7%
paliperidone (Invega)	1.0%
asenapine (Saphris)	0.8%
aripiprazole lauroxil (Aristada)	0.7%
clozapine (Clozaril)	0.5%
iloperidone (Fanapt)	0.3%
paliperidone palmitate (Erzofri)	0%
olanzapine/samidorphan (Lybalvi)	0%

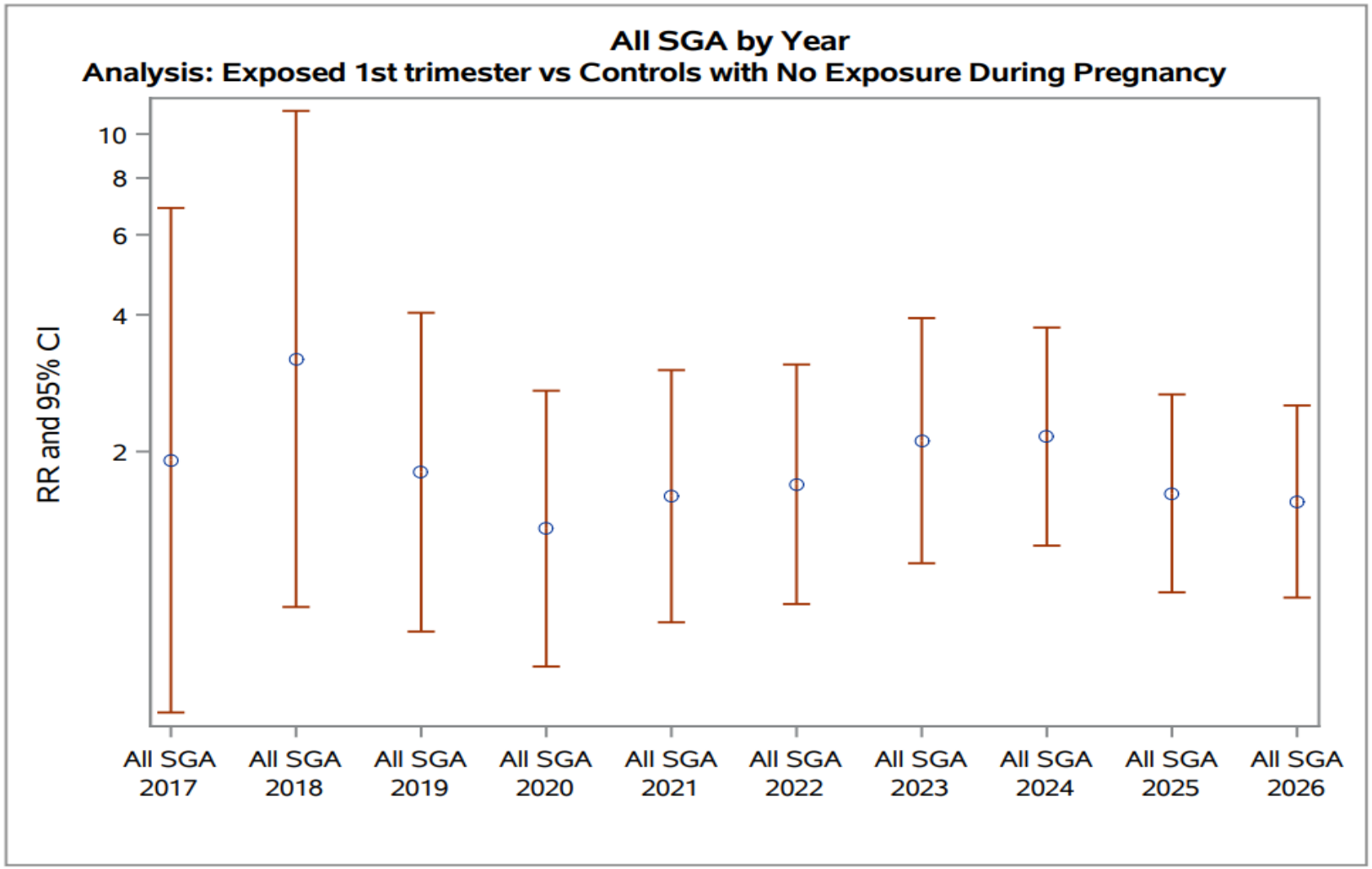
Data extracted 4/16/2026

Participants Enrolled by Year



Data extracted 4/16/2026

All SGAs: Unadjusted Risk Ratios and Confidence Intervals



[1]*Viguera AC, Freeman MP, Goez-Mogollon L, Sosinsky AZ, McElheny SA, Church TR, Young AV, Caplin PS, Chitayat, D, Hernandez-Diaz, S, Cohen LS. Reproductive Safety of Second-Generation Antipsychotics: Updated Data From the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. 2021. Journal of Clinical Psychiatry.*

Data extracted 4/17/2026

JCP CME: ORIGINAL RESEARCH

Reproductive Safety of Second-Generation Antipsychotics: Updated Data From the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics

Adele C. Viguera, MD, MPH[a,b,c,*]; Marlene P. Freeman, MD[a,b]; Lina Góez-Mogollón, MD, MSc[a]; Alexandra Z. Sosinsky, MS[d]; Sara A. McElheny, BA[a]; Taylor R. Church, BS[a]; Amanda V. Young, BA[a]; Phoebe S. Caplin, BA[a]; David Chitayat, MD[e]; Sonia Hernández-Díaz, MPH, DrPH[d]; and Lee S. Cohen, MD[a,b]

CME INSTITUTE Focus on Women's Mental Health

Table 4. Unadjusted and Adjusted Odds Ratios for Risk of Major Malformations Comparing Exposure Status With Second-Generation Antipsychotics (N = 1,344 Infants)

Group	n	Prevalence of Malformations	Odds Ratio	95% CI
First trimester exposure to SGAs (n = 640)	16	2.50%	Adjusted: 1.483	0.625–3.517
			Unadjusted: 1.264	0.612–2.610
Unexposed to SGA (n = 704)	14	1.99%	…	…

Viguera et al 2021

Archives of Women's Mental Health
https://doi.org/10.1007/s00737-021-01115-6

ORIGINAL ARTICLE

Reproductive safety of aripiprazole: data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics

Marlene P. Freeman [1,2] · Adele C. Viguera [1,2,3] · Lina Góez-Mogollón [1] · Amanda V. Young [1] · Phoebe S. Caplin [1] · Sara A. McElheny [1] · Taylor R. Church [1] · David Chitayat [4] · Sonia Hernández-Díaz [5] · Lee S. Cohen [1,2]

Received: 9 November 2020 / Accepted: 12 February 2021

Table 2 Odds ratio comparing number of malformations among infants exposed to aripiprazole ($N = 163$) versus comparison group ($N = 704$)

Group	*N*	Prevalence	Odds ratio	95% CI
1st trimester exposure to arippirazole ($N=163$)	7	4.26%	Unadjusted: 2.212 adjusted 1.349	0.878, 5.571 0.433, 4.917
Unexposed to second-generation antipsychotic ($N=704$)	14	1.99%	-	-

Reproductive Safety of Lurasidone and Quetiapine

JOURNAL OF WOMEN'S HEALTH
Volume 00, Number 00, 2023

DOI: 10.1089/jwh.2022.0310

Open camera or QR reader and scan code to access this article and other resources online.

Reproductive Safety of Lurasidone and Quetiapine: Update from the National Pregnancy Registry for Psychiatric Medications

Lee S. Cohen, MD,[1] Taylor R. Church, BS,[1,2] Marlene P. Freeman, MD,[1] Peter Gaccione, MA,[1] Phoebe S. Caplin, BA,[1] Lauren A. Kobylski, MPH,[1] Miranda Arakelian, BA,[1] Ella T. Rossa, BA,[1] David Chitayat, MD,[3] Sonia Hernández-Díaz, MPH, DrPH,[4] and Adele C. Viguera, MD, MPH[1,5]

- Recent data based on women exposed to lurasidone (n=134) and quetiapine (n=264) compared to controls (n=886) do not suggest increased risk for major congenital malformations

Publications

https://womensmentalhealth.org/research/pregnancyregistry/

Towards a Model of Integrated Use of Real-World Evidence ((RWE for Reproductive Safety Data

- What is the model of integration of real-world data from varying sources with data from drug or disease-based pregnancy registries
- Ideal solutions using real-world evidence with respect to enhanced confidence regarding reproductive safety of medicines used by pregnant women

.

2024 State of Real-World Evidence Policy - Duke University

Event

2024 State of Real-World Evidence Policy

REGISTER

July 25, 2024 — 12:00PM–4:45PM

Virtual via Zoom

Contact Information
Luke Durocher

margolisevents@duke.edu

Materials

Agenda_2024 State of RWE Policy_7.24.24.pdf (127.27 KB)

Speaker Bios_2024 State of RWE Policy.pdf (642.65 KB)

Slide Deck_2024 State of Real-World.pdf (6.25 MB)

JOURNAL OF WOMEN'S HEALTH
Volume 00, Number 00, 2026
Mary Ann Liebert, A Part of Sage

DOI: 10.1177/15409996261444636

Opportunities and Challenges to Leveraging Real-World Data for Post-Market Safety Studies in Pregnancy and Lactation: Meeting Proceedings

Carla Rodriguez-Watson, PhD,[1] Kaylan Ware, MPH,[1] Joy C. Eckert, MPH,[1]
Leonardo Roque Pereira, PharmD, MSc,[2] Emily Bratton, PhD,[3] and Kristin Palmsten, ScD[4]

JAMA Psychiatry | Original Investigation

Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations

Krista F. Huybrechts, MS, PhD; Sonia Hernández-Díaz, MD, DrPH; Elisabetta Patorno, MD, DrPH; Rishi J. Desai, PhD; Helen Mogun, MS; Sara Z. Dejene, BS; Jacqueline M. Cohen, PhD; Alice Panchaud, PhD; Lee Cohen, MD; Brian T. Bateman, MD, MSc

JAMA Psychiatry. 2016;73(9):938-946. doi:10.1001/jamapsychiatry.2016.1520
Published online August 17, 2016.

- Primary aim: determine the risk of major malformations among infants exposed to atypical antipsychotics
- Examined Medicaid claim data from 1,341,715 pregnancies
- After adjustment for confounding, the risk ratio for congenital malformation in exposed versus unexposed infants was 1.05 (95% CI=0.96-1.16)
- A slightly increased risk in overall and cardiac malformations was noted for risperidone

Molecular Psychiatry

www.nature.com/mp

IMMEDIATE COMMUNICATION OPEN

Check for updates

Sterol pathway disruption in pregnancy: a link to autism

Eric S. Peeples[1,2,3], A. Jerrod Anzalone[3,4], Ran Dai[4], Elizabeth Reisher[3,5], Zeljka Korade[1,3,6] and Karoly Mirnics[1,3,7]✉

Research

JAMA Pediatrics | Original Investigation

Risk for Autism Spectrum Disorders According to Period of Prenatal Antidepressant Exposure

A Systematic Review and Meta-analysis

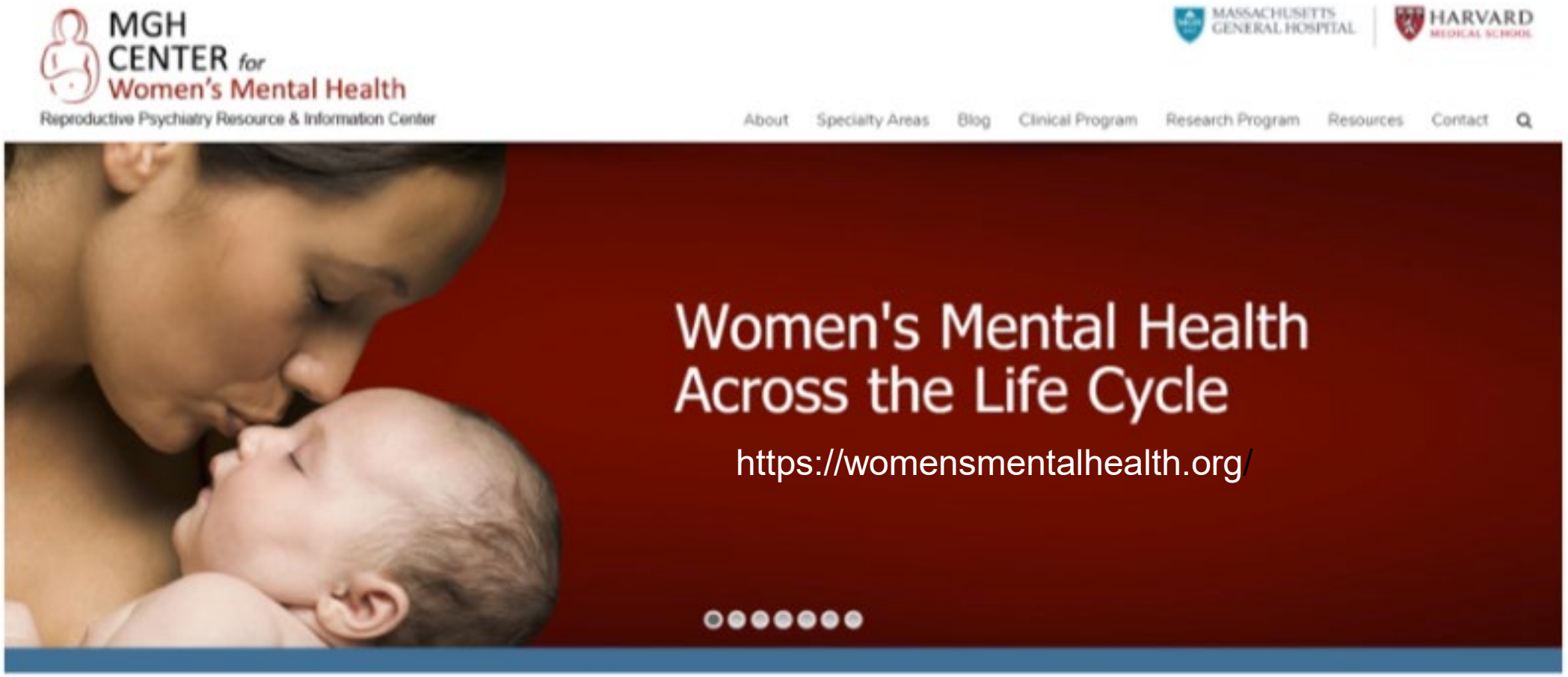
Antonia Mezzacappa, MD; Pierre-Alexandre Lasica; Francesco Gianfagna, MD, PhD; Odile Cazas, MD; Patrick Hardy, MD, PhD; Bruno Falissard, MD, PhD; Anne-Laure Sutter-Dallay, MD, PhD; Florence Gressier, MD, PhD

JAMA Pediatr. 2017;171(6):555-563. doi:10.1001/jamapediatrics.2017.0124
Published online April 17, 2017.

MGH National Pregnancy Registry for Psychiatric Medications: Lessons Learned

- Patients are using a growing number of medications to treat psychiatric disorder across therapeutic classes
- Rigorously derived reproductive safety data inform the risk/benefit decision regarding use of psychiatric medications before, during and after pregnancy
- Recruitment strategies for those patients using medications with sparse reproductive safety data need to be optimized
- Use of modern technology including AI may accelerate our ability to gather reproductive safety data from multiple sources including Pregnancy Registries.

Thank you


MGH
CENTER for
Women's Mental Health
Reproductive Psychiatry Resource & Information Center
MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL
About
Specialty Areas
Blog
Clinical Program
Research Program
Resources
Contact
Women's Mental Health
Across the Life Cycle
https://womensmentalhealth.org/

U.S. FOOD & DRUG ADMINISTRATION

BREAK

Industry Perspective

Keele Wurst PhD MS RPh, GSK, Head of Immunology and Fibrosis Epidemiology

GSK

Disclosure

Keele Wurst is employed by and is a shareholder of GSK.

Pregnant women need information

- **Challenging** for **pregnant** and **breastfeeding** women to make **informed** healthcare **decisions**
- **Critical information** specific to them is often **not available**

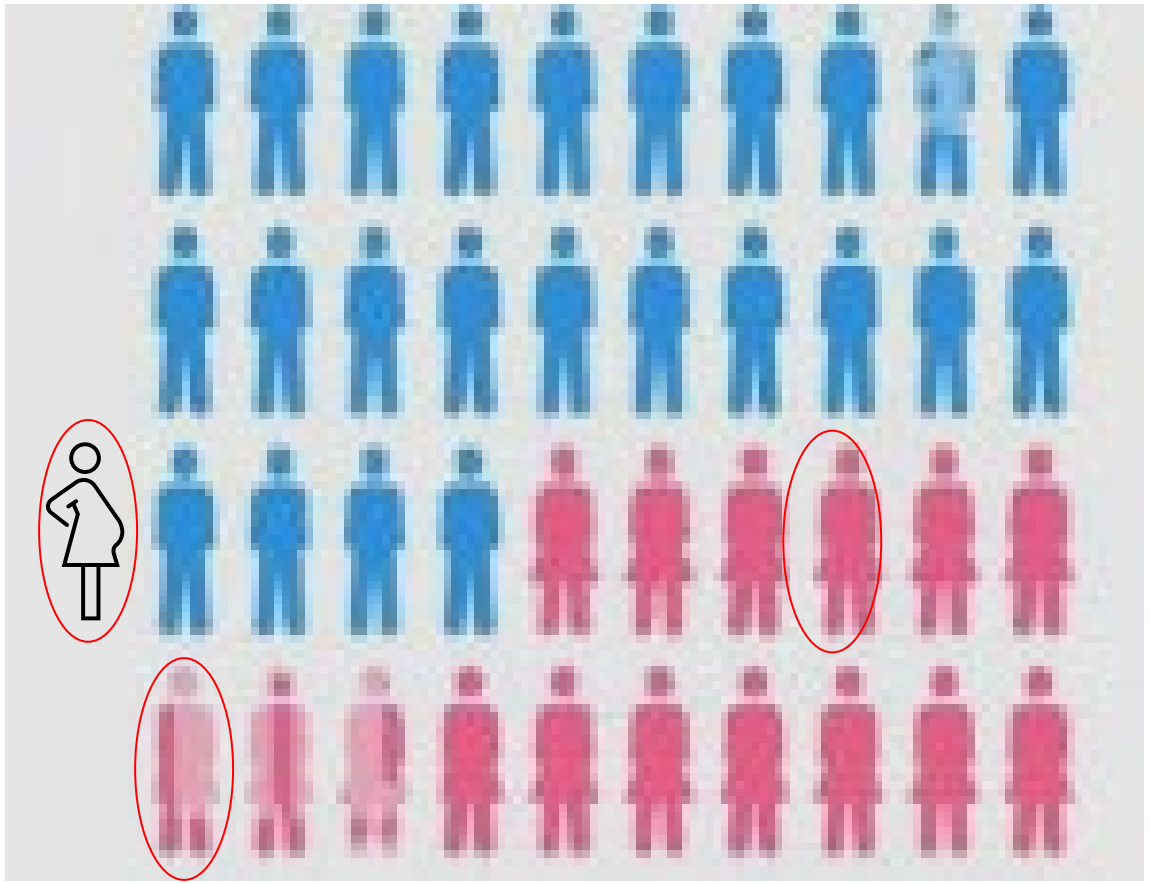
GSK

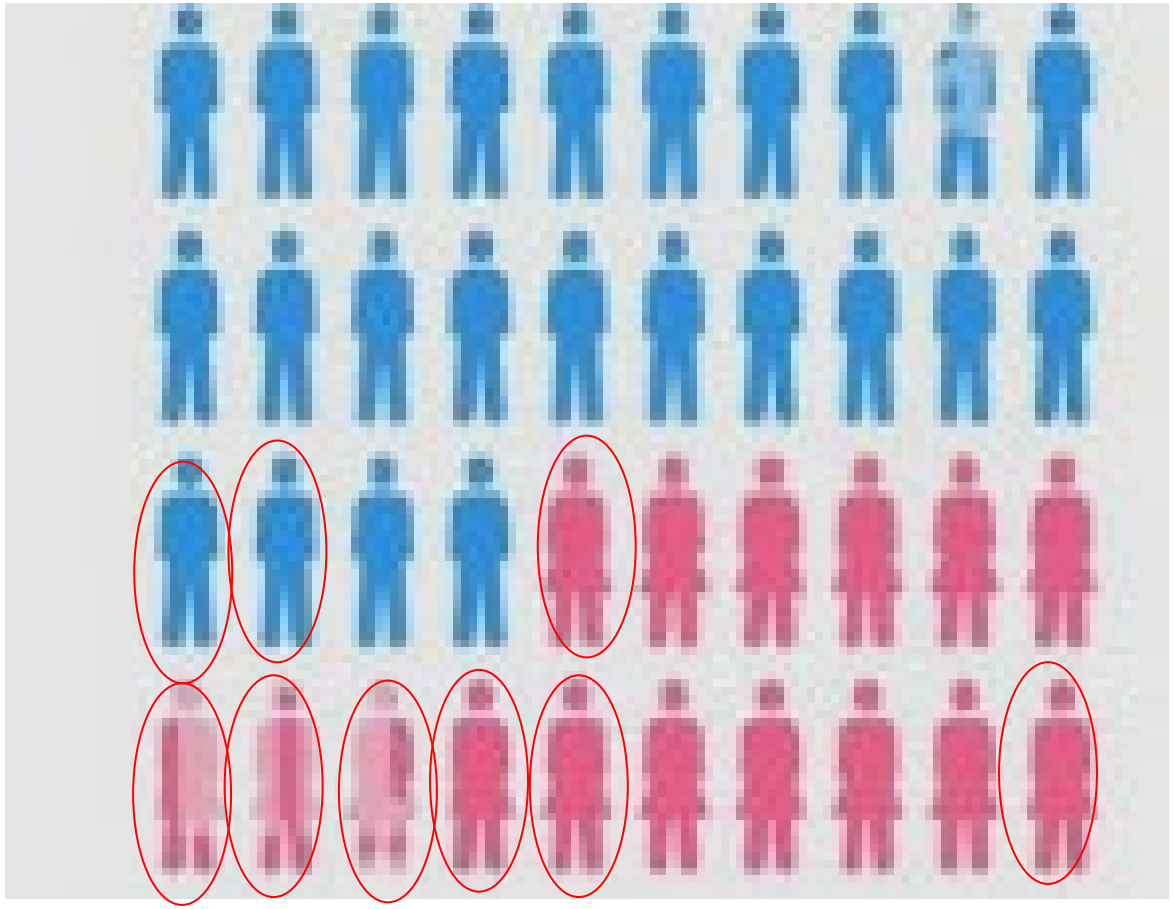
Industry Challenges

- Uptake of Medication/Vaccine
- Characteristics and disease state
- Multiple sources of data with different data collection methods and quality
- Differing regulations and post-marketing commitments across geographies
- Need for appropriate comparison group and sample size for analytics

GSK

Unknown uptake of a medication or vaccine





GSK

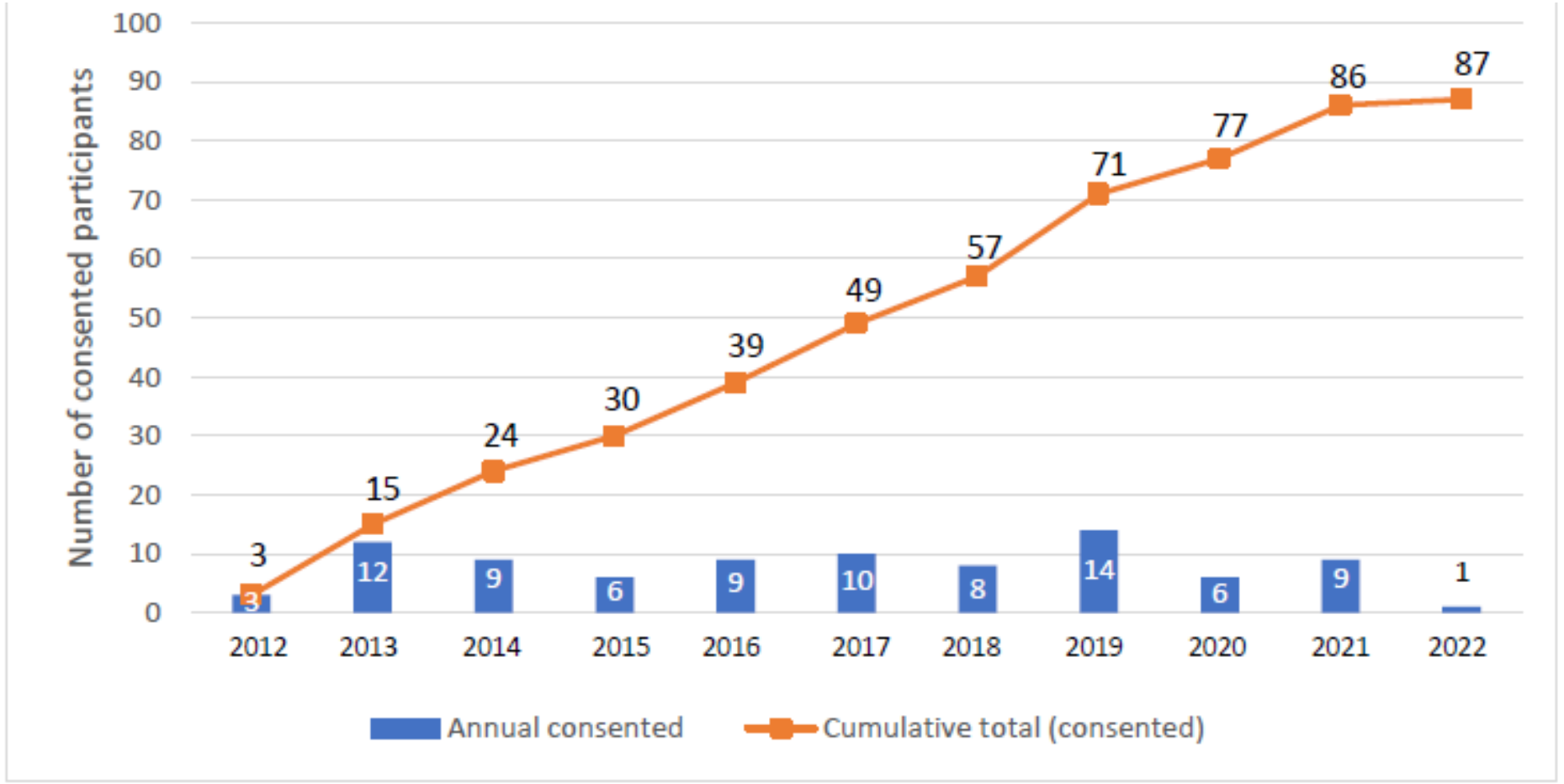
Usage in Clinical Practice

Characteristics of people taking the medicine or vaccine

- Prescriptions (e.g., medications, vaccines)
- Vitamins
- Over the counter medications
- Demographics (e.g., age, obesity)
- Behavior (e.g., smoking, alcohol)
- Medical conditions (e.g. diabetes)
- Disease severity

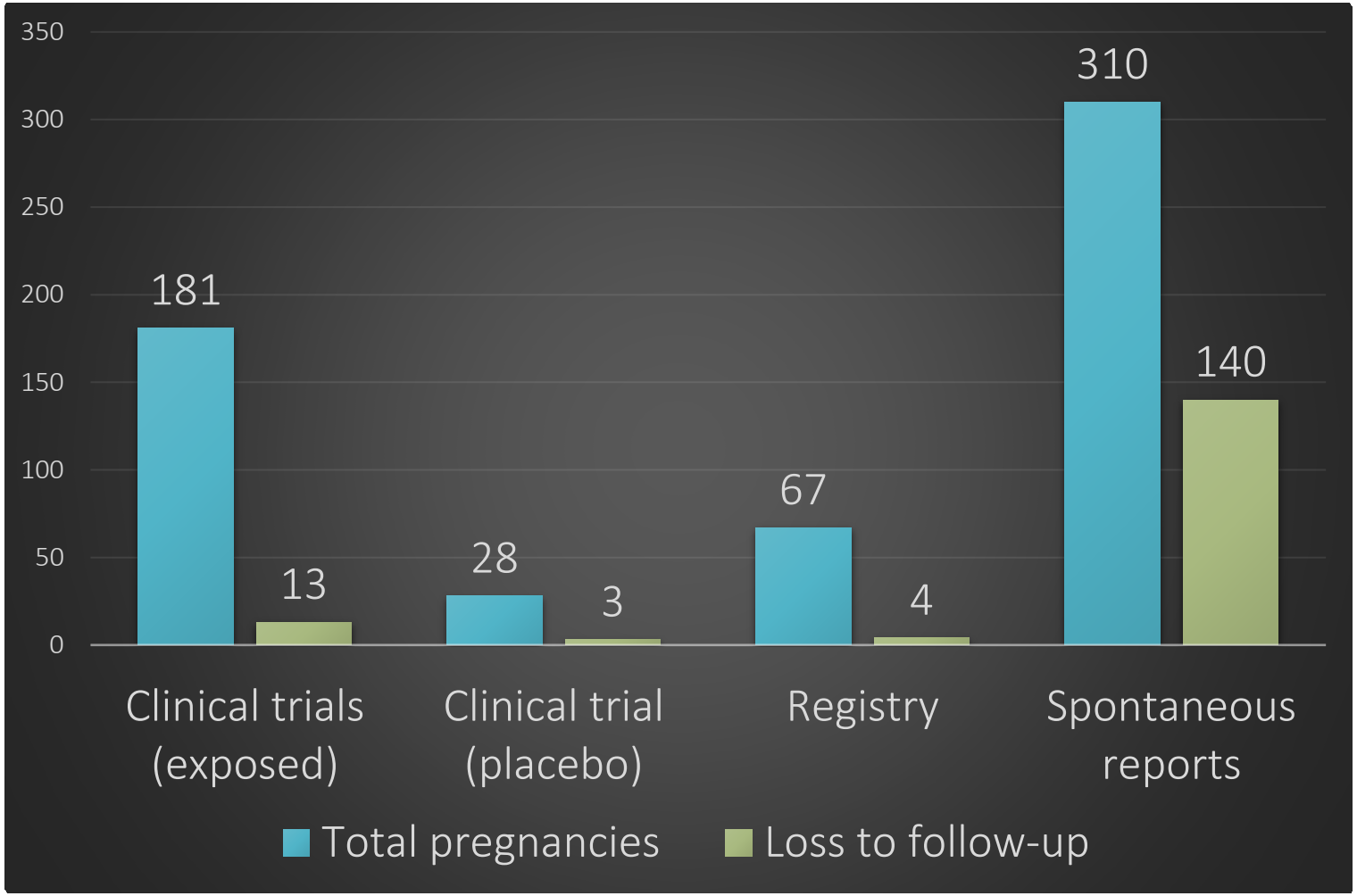
GSK

It takes time to generate prospectively collected data



Pregnancy exposures captured in multiple data sources

Summary of Benlysta exposed pregnancies recorded in clinical trials, registry and spontaneous reports (2012-2020)



Petri M, Landy H, Clowse MEB, *et al*. *Annals of the Rheumatic Diseases* 2023;82:217-225 (19 clinical trials n~10,000).

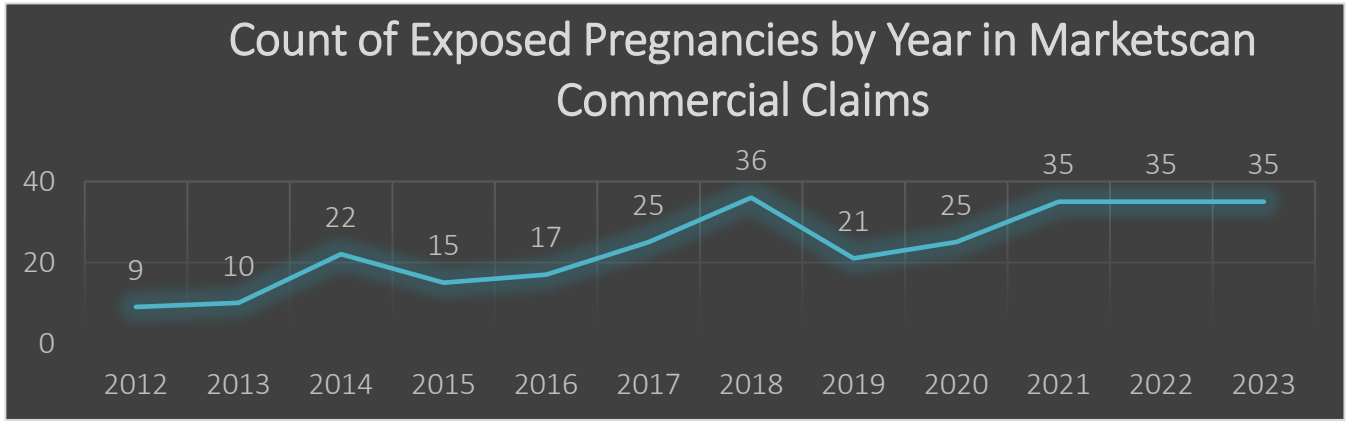
Real-world data exposure rates (2012-2023)

- 10,192 enrollees with exposure aged 15+
- 9,493 women with exposure
- 6,904 women aged 15-50 with exposure
- 776 women aged 15-50 with exposure and a pregnancy
- **177 women exposed during a pregnancy**

177 women exposed during a pregnancy

Trimester 1	Trimester 2	Trimester 3
Exposure: 151 women (85.31%)	Exposure: 90 women (50.85%)	Exposure: 62 (35.03%)

154 women had concomitant medication use

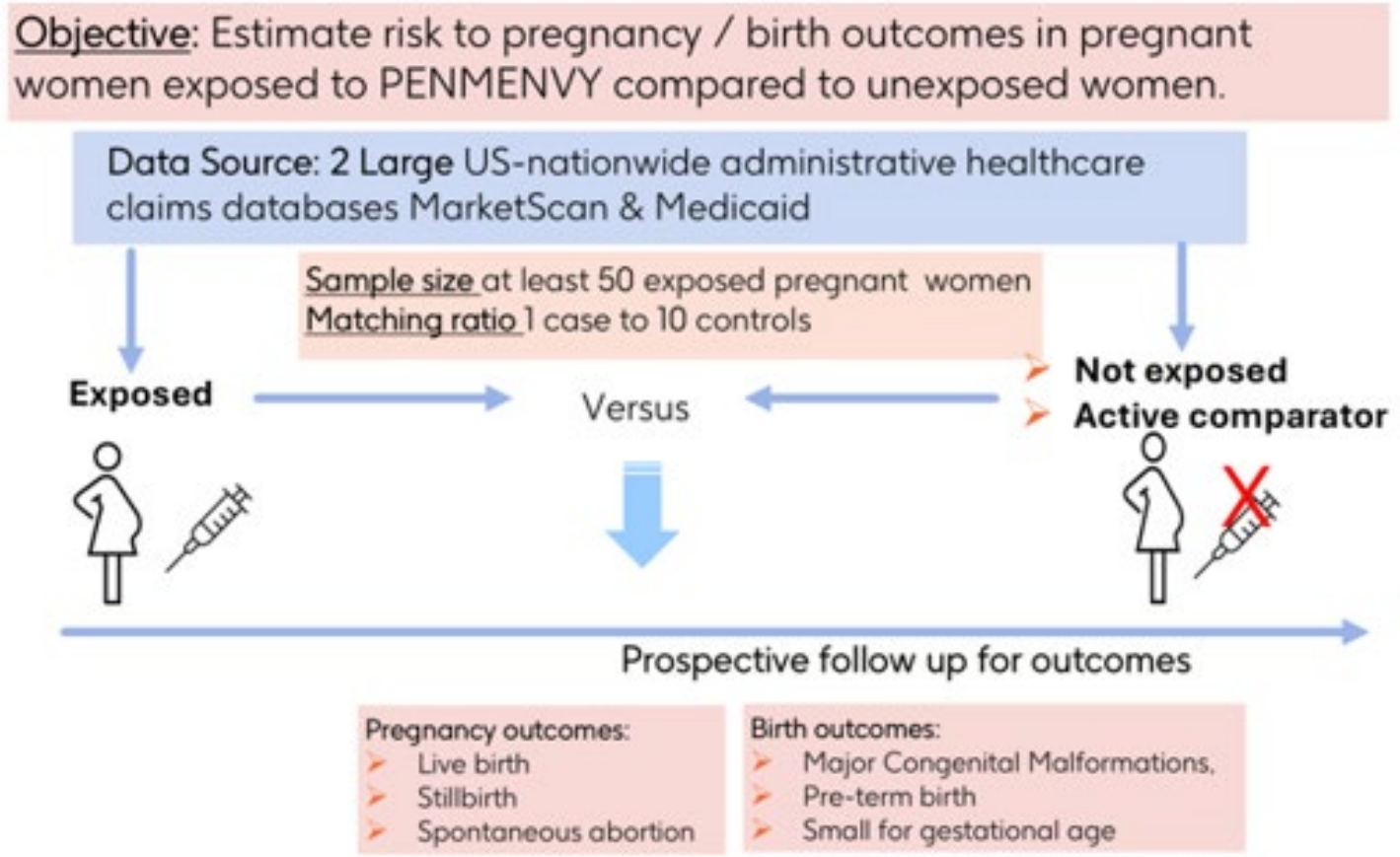


Note: Pregnancies can occur across multiple years so does not add up to 177

Marketscan Commercial ~200million covered at any time

GSK

Real world data pregnancy registry: A Pregnancy and Birth Outcomes Study After Exposure to PENMENVY Vaccine in the US: A Cohort Study



Projects - H4P

A stepwise approach is needed

Descriptive (utilization and characterization)

Analytic approaches with an appropriate comparison group

GSK

Perspective and challenges are similar across industry

Transcelerate BioPharma Industry survey results

Fernandes MFS, Alexe A et al. Ther Innov Regul Sci. 2025

Therapeutic Innovation & Regulatory Science (2025) 59:527–541
https://doi.org/10.1007/s43441-025-00764-4

REVIEW

Post-approval Activities Providing Data on the Safety of Medication Use During Pregnancy and Lactation—A TransCelerate Perspective

Maria Fernanda Scantamburlo Fernandes[1] · Amalia Alexe[2] · Olatayo Apara[3] · Lindsey Force[4] · Christine Ta Maria Weber[6] · Keele Wurst[7] · Nadezda Abramova[8] · Anju Garg[9] · Leesha Balramsingh-Harry[10] · Jessica Mårlind Würtele[11]

Received: 18 October 2024 / Accepted: 27 February 2025 / Published online: 16 March 2025

Abstract

Pregnant and lactating women are frequently excluded from clinical trials, leading to a significant global unmet nc data regarding medication use in this population. Post-approval safety activities on pregnancy and lactation a the main sources of information for product labeling to guide clinical practice. However, generating this infc take years, and the data often remains insufficient for healthcare providers and patients to make informed deci the differences in regulatory guidance on this issue and the evolving perspectives on the most appropriate ty approval activities on pregnancy and lactation, TransCelerate BioPharma conducted a survey of its member phi companies to evaluate common post-approval practices over the past 11 years. All survey participants reported post-approval activities on pregnancy, citing pregnancy registries as the most common type of activity, followed studies and enhanced pharmacovigilance. These activities resulted in outcomes, including updates to the prescrib tion, however these materialized after many years. Conversely, fewer post-approval activities on lactation were with limited impact on outcomes reported to date. These results emphasize the need for a comprehensive, n approach using a wide array of data sources for effective and timely post-approval surveillance to characterize use during pregnancy and lactation.

Keywords Post-approval safety activities · Post-approval surveillance · Medication use · Pregnancy · Lactation TransCelerate survey

Transcelerate Survey: Post-approval Activities Focused on Data Generation in Pregnancy

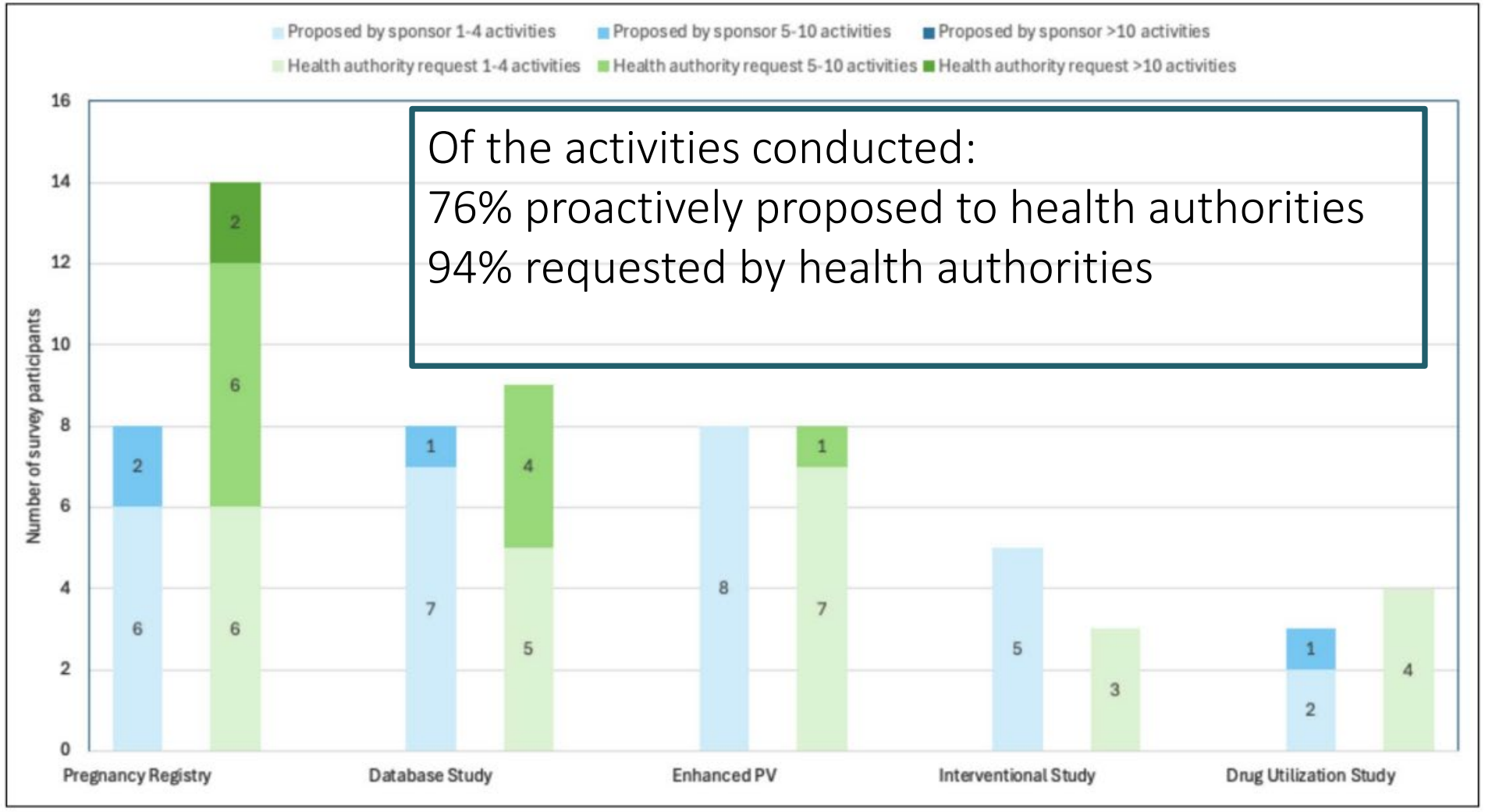


Figure 5. Types of post-approval activities on pregnancy: proposed by Sponsor/MAH vs requested by HAs.

Fernandes MFS, Alexe A et al. Ther Innov Regul Sci. 2025

It takes time to generate data

Time intervals between initial marketing authorization and package insert modification from the 29% that reported a modification of pregnancy labelling

- 50% reported between 5 and 10 years
- 50% reported time greater than 10 years

Fernandes MFS, Alexe A et al. Ther Innov Regul Sci. 2025

Transcelerate Survey: Post-approval Activity Results

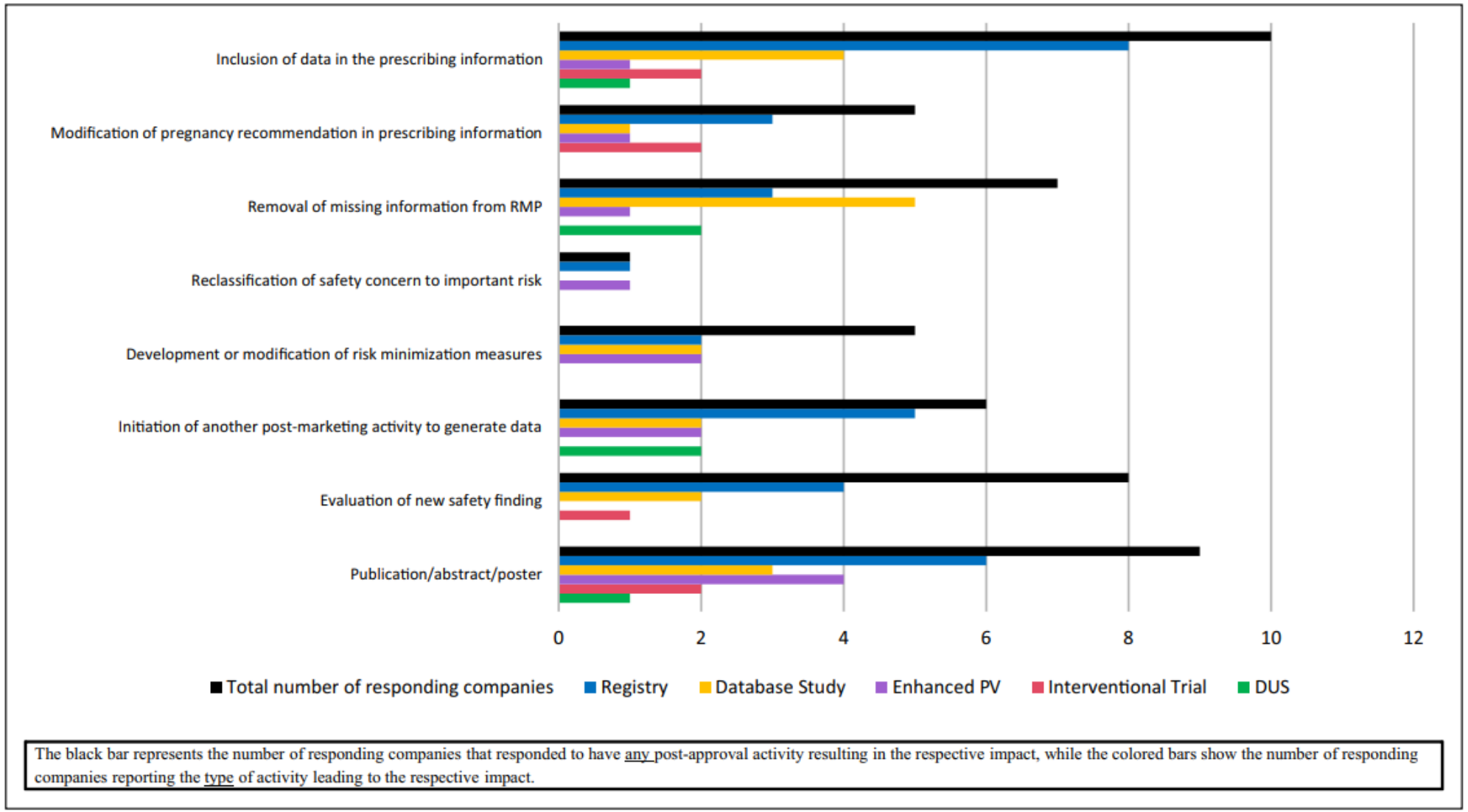
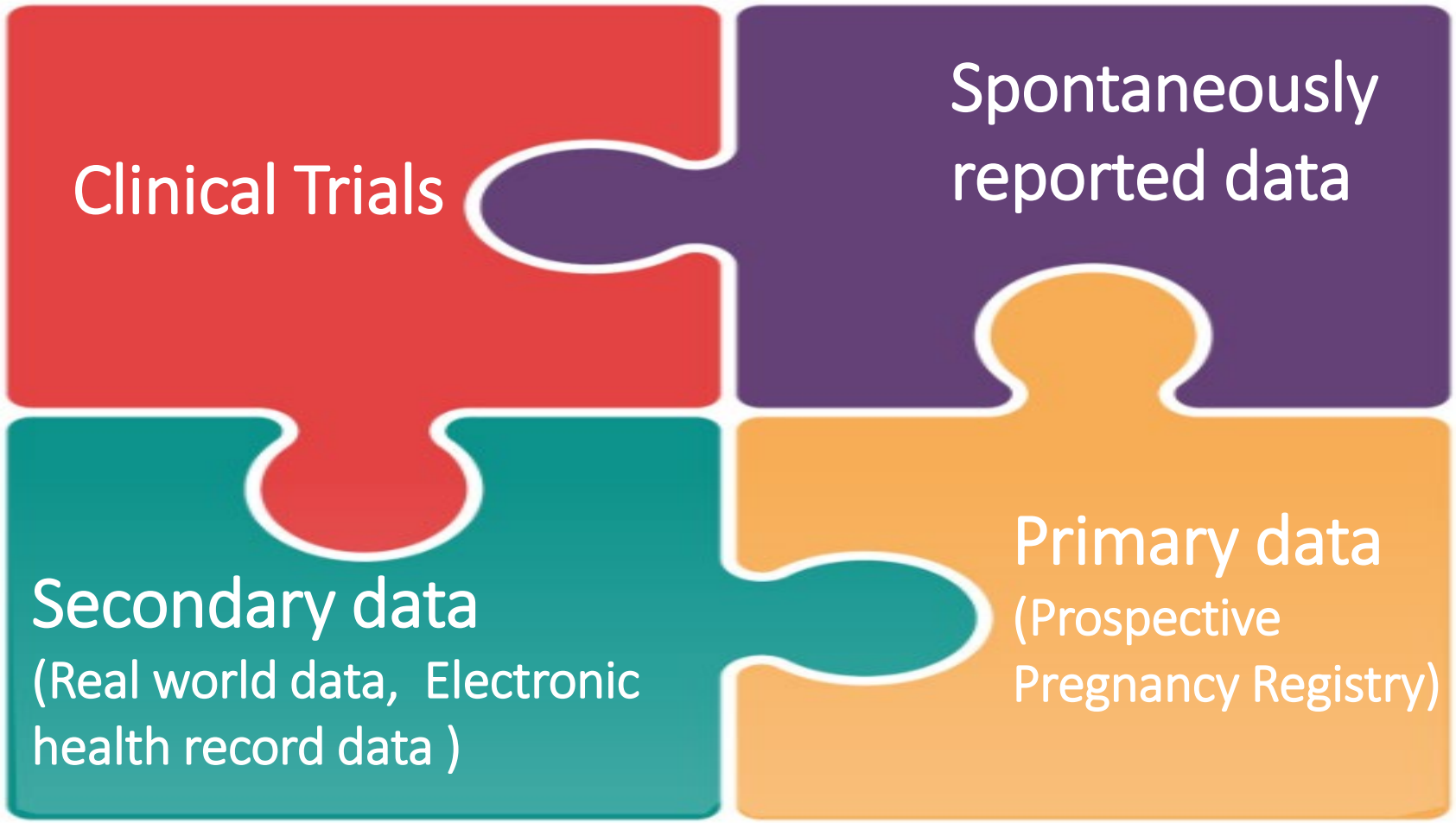


Figure 7. Impact of post-approval activities on pregnancy (proposed by Sponsor/MAH and requested by HAs).

Fernandes MFS, Alexe A et al. Ther Innov Regul Sci. 2025

Robust post-approval safety and effectiveness monitoring system



Introduction to Multi-Product Pregnancy Registries: Antiretroviral Pregnancy Registry

Jessica Albano, PhD MPH

Optimizing Pregnancy Registries
FDA Public Workshop | May 7-8, 2026

EPIPHANY
REAL-WORLD RESEARCH

Disclosures

- I serve as Pharmacoepidemiology Consultant and Advisory Committee Member to the APR; my opinions are my own.

Opening Remarks

- Non-consolidated registry efforts at the individual drug level are inefficient and costly endeavors that are unlikely to produce robust results in a timely manner leaving women and their physicians without the critical data they need to make informed decisions about their care.
- Trust is paramount and this requires transparency as well as oversight by an independent advisory committee.
- The impact of consistently reported and publicly available findings are compounded when standardized methods are employed, and results are comparable and generalizable.
- Awareness efforts are never enough and overcoming perceptions of participation barriers takes constant tending.

Background:

Multi-product / Multi-sponsor – Disease-based registries

Challenges

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

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

Communication
- Respect established lines of communication
- Documentation is critical

Competition
- Innovator companies set-up and implement

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

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

Advantages

Logical
- Avoid duplicated efforts
- Reduces population overlap

Economical
- Pool resources and budgets from multiple stakeholders

Efficient
- Minimize health care provider burden
- Consolidated KOL/SME expertise

Recruitment
- Reduced competition
- More robust awareness
- Increase incentive to participate

Methodological
- Standardized data collection, assessments and analysis
- Increased validity and power

Consistency
- Coherent assessment of available data
- Centralized message safety/risk profile

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

Introduction: Antiretroviral Pregnancy Registry

Lessons Learnt

- Growth is good (but complicated)
- Various levels of engagement is OK
- Keep it simple (and document meticulously)
- Minimize changes (but be proactive and innovate)
- Actively monitor data
- Engage stakeholders
- Ensure streamlined communication of findings (and disseminate widely)

Received: 22 November 2023 | Revised: 22 March 2024 | Accepted: 8 April 2024
DOI: 10.1002/pds.5801

WILEY

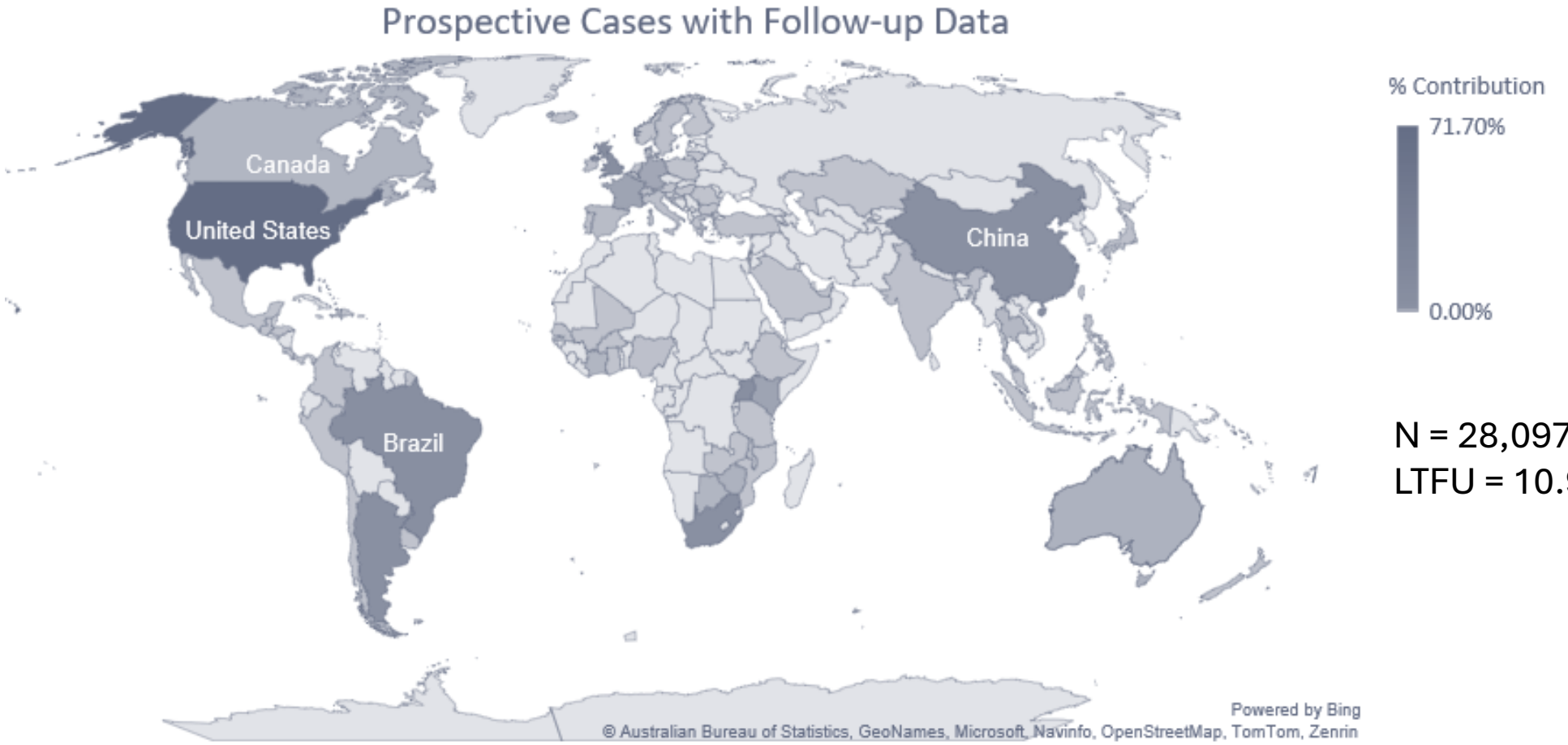
ORIGINAL ARTICLE

The Antiretroviral Pregnancy Registry: Three decades of prospective monitoring for birth defects

Jessica D. Albano[1] | Angela E. Scheuerle[2] | D. Heather Watts[3] | Karen P. Beckerman[4] | Lynne M. Mofenson[5] | Andreas Pikis[6] | Vani Vannappagari[7] | Daniel Seekins[8] | Taylor S. Cook[1] | Hugh Tilson[9] | Antiretroviral Pregnancy Registry Steering Committee

Albano, et al. Pharmacoepidemiol Drug Saf 2024;33(6):e5801.

APR: Enrollment



N = 28,097
LTFU = 10.9%

APR Steering Committee. Interim Report; 2025.

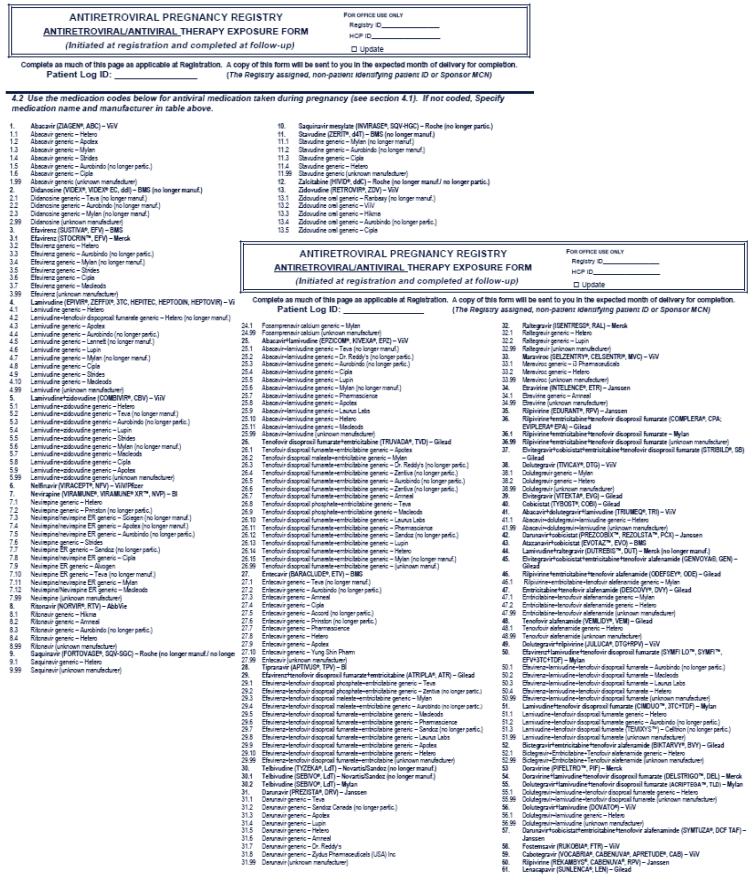
APR: Products & Manufacturers

Monitored Drugs

- 61 brand
- 174 generic

Indications

- HIV treatment
- HIV prevention
  - PrEP
  - PEP
- HBV



ANTIRETROVIRAL PREGNANCY REGISTRY

ANTIRETROVIRAL/ANTIVIRAL THERAPY EXPOSURE FORM

(Initiated at registration and completed at follow-up)

FOR OFFICE USE ONLY
Registry ID:_____
HCP ID:_____
☐ Update

Complete as much of this page as applicable at Registration. A copy of this form will be sent to you in the expected month of delivery for completion.
Patient Log ID: _____ *(The Registry assigned, non-patient identifying patient ID or Sponsor MCN)*

4.2 Use the medication codes below for antiviral medication taken during pregnancy (see section 4.1). If not coded, Specify medication name and manufacturer in table above.

1. Abacavir (ZIAGEN®, ABC) – ViiV
1.1 Abacavir generic – Hetero
1.2 Abacavir generic – Apotex
1.3 Abacavir generic – Mylan
1.4 Abacavir generic – Strides
1.5 Abacavir generic – Aurobindo (no longer partic.)
1.6 Abacavir generic – Cipla
1.99 Abacavir generic (unknown manufacturer)
2. Didanosine (VIDEX®, VIDEX® EC, ddI) – BMS (no longer manuf.)
2.1 Didanosine generic – Teva (no longer manuf.)
2.2 Didanosine generic – Aurobindo (no longer manuf.)
2.3 Didanosine generic – Mylan (no longer manuf.)
2.99 Didanosine (unknown manufacturer)
3. Efavirenz (SUSTIVA®, EFV) – BMS
3.1 Efavirenz (STOCRIN™, EFV) – Merck
3.2 Efavirenz generic – Hetero
3.3 Efavirenz generic – Aurobindo (no longer partic.)
3.4 Efavirenz generic – Mylan (no longer manuf.)
3.5 Efavirenz generic – Strides
3.6 Efavirenz generic – Cipla
3.7 Efavirenz generic – Macleods
3.99 Efavirenz (unknown manufacturer)
4. Lamivudine (EPIVIR®, ZEFFIX®, 3TC, HEPITEC, HEPTODIN, HEPTOVIR) – Vi
4.1 Lamivudine generic – Hetero
4.2 Lamivudine+tenofovir disoproxil fumarate generic – Hetero (no longer manuf.)
4.3 Lamivudine generic – Apotex
4.6 Lamivudine generic – Aurobindo (no longer partic.)
4.9 Lamivudine generic – Lannett (no longer manuf.)
4.6 Lamivudine generic – Lupin
4.7 Lamivudine generic – Mylan (no longer manuf.)
4.8 Lamivudine generic – Cipla
4.9 Lamivudine generic – Strides
4.10 Lamivudine generic – Macleods
4.99 Lamivudine (unknown manufacturer)
5. Lamivudine+zidovudine (COMBIVIR®, CBV) – ViiV
5.1 Lamivudine+zidovudine generic – Hetero
5.2 Lamivudine+zidovudine generic – Teva (no longer manuf.)
5.3 Lamivudine+zidovudine generic – Aurobindo (no longer partic.)
5.4 Lamivudine+zidovudine generic – Lupin
5.5 Lamivudine+zidovudine generic – Strides
5.6 Lamivudine+zidovudine generic – Mylan (no longer manuf.)
5.7 Lamivudine+zidovudine generic – Macleods
5.8 Lamivudine+zidovudine generic – Cipla
5.9 Lamivudine+zidovudine generic – Apotex
5.99 Lamivudine+zidovudine generic (unknown manufacturer)
6. Nelfinavir (VIRACEPT®, NFV) – ViiV/Pfizer
7. Nevirapine (VIRAMUNE®, VIRAMUNE® XR™, NVP) – BI
7.1 Nevirapine generic – Hetero
7.2 Nevirapine generic – Prinston (no longer partic.)
7.3 Nevirapine/nevirapine ER generic – Sciegen (no longer manuf.)
7.4 Nevirapine/nevirapine ER generic – Apotex (no longer manuf.)
7.5 Nevirapine/nevirapine ER generic – Aurobindo (no longer partic.)
7.6 Nevirapine generic – Strides
7.7 Nevirapine/nevirapine ER generic – Sandoz (no longer partic.)
7.8 Nevirapine/nevirapine ER generic – Cipla
7.9 Nevirapine/nevirapine ER generic – Alvogen
7.10 Nevirapine ER generic – Teva (no longer manuf.)
7.11 Nevirapine/nevirapine ER generic – Mylan
7.12 Nevirapine/Nevirapine ER generic – Macleods
7.99 Nevirapine (unknown manufacturer)
8. Ritonavir (NORVIR®, RTV) – AbbVie
8.1 Ritonavir generic – Hikma
8.2 Ritonavir generic – Amneal
8.3 Ritonavir generic – Aurobindo (no longer partic.)
8.4 Ritonavir generic – Hetero
8.99 Ritonavir (unknown manufacturer)
9. Saquinavir (FORTOVASE®, SQV-SGC) – Roche (no longer manuf./ no longer
9.1 Saquinavir generic – Hetero
9.99 Saquinavir (unknown manufacturer)
10. Saquinavir mesylate (INVIRASE®, SQV-HGC) – Roche (no longer partic.)
11. Stavudine (ZERIT®, d4T) – BMS (no longer manuf.)
11.1 Stavudine generic – Mylan (no longer manuf.)
11.2 Stavudine generic – Aurobindo (no longer manuf.)
11.3 Stavudine generic – Cipla
11.4 Stavudine generic – Hetero
11.99 Stavudine generic (unknown manufacturer)
12. Zalcitabine (HIVID®, ddC) – Roche (no longer manuf./ no longer partic.)
13. Zidovudine (RETROVIR®, ZDV) – ViiV
13.1 Zidovudine oral generic – Ranbaxy (no longer manuf.)
13.2 Zidovudine oral generic – ViiV
13.3 Zidovudine oral generic – Hikma
13.4 Zidovudine oral generic – Aurobindo (no longer partic.)
13.5 Zidovudine oral generic – Cipla

ANTIRETROVIRAL PREGNANCY REGISTRY

ANTIRETROVIRAL/ANTIVIRAL THERAPY EXPOSURE FORM

(Initiated at registration and completed at follow-up)

FOR OFFICE USE ONLY
Registry ID:_____
HCP ID:_____
☐ Update

Complete as much of this page as applicable at Registration. A copy of this form will be sent to you in the expected month of delivery for completion.
Patient Log ID: _____ *(The Registry assigned, non-patient identifying patient ID or Sponsor MCN)*

24.1 Fosamprenavir calcium generic – Mylan
24.99 Fosamprenavir calcium (unknown manufacturer)
25. Abacavir+lamivudine (EPZICOM®, KIVEXA®, EPZ) – ViiV
25.1 Abacavir+lamivudine generic – Teva (no longer manuf.)
25.2 Abacavir+lamivudine generic – Dr. Reddy's (no longer partic.)
25.3 Abacavir+lamivudine generic – Aurobindo (no longer partic.)
25.4 Abacavir+lamivudine generic – Cipla
25.5 Abacavir+lamivudine generic – Lupin
25.6 Abacavir+lamivudine generic – Mylan (no longer manuf.)
25.7 Abacavir+lamivudine generic – Pharmascience
25.8 Abacavir+lamivudine generic – Apotex
25.9 Abacavir+lamivudine generic – Laurus Labs
25.10 Abacavir+lamivudine generic – Hetero
25.11 Abacavir+lamivudine generic – Macleods
25.99 Abacavir+lamivudine (unknown manufacturer)
26. Tenofovir disoproxil fumarate+emtricitabine (TRUVADA®, TVD) – Gilead
26.1 Tenofovir disoproxil fumarate+emtricitabine generic – Apotex
26.2 Tenofovir disoproxil maleate+emtricitabine generic – Mylan
26.3 Tenofovir disoproxil fumarate+emtricitabine generic – Dr. Reddy's (no longer partic.)
26.4 Tenofovir disoproxil fumarate+emtricitabine generic – Zentiva (no longer partic.)
26.5 Tenofovir disoproxil fumarate+emtricitabine generic – Aurobindo (no longer partic.)
26.6 Tenofovir disoproxil fumarate+emtricitabine generic – Zentiva (no longer partic.)
26.7 Tenofovir disoproxil fumarate+emtricitabine generic – Amneal
26.8 Tenofovir disoproxil phosphate+emtricitabine generic – Teva
26.9 Tenofovir disoproxil phosphate+emtricitabine generic – Macleods
26.10 Tenofovir disoproxil fumarate+emtricitabine generic – Laurus Labs
26.11 Tenofovir disoproxil fumarate+emtricitabine generic – Pharmascience
26.12 Tenofovir disoproxil fumarate+emtricitabine generic – Sandoz (no longer partic.)
26.13 Tenofovir disoproxil fumarate+emtricitabine generic – Lupin
26.14 Tenofovir disoproxil fumarate+emtricitabine generic – Hetero
26.15 Tenofovir disoproxil fumarate+emtricitabine generic – Mylan (no longer manuf.)
26.99 Tenofovir disoproxil fumarate+emtricitabine generic – (unknown manuf.)
27. Emtricitabir (BARACLUDE®, ETV) – BMS
27.1 Entecavir generic – Teva (no longer manuf.)
27.2 Entecavir generic – Aurobindo (no longer partic.)
27.3 Entecavir generic – Amneal
27.4 Entecavir generic – Cipla
27.5 Entecavir generic – Accord (no longer partic.)
27.6 Entecavir generic – Prinston (no longer partic.)
27.7 Entecavir generic – Pharmascience
27.8 Entecavir generic – Hetero
27.9 Entecavir generic – Apotex
27.10 Entecavir generic – Yung Shin Pharm
27.99 Entecavir (unknown manufacturer)
28. Tipranavir (APTIVUS®, TPV) – B
29. Efavirenz+tenofovir disoproxil fumarate+emtricitabine (ATRIPLA®, ATR) – Gilead
29.1 Efavirenz+tenofovir disoproxil phosphate+emtricitabine generic – Teva
29.2 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Zentiva (no longer partic.)
29.3 Efavirenz+tenofovir disoproxil maleate+emtricitabine generic – Mylan
29.4 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Aurobindo (no longer partic.)
29.5 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Macleods
29.6 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Pharmascience
29.7 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Sandoz (no longer partic.)
29.8 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Laurus Labs
29.9 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Apotex
29.10 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Hetero
29.99 Efavirenz+tenofovir disoproxil fumarate+emtricitabine (unknown manufacturer)
30. Telbivudine (TYZEKA®, LdT) – Novartis/Sandoz (no longer manuf.)
30.1 Telbivudine (SEBIVO®, LdT) – Novartis/Sandoz (no longer manuf.)
30.2 Telbivudine (SEBIVO®, LdT) – Mylan
31. Darunavir (PREZISTA®, DRV) – Janssen
31.1 Darunavir generic – Teva
31.2 Darunavir generic – Sandoz Canada (no longer partic.)
31.3 Darunavir generic – Apotex
31.4 Darunavir generic – Lupin
31.5 Darunavir generic – Hetero
31.6 Darunavir generic – Amneal
31.7 Darunavir generic – Dr. Reddy's
31.8 Darunavir generic – Zydus Pharmaceuticals (USA) Inc
31.99 Darunavir (unknown manufacturer)
32. Raltegravir (ISENTRESS®, RAL) – Merck
32.1 Raltegravir generic – Hetero
32.2 Raltegravir generic – Lupin
32.99 Raltegravir (unknown manufacturer)
33. Maraviroc (SELZENTRY®, CELSENTRI®, MVC) – ViiV
33.1 Maraviroc generic – D Pharmaceuticals
33.2 Maraviroc generic – Hetero
33.99 Maraviroc (unknown manufacturer)
34. Etravirine (INTELENCE®, ETR) – Janssen
34.1 Etravirine generic – Amneal
34.99 Etravirine (unknown manufacturer)
35. Rilpivirine (EDURANT®, RPV) – Janssen
36. Rilpivirine fumaric+tenofovir disoproxil fumarate (COMPLERA®, CPA; EVIPLERA® EPA) – Gilead
36.1 Rilpivirine fumaric+tenofovir disoproxil fumarate – Mylan
36.99 Rilpivirine fumaric+tenofovir disoproxil fumarate (unknown manufacturer)
37. Elvitegravir+cobicistat+emtricitabine+tenofovir disoproxil fumarate (STRIBILD®, SB) – Gilead
38. Dolutegravir (TIVICAY®, DTG) – ViiV
38.1 Dolutegravir generic – Mylan
38.2 Dolutegravir generic – Hetero
38.99 Dolutegravir (unknown manufacturer)
39. Elvitegravir (VITEKTA®, EVG) – Gilead
40. Cobicistat (TYBOST®, COB) – Gilead
41. Abacavir+dolutegravir+lamivudine (TRIUMEQ®, TRI) – ViiV
41.1 Abacavir+dolutegravir+lamivudine generic – Hetero
41.99 Abacavir+dolutegravir+lamivudine (unknown manufacturer)
42. Darunavir+cobicistat (PREZCOBIX™, REZOLSTA™, PCX) – Janssen
43. Atazanavir+cobicistat (EVOTAZ™, EVO) – BMS
44. Lamivudine+Raltegravir (DUTREBIS™, DUT) – Merck (no longer manuf.)
45. Elvitegravir+cobicistat+emtricitabine+tenofovir alafenamide (GENVOYA®, GEN) – Gilead
46. Rilpivirine fumaric+tenofovir alafenamide (ODEFSEY®, ODE) – Gilead
46.1 Rilpivirine+emtricitabine+tenofovir alafenamide generic – Mylan
47. Emtricitabine+tenofovir alafenamide (DESCOVY®, DVY) – Gilead
47.1 Emtricitabine+tenofovir alafenamide generic – Mylan
47.2 Emtricitabine+tenofovir alafenamide generic – Hetero
47.99 Emtricitabine+tenofovir alafenamide (unknown manufacturer)
48. Tenofovir alafenamide (VEMLIDY®, VEM) – Gilead
48.1 Tenofovir alafenamide generic – Hetero
48.99 Tenofovir alafenamide (unknown manufacturer)
49. Dolutegravir+rilpivirine (JULUCA®, DTG+RPV) – ViiV
50. Efavirenz+lamivudine+tenofovir disoproxil fumarate (SYMFI LO™, SYMFI™, EFV/3TC/TDF) – Mylan
50.1 Efavirenz+lamivudine+tenofovir disoproxil fumarate – Aurobindo (no longer partic.)
50.2 Efavirenz+lamivudine+tenofovir disoproxil fumarate – Macleods
50.3 Efavirenz+lamivudine+tenofovir disoproxil fumarate – Laurus Labs
50.4 Efavirenz+lamivudine+tenofovir disoproxil fumarate – Hetero
50.99 Efavirenz+lamivudine+tenofovir disoproxil fumarate (unknown manufacturer)
51. Lamivudine+tenofovir disoproxil fumarate (CIMDUO™, 3TC+TDF) – Mylan
51.1 Lamivudine+tenofovir disoproxil fumarate generic – Hetero
51.2 Lamivudine+tenofovir disoproxil fumarate generic – Aurobindo (no longer partic.)
51.3 Lamivudine+tenofovir disoproxil fumarate (TEMIXYS™) – Cadilla (no longer partic.)
51.99 Lamivudine+tenofovir disoproxil fumarate (unknown manufacturer)
52. Elvitegravir+emtricitabine+tenofovir alafenamide (BIKTARVY®, BVY) – Gilead
52.1 Elvitegravir+Emtricitabine+Tenofovir alafenamide generic – Hetero
52.99 Elvitegravir+Emtricitabine+Tenofovir alafenamide (unknown manufacturer)
53 Doravirine (PIFELTRO™, PIF) – Merck
54. Doravirine+lamivudine+tenofovir disoproxil fumarate (DELSTRIGO™, DEL) – Merck
55. Dolutegravir+lamivudine+tenofovir disoproxil fumarate (AOR/TPSIA™, TLD) – Mylan
55.1 Dolutegravir+lamivudine+tenofovir disoproxil fumarate generic – Hetero
55.99 Dolutegravir+lamivudine+tenofovir disoproxil fumarate (unknown manufacturer)
56. Dolutegravir+Rilpivirine (DOVATO®) – ViiV
56.1 Dolutegravir+lamivudine generic – Hetero
56.99 Dolutegravir+lamivudine (unknown manufacturer)
57. Darunavir+cobicistat+emtricitabine+tenofovir alafenamide (SYMTUZA®, DCF TAF) – Janssen
58. Fostemsavir (RUKOBIA®, FTR) – ViiV
59. Cabotegravir (VOCABRIA®, CABENUVA®, APRETUDE®, CAB) – ViiV
60. Rilpivirine (REKAMBYS®, CABENUVA®, RPV) – Janssen
61. Lenacapavir (SUNLENCA®, LEN) – Gilead

Sponsors:

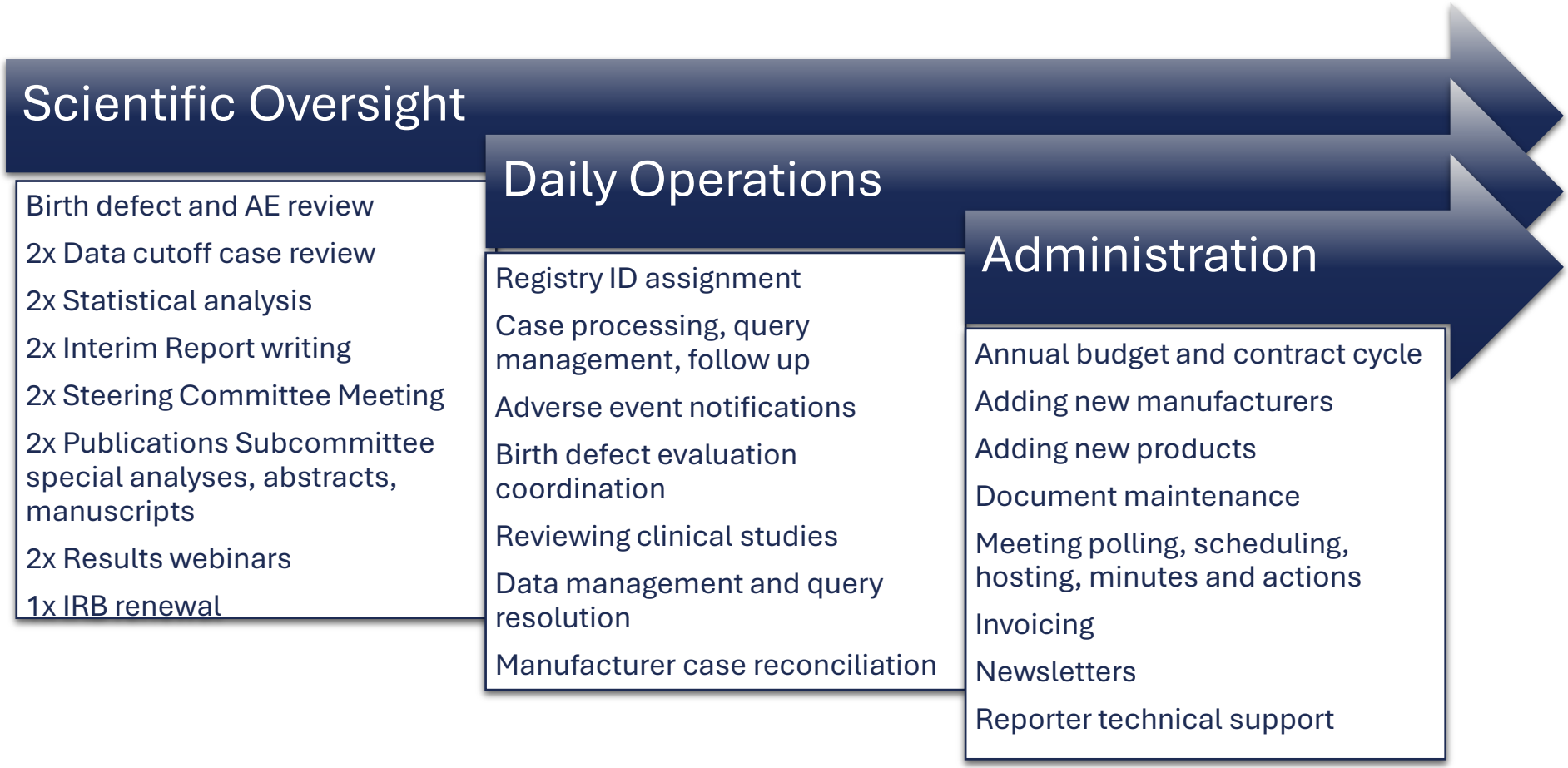
AbbVie, Alvogen, Amneal Pharmaceuticals, Apotex, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb Company, Cipla, Dr. Reddy's Laboratories, Gilead Sciences, Hetero Labs, Hikma Pharmaceuticals USA, i3 Pharmaceuticals, Janssen Scientific Affairs, Lannett Company, Laurus Labs, Lupin Pharmaceuticals, Macleods Pharmaceuticals, Merck & Co., Mylan Inc., Pharmascience, Qilu Pharmaceuticals, SigmaPharm Laboratories, Strides Pharma Science, Teva Pharmaceuticals USA, ViiV Healthcare, Yung Shin Pharm., and Zydus Pharmaceuticals

APR Steering Committee. Interim Report; 2025.

APR: Methods

- IRB approved waivers of informed consent and authorization for use and disclosure of protected health information
- Anonymous reports of exposed pregnancies using a unique Registry assigned identification number
- Primary outcome is prevalence of major birth defects at the time of birth
- Primary prospective analysis is multi-tiered
  - Overall prevalence for all drugs monitored, drug class level, individual drug level
- Comparison groups
  - External (background) reference group(s) MACDP, TBDR
  - Internal comparison group(s)

APR: Annual Timeline



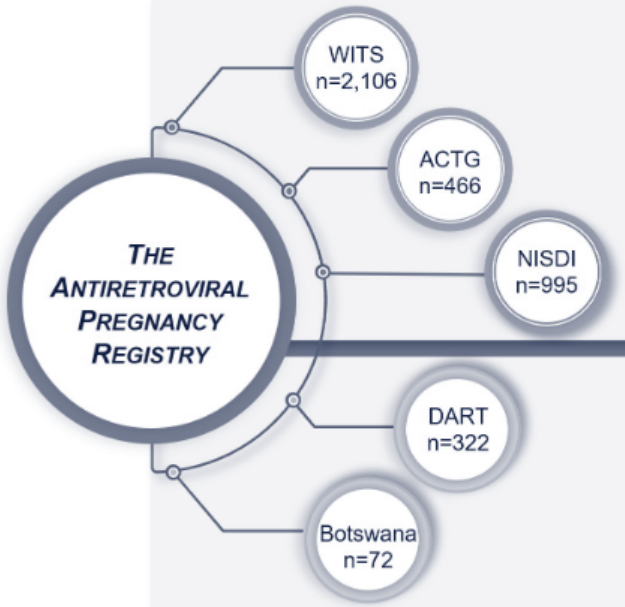
APR: Governance

Documents

- Protocol
- Statistical Analysis Plan
- Case Report Forms
- Case Review Guidelines
- Birth Defect Review Criteria
- Project Management Plan
- Data Management Plan
- Safety Management Plan
- Awareness Plan
- Policies and Procedures
- Timeline
- Templates
- Contracts

Albano, et al. Pharmacoepidemiol Drug Saf 2024;33(6):e5801.

APR: Data Integrations



Observational Studies:

- Complete data included in the primary Registry analysis.
- Rationale: these reports were *a priori* no different from the Registry reports as no intervention or extended follow-up occurs for subjects in these studies.
- Prompted additional signal detection analyses.

Clinical Studies:

- Reports of pregnancy exposures from clinical trials of ARV drugs in non-pregnant populations are included in the primary prospective analysis if they are prospectively reported and otherwise meet the criteria for inclusion.

- Women and Infants Transmission Study (WITS)[11] conducted in the US
- AIDS Clinical Trial Group (ACTG) 367 conducted in the US (data not published)
- Maternal Antiretroviral Use During Pregnancy and Infant Congenital Anomalies (NISDI Perinatal Study)[12] conducted in Brazil and Argentina
- Development of Antiretroviral Therapy in Africa study (DART)[13] conducted in Uganda and Zimbabwe among 3300 enrolled subjects
- Botswana[14] conducted in urban centers among 451 female subjects who received highly active antiretroviral therapy

Albano, et al. Pharmacoepidemiol Drug Saf 2024;33(6):e5801.

APR: Results Dissemination

THE ANTIRETROVIRAL PREGNANCY REGISTRY
INTERIM REPORT

1 JANUARY 1989 THROUGH 31 JULY 2025

(Issued: December 2025)

(Expiration: 6 months after issue)

For:

ABACAVIR (ZIAGEN®, ABC)
ABACAVIR+DOLUTEGRAVIR+LAMIVUDINE (TRIUMEQ®, TRI)
ABACAVIR+LAMIVUDINE (EPZICOM®, EPZ)
ABACAVIR+LAMIVUDINE+ZIDOVUDINE (TRIZIVIR®, TZV)
ADEFOVIR DIPIVOXIL (HEPSERA®, ADV) *(HEPSERA NO LONGER MANUFACTURED AS OF 2025)*
AMPRENAVIR (AGENERASE®, APV) *(AGENERASE NO LONGER MANUFACTURED AS OF 2007)*
ATAZANAVIR (REYATAZ®, ATV)
ATAZANAVIR+COBICISTAT (EVOTAZ®, EVO)
BICTEGRAVIR+EMTRICITABINE+TENOFOVIR ALAFENAMIDE (BIKTARVY®, BFF/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) *(VIDEX NO LONGER MANUFACTURED AS OF 2025)*
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™, EPV/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®, YEZTUGO®, LEN)
LOPINAVIR+RITONAVIR (KALETRA®, ALUVIA®, LPV/r)
MARAVIROC (SELZENTRY®, CELSENTRI®, MVC)
NELFINAVIR (VIRACEPT®, NFV)
NEVIRAPINE (VIRAMUNE®, VIRAMUNE XR®, NVP)
RALTEGRAVIR (ISENTRESS®, RAL)
RILPIVIRINE (EDURANT®, REKAMBYS®, CABENUVA®, 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) *(ZERIT NO LONGER MANUFACTURED AS OF 2025)*
TELBIVUDINE (SEBIVO®, TYZEKA®, LdT) *(TYZEKA NO LONGER MANUFACTURED AS OF 2016)*
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, Alvogen, Amneal Pharmaceuticals, Apotex, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb Company, Cipla, Dr. Reddy's Laboratories, Gilead Sciences, Hetero Labs, Hikma Pharmaceuticals USA, i3 Pharmaceuticals, Janssen Scientific Affairs, Lannett Company, Laurus Labs, Lupin Pharmaceuticals, Macleods Pharmaceuticals, Merck & Co., Mylan Inc., Pharmascience, Qilu Pharmaceuticals, SigmaPharm Laboratories, Strides Pharma Science, Teva Pharmaceuticals USA, ViiV Healthcare, Yung Shin Pharm., and Zydus Pharmaceuticals

ACTHIV
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

ACTHIV INSTITUTE
A Division of American Academy of CME, Inc.

Clinical Gap and Educational Need

Learning Objectives

Activity Faculty

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Senior HIV Technical Advisor
Elizabeth Glaser Pediatric AIDS Foundation

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Division of Genetics and Metabolism Professor
Department of Pathology
Division of Genetic Diagnostics Director
Rare Disease Center of Excellence
UT Southwestern Medical Center

Target Audience

Accreditation and Credit Designation

ACTHIV Resources for the HIV Care Team

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Additional Online Learning

VIRTUAL GRAND ROUNDS

Case Studies in Mental Health Screening and Team Care for People Living with HIV CME/CNE

Case Studies in HIV Testing: Deciding Who to Test and How to Discuss Results CME/CNE

Case Studies in Syphilis and Mpox CME/CNE

Case Studies in Initial HIV Management: When, What, and How CME/CNE

Case Studies in HIV Prevention Among Communities at High Risk for HIV CME/CNE CME/CNE

Case Studies in Identifying and Addressing Intimate Partner Violence among People with HIV CME/CNE CME/CNE

Case-Based Management of Hepatitis C in Persons with HIV CME/CNE

Dermatology for People with HIV CME/CNE

Principles of Antiretroviral Therapy CME/CNE

Cardio-metabolic Complications of ART CME/CNE

Opportunistic Infection Cases in People with HIV CME/CNE

Update on the Diagnosis and Treatment of STIs CME/CNE

Mental Health and Substance Use in PWH CME/CNE

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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

Recommendations for the Use of Antiretroviral Drugs During Pregnancy

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

Overview

Panel's Recommendations

BHIVA
British HIV Association

BHIVA pregnancy guidelines 2025: non-technical summary

HIV in pregnancy

The British HIV Association (BHIVA) produces medical guidelines about HIV treatment and care. All guidelines review the evidence for the best care. These guidelines are for clinicians providing HIV care, but it is important that you also know what is in them, and what they might mean for you if you are thinking about becoming pregnant or are pregnant when you are diagnosed with HIV. This non-technical summary aims to provide the main points about how you and your baby should be cared for, so not all the recommendations in the guidelines are included. You can find more details in the full guidelines at: https://www.bhiva.org/pregnancy-guidelines

What is covered in the HIV in pregnancy guidelines?

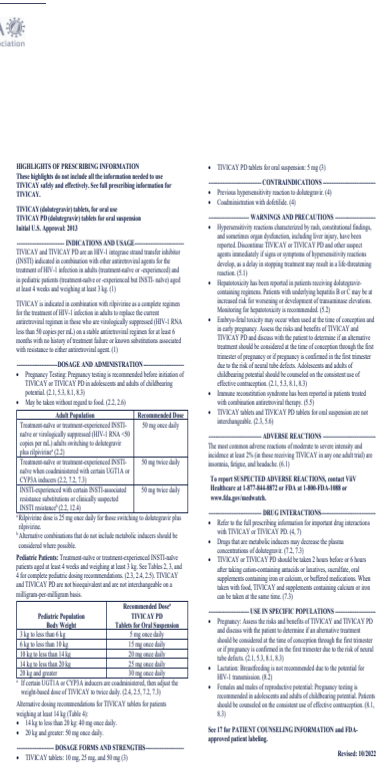
- Involvement in decision-making and general recommendations for supporting the wellbeing of pregnant women/people living with HIV.
- What antiretroviral treatment combinations are recommended when planning for, during and after pregnancy.
- Recommendations for the care and monitoring of women/people living with HIV during pregnancy and birth, and afterwards.
- Recommendations for the care of babies born to women/people living with HIV and infant feeding.
- Recommendations for the care of pregnant women/people with HIV and hepatitis.

General recommendations

Pregnant women/people living with HIV should be looked after by a multidisciplinary team (MDT) during and after pregnancy which should be led by a named healthcare professional. You should be offered peer support and asked about your mental health throughout pregnancy and after birth. You should have the same routine pregnancy monitoring as women/people who are not living with HIV (for example, ultrasound scans as per national pregnancy guidelines). You should be offered the same tests as other women/people living with HIV who are not pregnant (for example, CD4 count and viral load) and also tests for sexually transmitted diseases.

Involvement in decision-making

The guidelines emphasise that you should be involved in all decisions about your care and pregnancy and that peer support from other people living with HIV is important. There is a network of women living with HIV who are trained as mentor mothers who can share their knowledge and experience to help you to be involved effectively in the choices you make around your pregnancy and health (https://4mmm.org/). Some clinics also have peer navigators; these are people living with HIV themselves who are trained to help you to find the healthcare professionals you need to provide support. There are also many HIV organisations that will support you during pregnancy and birth, and beyond.



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

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[1] (2.2)	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers (2.2, 7.2, 7.3)	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[2] (2.2, 12.4)	50 mg twice daily

[1]Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.
[2]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[1] 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

[1] 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 three 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

Closing Gaps & Overcoming Barriers

- Time lag between FDA approval of ARV, initiation of clinical trials of ARV in pregnant women, availability of pregnancy-specific safety data and updates to treatment guidelines means that pregnant/women of reproductive potential are less likely to receive newer/safer/more effective medications compared to other adults with HIV
- Anonymous online surveys independently developed and deployed in the US (66 responders) and Australia (80 responders) among healthcare providers treating pregnant women with HIV
  - Lack of awareness – APR's existence or that non-US reports are accepted
  - Perceived barriers – Uncertain of process or incomplete access to all necessary maternal or pediatric data

Short, et al. Open Forum Infect Dis 2024. 11(8):ofae423; Mantas, et al. Open Forum Infect Dis 2025. 12(2):ofaf023.

Closing Remarks

- Non-consolidated registry efforts at the individual drug level are inefficient and costly endeavors that are unlikely to produce robust results in a timely manner leaving women and their physicians without the critical data they need to make informed decisions about their care.
- Trust is paramount and this requires transparency as well as oversight by an independent advisory committee.
- The impact of consistently reported and publicly available findings are compounded when standardized methods are employed, and results are comparable and generalizable.
- Awareness efforts are never enough and overcoming perceptions of participation barriers takes constant tending.

Acknowledgements

Thank you to all the dedicated clinicians submitting cases to the APR, the valuable contributions of the Steering Committee including members of the Advisory Committee and Sponsor Representatives and the amazing efforts of the Registry Coordinating Center staff at Syneos Health.

Key References

- Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 July 2025. Morrisville, NC: Registry Coordinating Center; 2025. Available from URL: www.APRegistry.com.
- Albano JD, et al. The Antiretroviral Pregnancy Registry: Three decades of prospective monitoring for birth defects. Pharmacoepidemiol Drug Saf. 2024;33(6):e5801.
- Chambers C, et al. The safety of asthma medications during pregnancy and lactation: Clinical management and research priorities. Journal of Allergy and Clinical Immunology, 2021; 147, 2009-2020.
- Short WR, et al. Safety of Antiretroviral Exposure During Pregnancy: Opportunities to Close Data Gaps. Open Forum Infect Dis. 2024 Jul 23;11(8):ofae423.
- Mantas S, et al. Barriers to Clinician Reporting to the Antiretroviral Pregnancy Registry From Within and Outside the United States. Open Forum Infect Dis. 2025 Jan 15;12(2):ofaf023.

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U.S. FOOD & DRUG ADMINISTRATION

Session 1 Panel Discussion

U.S. FOOD & DRUG ADMINISTRATION

LUNCH BREAK

U.S. FOOD & DRUG ADMINISTRATION

Session 2: Optimizing Design of Pregnancy Registries in Context of Totality of Evidence

Optimizing Pregnancy Registration: Patient Perspective

Kayla Stomack MPH, DVM, CVA, CTNP

Patient Timeline

Diagnosed August 2024

Kesimpta October 2024

Pregnancy Confirmed Dec 31st

Care coordinator follow-up: Mother-To-Baby Registry

Mother-To-Baby Registry

February 2025

Study Guidelines

- Initial call 45 minutes
- Pregnancy Calls 10-15 minutes
- Diary of medication, symptoms, mood
- Following Pregnancy: 15-30 min call; baby’s info
- Breastfeeding: 2 and 6 month post-partum: 20 min
- Baby’s 1 year check-up

Study breakdown

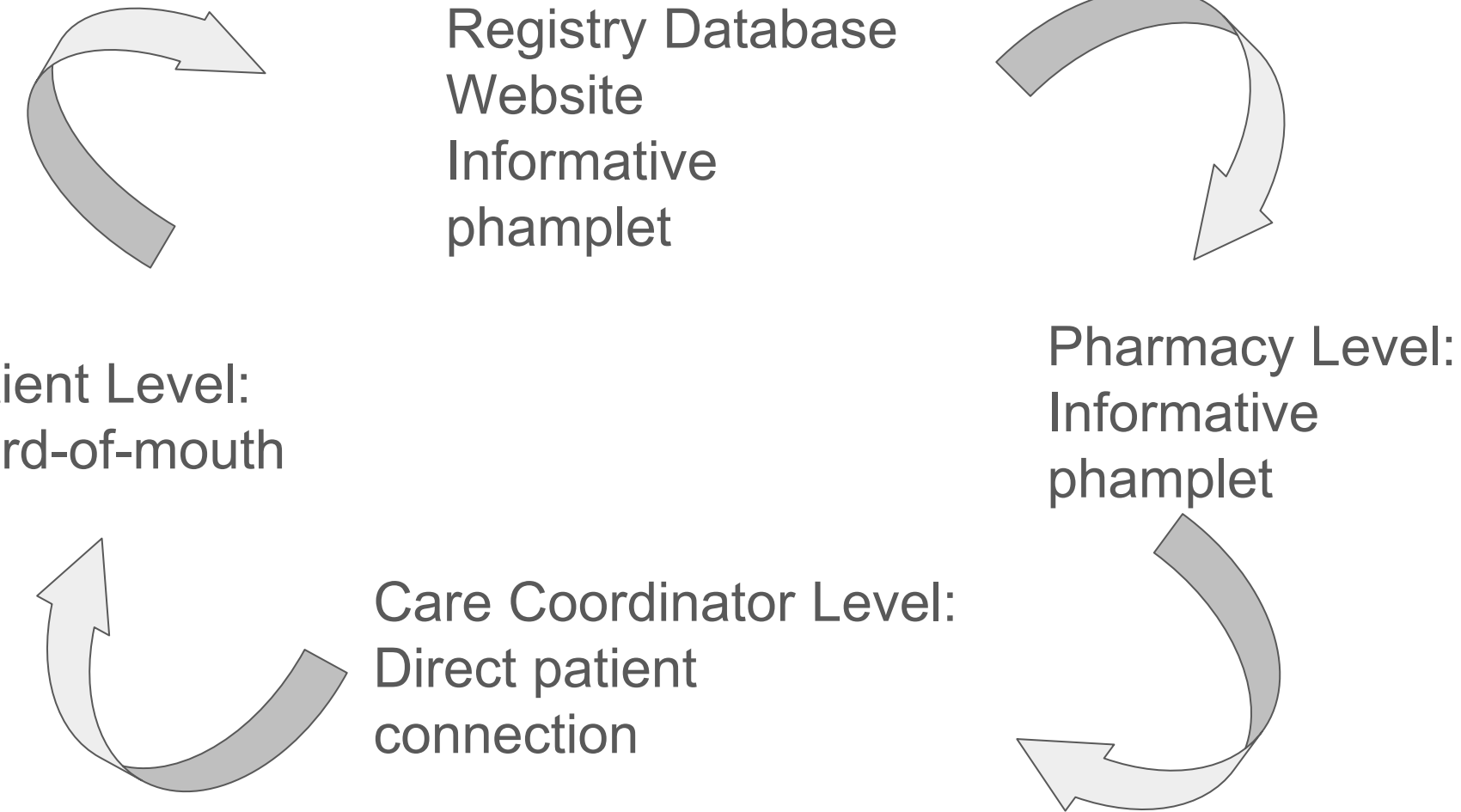
Pro

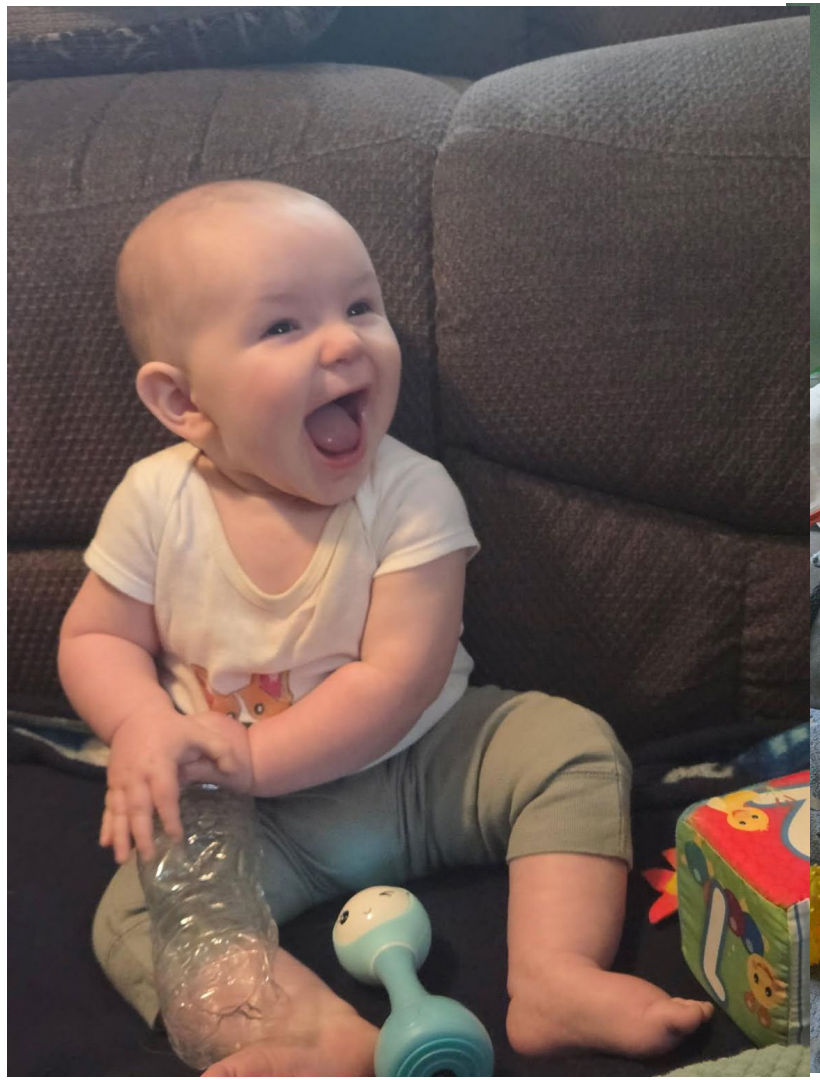
- Ease of data collection
- Assistance with science

Cons

- Data incentive
- Risk with data breach
- Informed by care coordinator

Registry Improvement: multi-modal






I'VE GOT A
LITTLE

U.S. FOOD & DRUG ADMINISTRATION

Patient Perspective: Lisa Feret

HARVARD PROGRAM ON PERINATAL
AND PEDIATRIC PHARMACOEPIDEMIOLOGY

Optimizing Pregnancy Registries
in Context of Totality of Evidence

Sonia Hernandez-Diaz

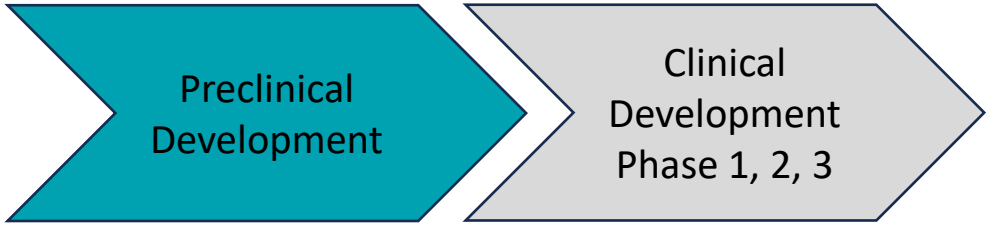
CAUSALab
A Center to Learn What Works

HARVARD
T.H. CHAN
SCHOOL OF PUBLIC HEALTH

How do we generate Real World Evidence (RWE) in pregnancy?

Sources of evidence through drug life cycle

- **Pre-approval Approaches:**
  - Pharmacologic or toxicologic studies - poor predictors
  - Animal studies - poor predictors
  - Clinical trials - exclude pregnant women



Sources of evidence through drug life cycle

- **Post-approval Approaches**:
  - Case reports - clues; false alarms; may identify high-risks
  - Experimental studies - too small, too short
  - Non-experimental (observational) studies ("Real-World Data")
    - Cohort
    - Case-Control

How do we generate RWE in pregnancy?

- **Primary data: Designed for Research**
  - Cohorts, wide range of exposures - Collaborative Perinatal Project, MoBa
  - Cohorts, specific exposures – Exposure Pregnancy Registries
  - Case control studies – Case Control Surveillance (Slone, BDSTEPS, EUROCAT)
- **Secondary data: Designed for Other Purposes**
  - Automated claims databases (e.g., Medicaid Analytic eXtract, MarketScan, Optum)
  - Computerized medical records, EHR – (e.g., Kaiser, Epic Cosmos, UK-CPRD)
  - National registries (e.g., Nordic linked registries)
  - Provincial registries (e.g., Régie de l'assurance maladie du Québec, Saskatchewan)

RWE for pregnancy through drug life cycle

- Causal inference (safety studies)
- Natural history of pregnancy for a condition → external reference
- Utilization of medications around pregnancy → inform registry feasibility
- Identification of treated + pregnant → enroll in pregnancy registry
- Pragmatic follow-up for pregnancy registry

Surveillance strategy

- **Pharmacovigilance**
  - To identify dramatic effects for uncommon outcomes (patterns)
- **Exposure pregnancy registries**
  - To identify dramatic effects for uncommon outcomes or moderate effects for common ones

→ Goal of pregnancy registries = Rule out "thalidomides"

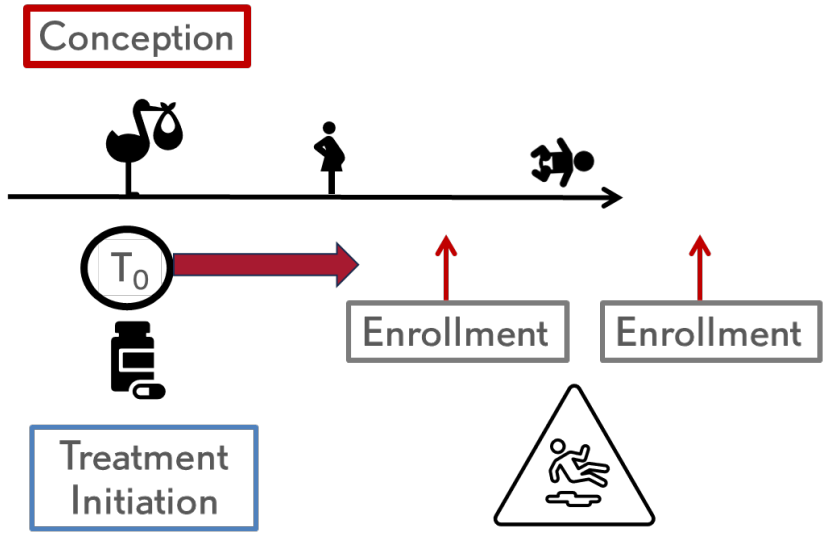
- **Health care databases**
  - To evaluate large or moderate effects for relatively common outcomes or commonly used prescription drugs
- **Case control surveillance**
  - To evaluate moderate effects for suspected uncommon outcomes (e.g., specific malformation) for commonly used drug

Mitchell AA. Systematic Identification of Drugs That Cause Birth Defects-- A New Opportunity. New England Journal of Medicine 2003;349:2556-2559.

Case Reports

- Strengths
  - Identify (promptly) pregnancy-related drug safety signals for further evaluation
- Limitations
  - Underreporting and selective reporting
  - No information on the denominator
    - Does not generate risk estimates
  - No reference group
    - Does not quantify associations
  - Cannot distinguish causation from chance or confounding

Pregnancy Exposure Registries

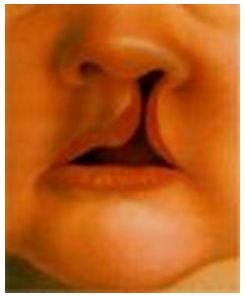


- Strengths
  - Prospective drug information
  - Collects information directly from participants and/or health care providers (e.g., sociodemographic characteristics)
  - Can study multiple drugs and multiple outcomes including labs, lactation, IQ
  - Assess real drug use
  - Adjudicated outcomes
  - Can estimate risks
- Selection limitations
  - Non-representative (self-referral)
  - Some lack control group (non-comparable external reference)
  - Left truncation. Enrollment late in pregnancy
- Power limitations
  - Ad-hoc data collection is timely & costly
  - Information on one or few drugs
  - Challenging recruitment (low enrollment)
  - Challenging retention (short follow-up & losses to follow-up)

Health Care Databases

- Strengths
  - Data exist, less costly & timely
  - Large numbers
  - Real world experience. Population based. No selection bias
  - Prospective information on multiple pharmaceuticals
  - Internal active comparator groups
  - Information on multiple outcomes
  - Information on a wide range of clinical confounders
- Data quality limitations
  - Prescription ≠ dispensation ≠ actual use
  - No over-the-counter, some vaccinations
  - Outcomes based on recorded diagnoses and procedures
  - Limited information on some potential confounders (e.g., socioeconomic, BMI)
  - Other key elements may be missing (e.g., LMP date, biomarkers)
- Limited power when exposure & outcome are infrequent

Example: Topiramate

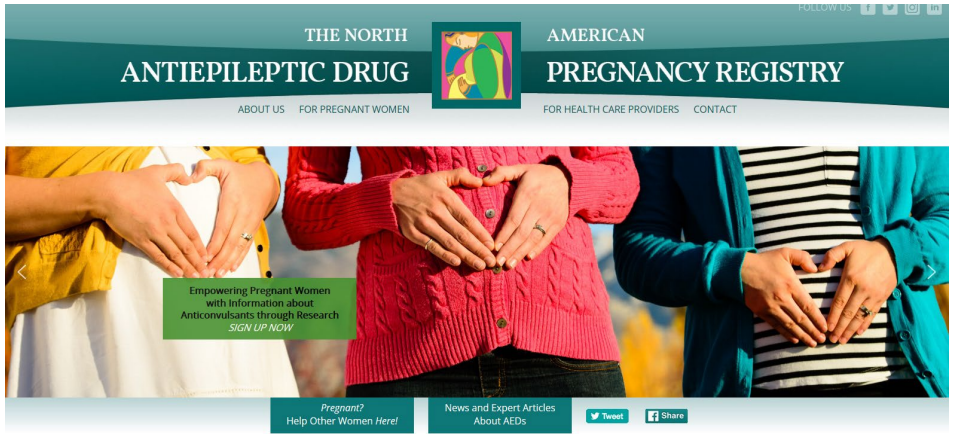


- **Background:** One report had suggested an increased risk of oral clefts after in utero exposure to topiramate
- **Aim:** To estimate the risk of oral clefts in infants whose mothers had taken topiramate as monotherapy during the first trimester of pregnancy
- **Note**: Oral cleft is now an FDA labeled risk

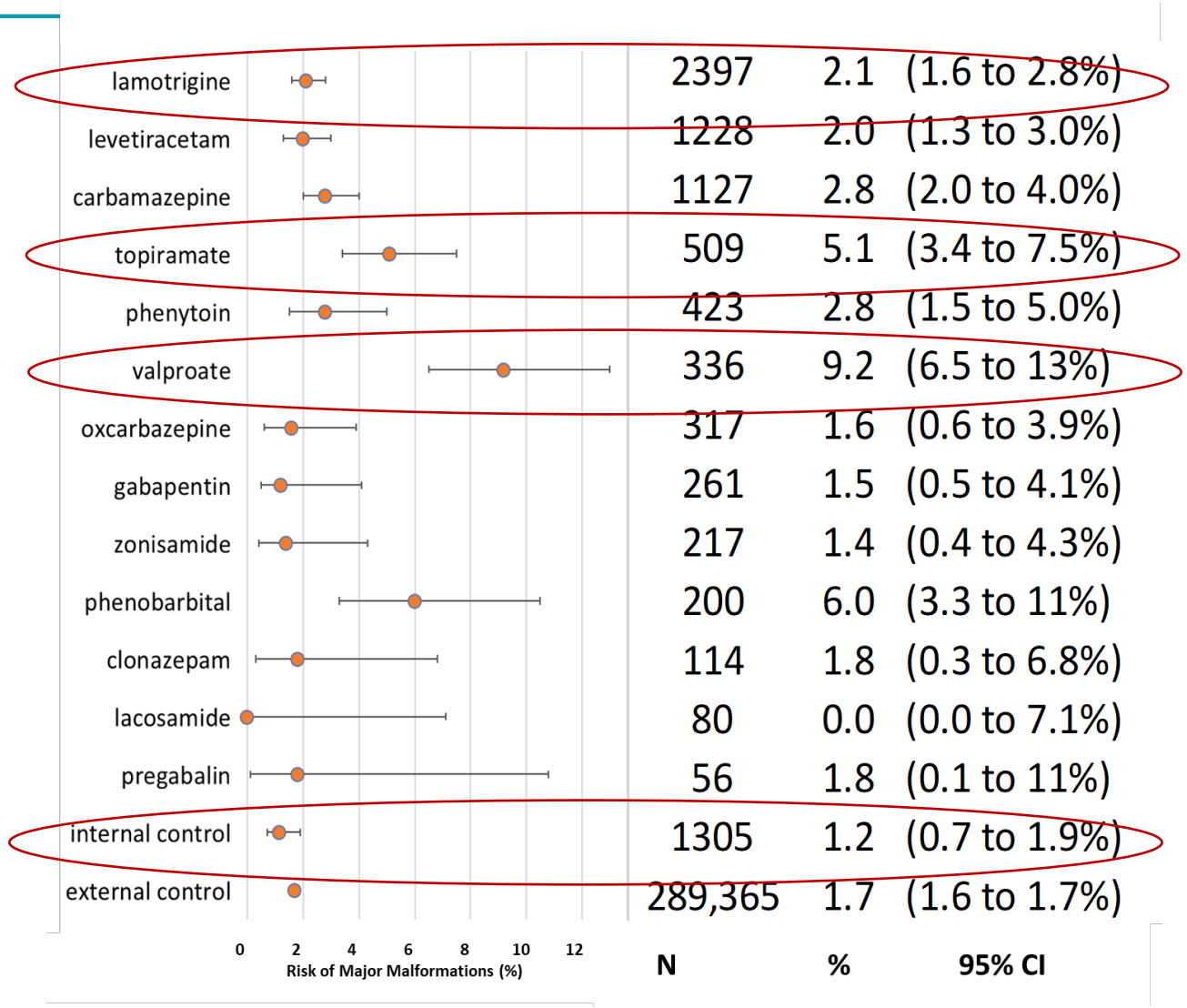
Hunt S et al. Topiramate in pregnancy: Preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology 2008;71;272-276

North American Antiepileptic Drugs Pregnancy Registry

- **Disease-based multi-drug registry**
  - Enrolls pregnant women taking Antiseizure Medications (ASMs), and a reference group of unexposed
- **Three telephone interviews collect data on:**
  - ASM use, demographic characteristics, epilepsy, vitamin use and the presence of malformations
- **Malformations adjudicated by teratologist**



Risk of malformations for specific ASM in monotherapy and the control groups



North American Antiepileptic Drugs Pregnancy Registry

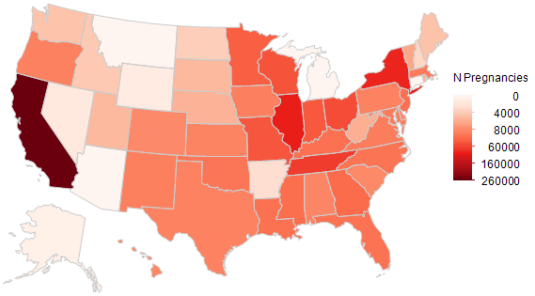
- 4 of initial 11 malformations were oral clefts (13.5/1,000)
  - Remained with more data: 7 out of 509 (13.7/1,000)
- Frequency in the external control group: 1/1,000
- Conclusion: Need to replicate

Hernández-Díaz S et al. Comparative Safety of Antiepileptic Drugs during Pregnancy. Neurology 2012;78:1692-1699.

Hernández-Díaz S et al. Use of Antiseizure Medications Early in Pregnancy and the Risk of Major Malformations in the Newborn. Neurology. 2025;105(3):e213786.

Medicaid Analytic eXtract (MAX)

- Joint state and federal health insurance program for low-income families
  - Covers ~50% of births in the U.S
- Medicaid enrollment & health care utilization data
  - Demographics, insurance enrollment information
  - Diagnostic and procedures codes
  - Dispensed outpatient prescription medications
- Cohort: Woman-infant linkage
  - 1.3 M pregnancies ending in live birth



Palmsten K, Huybrechts KF, Mogun H, Kowal MK, Williams PL, Michels KB, Setoguchi S, Hernández-Díaz S. Harnessing the Medicaid Analytic eXtract (MAX) to Evaluate Medications in Pregnancy: Design Considerations. PLoS One 2013;8(6):e67405

Medicaid Database

	Unexposed	Lamotrigine	Topiramate
	n = 1,322,955	n = 2796	n = 2425
Oral clefts			
Prevalence (per 1,000)	1.1	1.5	4.1
Unadjusted RR (95%CI)		Reference	2.30 (0.69-7.64)
PS-Adjusted RR (95%CI)			2.38 (0.71-7.96)

Hernandez-Diaz S, Huybrechts KF, Desai RJ, Cohen JM, Mogun H, Pennell PB, Bateman BT, Patorno E. Topiramate use early in pregnancy and the risk of oral clefts. A pregnancy cohort study. Neurology. 2017; 90(4):e342-e351.

Case Control Surveillance

- **Two North American birth defects case control studies**
  - Slone Epidemiology Center Birth Defects Study (BDS)
  - Centers for Disease Control and Prevention National Birth Defects Prevention Study (NBDPS)

- **The two studies have many similarities:**
  - Study design
  - Data collection methods (e.g. identification of cases and controls; telephone interview)
  - Case classification by expert clinical reviewers
  - Controls are live born infants without birth defects

Case Control Surveillance

Results from pooled data

	No ASM	Topiramate	Adjusted* OR (95% CI)
Controls	15,367	6	Reference
Oral clefts	3,034	7	5.36 (1.49 – 20.07)

ASM, antiseizure medication; Oral clefts included cleft lip with or without cleft palate
OR, odds ratio; CI, confidence interval

* Conditional on year and region of birth, and study

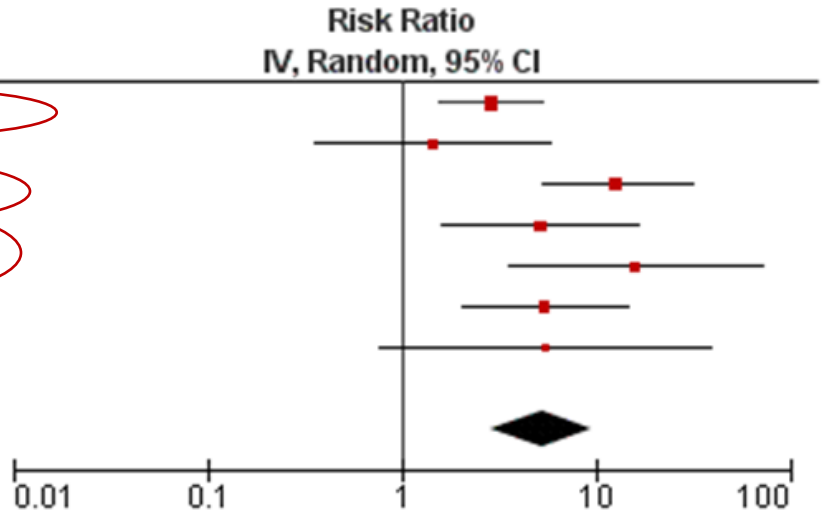
Margulis AV, Mitchell AA, Gilboa SM, Werler MM, Mittleman MA, Glynn RJ, Hernández-Díaz S, and the National Birth Defects Prevention Study. Use of topiramate in pregnancy and the risk of oral clefts. Am J Obstet Gynecol 2012;207:405.e1-7.

Oral Clefts - Topiramate vs no-use

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Hernandez-Diaz S 2017	1.06471074	0.31676355	22.4%	2.90 [1.56, 5.40]
Green 2012	0.36464311	0.71037455	11.5%	1.44 [0.36, 5.79]
Hernandez-Diaz 2012	2.55100645	0.45529358	17.9%	12.82 [5.25, 31.29]
Margulis(1) 2012	1.6467337	0.59158516	14.1%	5.19 [1.63, 16.55]
Margulis(2) 2012	2.77633171	0.764466	10.5%	16.06 [3.59, 71.86]
Mines 2014	1.69744879	0.50470669	16.4%	5.46 [2.03, 14.68]
Molgaard-Nielsen 2011	1.70292826	1.00347107	7.2%	5.49 [0.77, 39.24]
Total (95% CI)			**100.0%**	**5.27 [2.88, 9.65]**

Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 12.65$, df = 6 (P = 0.05); $I^2 = 53\%$

Test for overall effect: Z = 5.38 (P < 0.00001)



If pooled results are valid, the risk of oral clefts would increase from approximately 1 per 1,000 births to 5 per 1,000 births with topiramate use

Hernandez-Diaz S, Huybrechts KF, Desai RJ, Cohen JM, Mogun H, Pennell PB, Bateman BT, Patorno E. Topiramate use early in pregnancy and the risk of oral clefts. A pregnancy cohort study. Neurology. 2017; 90(4):e342-e351.

What do we need from RWE?

All outside Randomized Control Trial territory

- Generating clinically useful evidence for medications and vaccines use in pregnancy based on RWD is
  - A question of methods (valid estimates)
  - A question of numbers (precise estimates)
  - A question of time (rapid response)

A question of methods

- **Population eligibility and ascertainment:** Who enrolls
- **Reference group**: Who is comparable
  - Same indication, active internal reference
  - Reduces confounding + clinically relevant comparison
  - → **Disease-based multi-drug registry**
- **Follow-up (time zero and duration):** When to enroll

Target Trial Emulation may help

- Causal inference from RWD can be conceptualized as an attempt to emulate a hypothetical randomized trial: the Target Trial
- The Target Trial framework:
  1. Ask a causal question
  2. Specify the protocol for the Target Trial
  3. Explicitly describe how each aspect of the target trial protocol is emulated using observational data

- This process can help identify and avoid biases including confounding, immortal time bias, and prevalent user bias

Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758-764.

Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016:79:70-75

A question of numbers

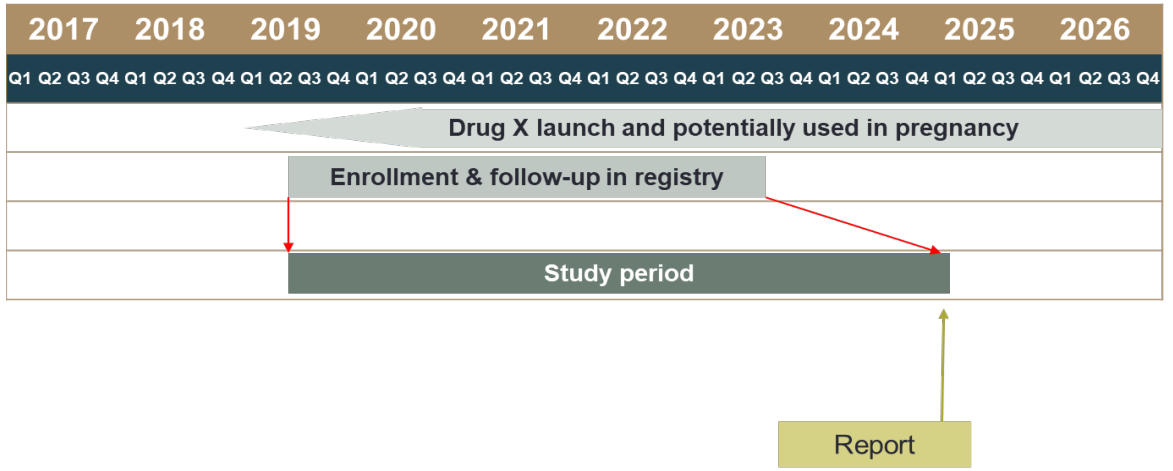
- **Pregnancy Registries** are the first line of evidence to identify teratogens because they can enroll women soon after drug approval
- However, they may fail to produce robust safety data, particularly for newly introduced drugs for relatively rare conditions
  - Targeted enrollment usually ranges between **100 and 500** pregnancies
  - Only 14% of registries achieve target enrolment

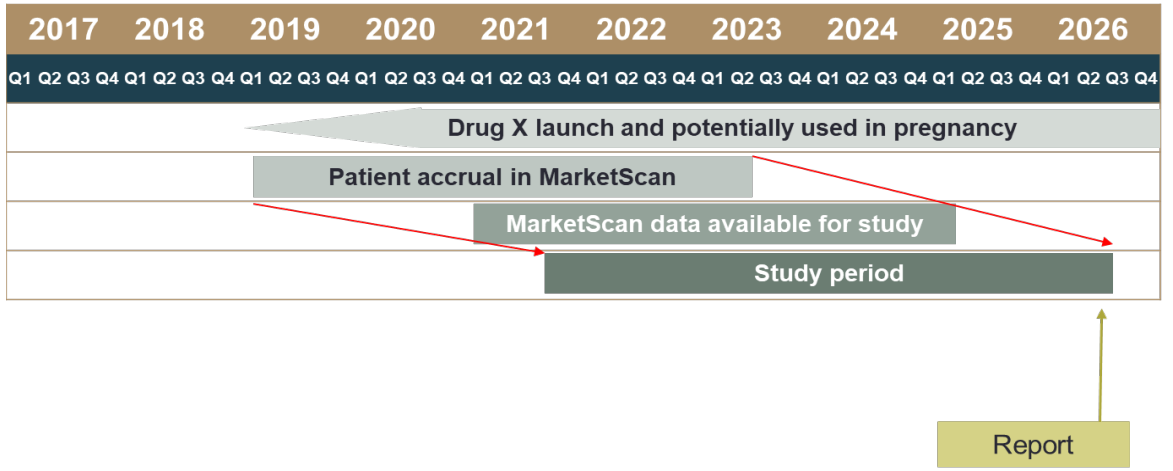
Sahin L. Pregnancy exposure registries and other post-approval studies: current status and observations. Data on file. Center for Drug Evaluation and Research, Office of New Drugs, FDA; 2014. Available at: http://www.fda.gov/downloads/Drugs/NewsEvents/UCM399660.pdf.

Gelperin K, Hammad H, Leishear K, Bird ST, Taylor L, Hampp C, et al. A systematic review of pregnancy exposure registries: examination of protocol-specified pregnancy outcomes, target sample size, and comparator selection. Pharmacoepidemiol Drug Saf. 2017 Feb;26(2):208-14.

A question of time

- **Ad hoc exposure pregnancy registries**
  - Enroll → Use accumulates → 10 months+
- **Health care databases**
  - Use in pregnancy accumulates → records → 10+ months → **research access**
  - As the gap between data recording and research access tightens, databases become more attractive for rapid cycle analytics





What can we do better?

Enhanced pharmacovigilance

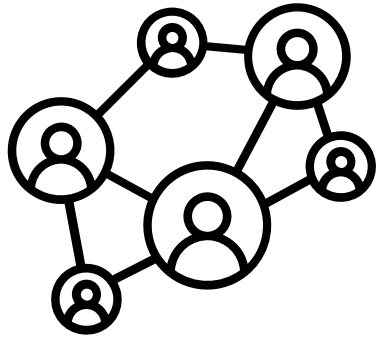
- Collect pregnancy information from unplanned pregnancy exposures during pre-approval trials
- Monitoring of healthcare databases with hypothesis-generating screening of any pregnancy event
  - Tree-Based Scan Statistics (TBSS)

Huybrechts KF et al. Active Surveillance of the Safety of Medications Used During Pregnancy. Am J Epidemiol. 2021;190(6); 1159–1168.

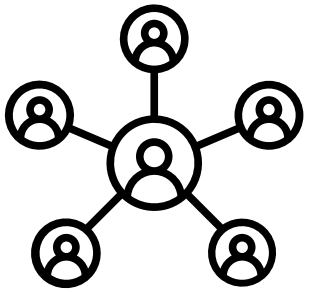
Thai TN et al. Triple challenges-small sample size in both exposure and control groups to scan rare maternal outcomes in a signal identification approach: a simulation study. Am J Epidemiol. 2024;193(12):1805-1813.

Improved Databases

- By **increasing number of subjects**
  - Linking with other databases (e.g., pooled multi-database studies or consortia such as ConcePTION, InPreSS, Sentinel)
  - Linking with RCTs and pregnancy registries

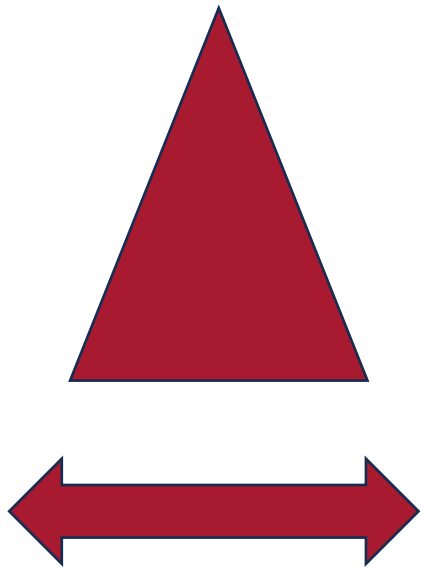


- By **increasing information** for subjects
  - Reviewing medical charts, conducting surveys or laboratory tests
  - Linking to existing data sources (e.g., **pregnancy registers**)



More Efficient Pregnancy Registries

- Individual pregnancy registry
- Multi-drug disease-based pregnancy registry
- Universal pregnancy registry (common but flexible data models)



- One database
- Multi-database
- Consortia (granular but flexible, common data models)

Efficient, affordable, rapid, more valid synergies

Timely and credible RWE in pregnancy

HARVARD PROGRAM ON PERINATAL AND PEDIATRIC PHARMACOEPIDEMIOLOGY

www.harvardpreg.org

CAUSAL INFERENCE IN PREGNANCY

Join the listserv for course updates

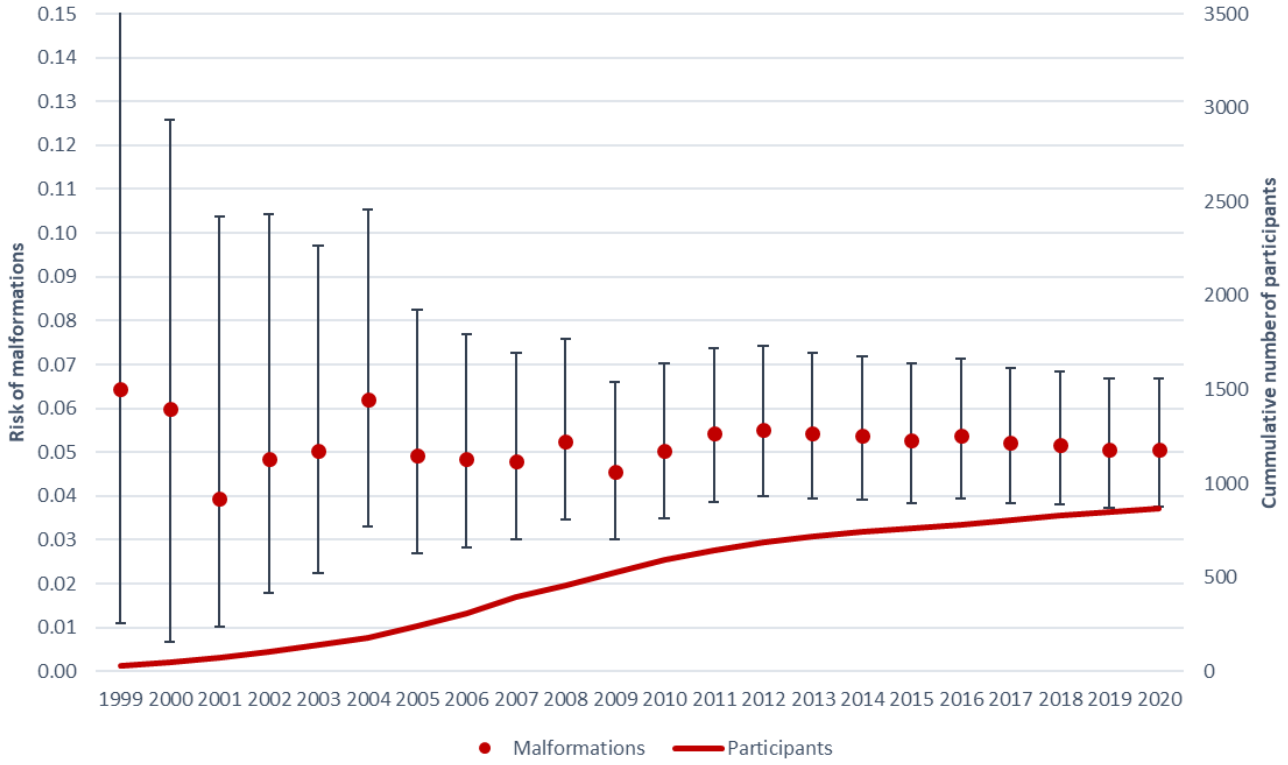
CAUSALab

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

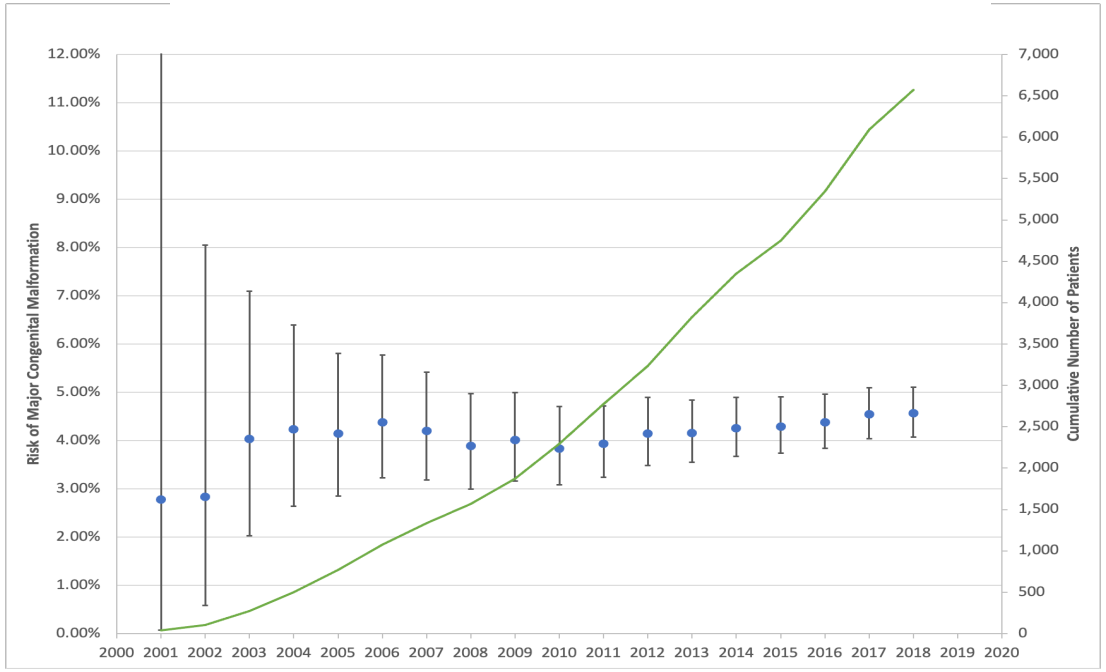
Any major congenital malformation

Cumulative risk of major malformations (95% confidence interval) and number of participants exposed during the first trimester per year

Pregnancy Registry



Health Care Utilization Database



Industry perspectives on integration of evidence from non-registry sources

Marie Teil, MD
Global Head Special Patient Populations
UCB Biopharma

Disclosure

Marie Teil is employed and a shareholder of UCB Biopharma.

The following presentation reflects the personal views of the speaker and does not necessarily reflect the views of UCB Biopharma.

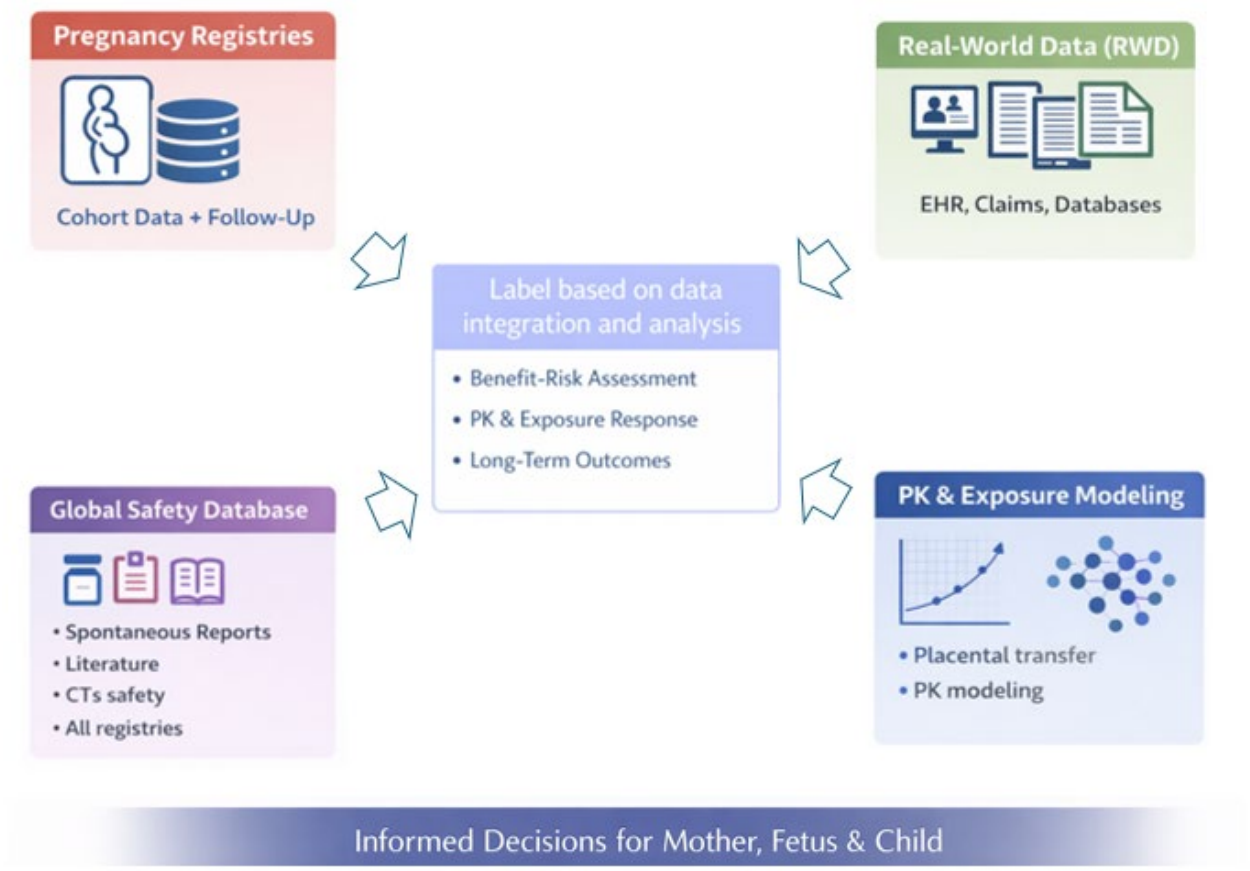
Why does integration of evidence matter?

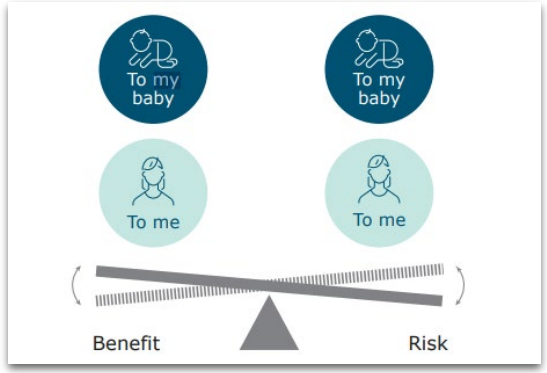
70%

of pregnant women in the U.S. take at least one prescription drug during pregnancy.

- Pregnant women may need treatment for chronic or acute conditions
- Evidence about **potential risk of uncontrolled disease activity** during pregnancy is sparse
- Robust evidence about **potential risk of medicines** use during pregnancy is largely lacking
- About 10-15 yrs for an updated label

Integrating evidence from multiple sources





Benefit–risk assessment across maternal/fetal/neonatal

EHR, Claims, Database Studies

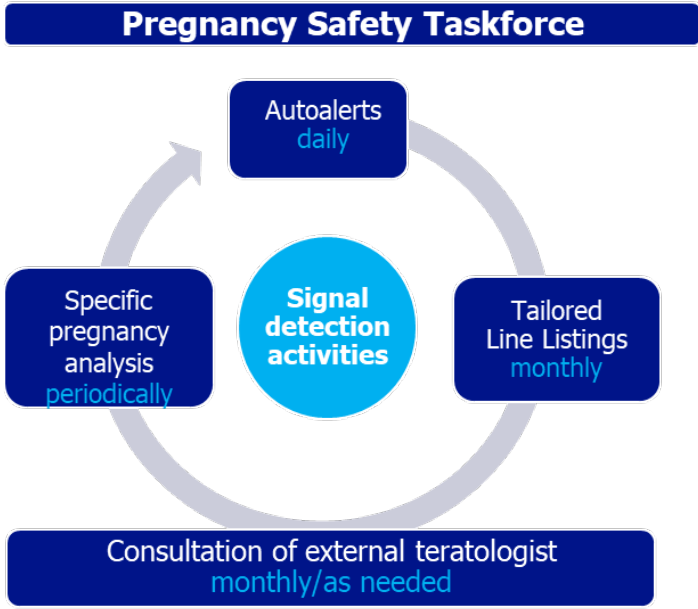
- ***Strengths:***
  - Potential to have a larger sample size
  - Potential to complete study faster
  - No recruitment/enrollment challenges

- ***Limitations:***
  - Requires mother-infant linkage
  - Exposure and timing of exposure cannot be confirmed: based on pharmacy dispensing
  - Potential exposure and outcome misclassification (estimates based on algorithms)
  - Validation needed

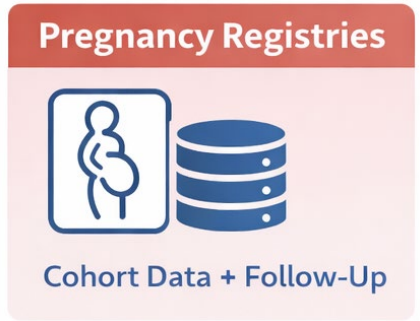
Enhanced Pharmacovigilance Activities

- ***Strengths:***
  - Early data from beginning of development
  - Large data sets
  - All prospective and retrospective pregnancy cases reported to MAH

- ***Limitations:***
  - Gaps in pregnancy outcomes
  - 10/15 years to start having valuable data for informed decision
  - No control group – rely on historical controls



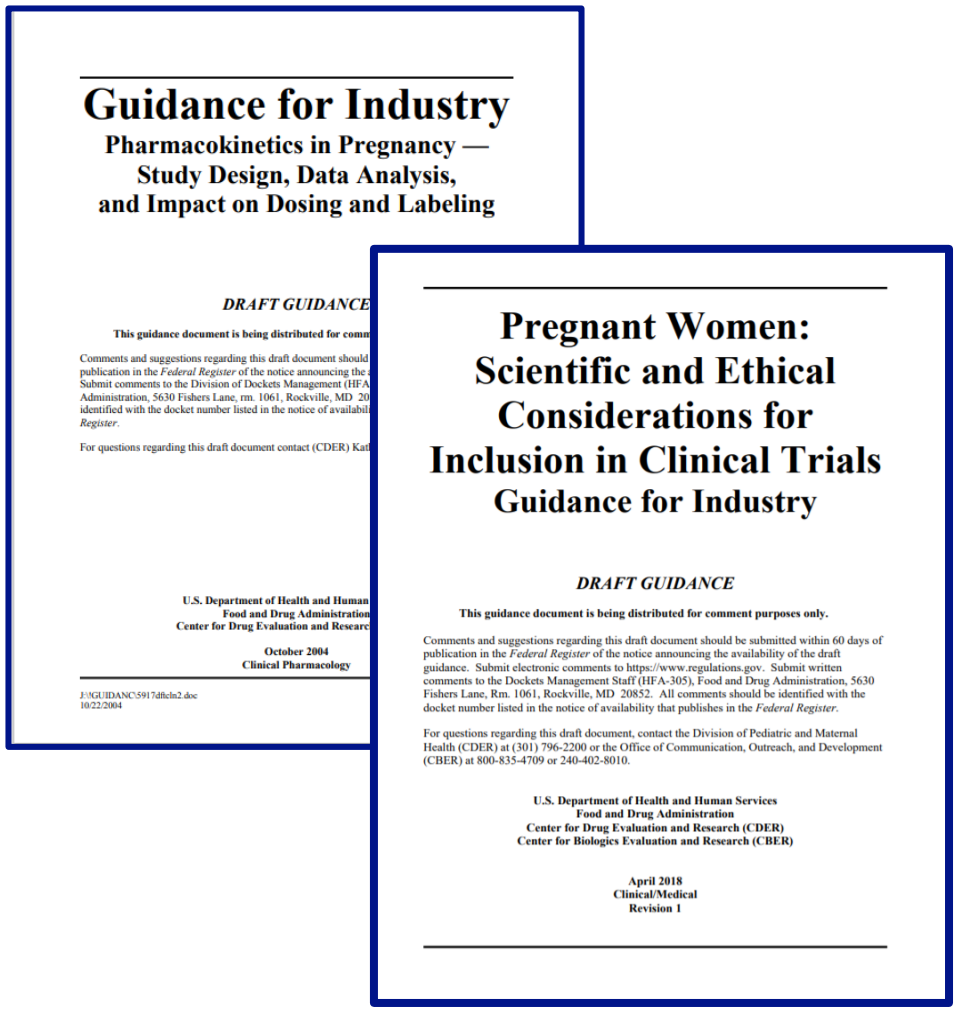
Pregnancy Registries



- ***Strengths:***
  - Prospective observational cohort study
  - Disease matched comparator cohort
  - Infants are followed up to one year of age
  - Multiple outcomes beyond major malformations, i.e. patterns of malformations, miscarriage, termination, stillbirth, preterm birth, SGA

- ***Limitations:***
  - Enrollment and retention challenges
  - Smaller sample size
  - Length of completion

PK Modeling – Placental Transfer



Guidance for Industry

Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comm

Comments and suggestions regarding this draft document should
publication in the *Federal Register* of the notice announcing the
Submit comments to the Division of Dockets Management (HFA
Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20
identified with the docket number listed in the notice of availabil
Register.

For questions regarding this draft document contact (CDER) Kat

U.S. Department of Health and Human
Food and Drug Administration
Center for Drug Evaluation and Researc

October 2004
Clinical Pharmacology

J:\GUIDANC\5917dftcln2.doc
10/22/2004

Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

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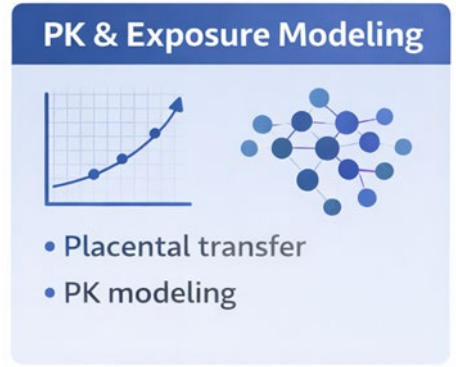
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management 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 the Division of Pediatric and Maternal Health (CDER) at (301) 796-2200 or the Office of Communication, Outreach, and Development (CBER) 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)

April 2018
Clinical/Medical
Revision 1



Expected in 2027

Objective

To provide recommendations for the **appropriate inclusion and/or retention of pregnant and/or breastfeeding individuals in clinical trials** and facilitate the generation of robust clinical data that allow for evidence-based decision making on the safe and effective use of medicinal products by these individuals and their healthcare providers.

Scope

Includes pre- and post-marketing clinical trials of investigational products for indications in the general population and indications specific to pregnant or breastfeeding individuals.

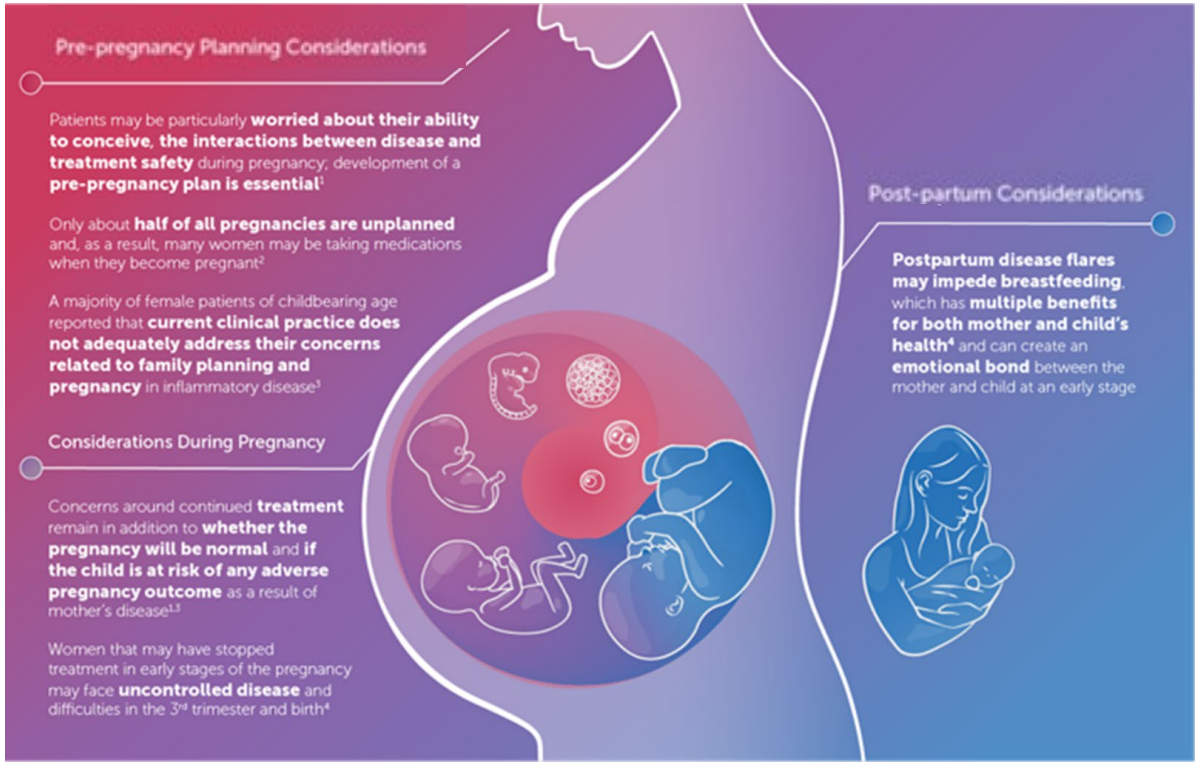
Certolizumab pegol: A Case Study

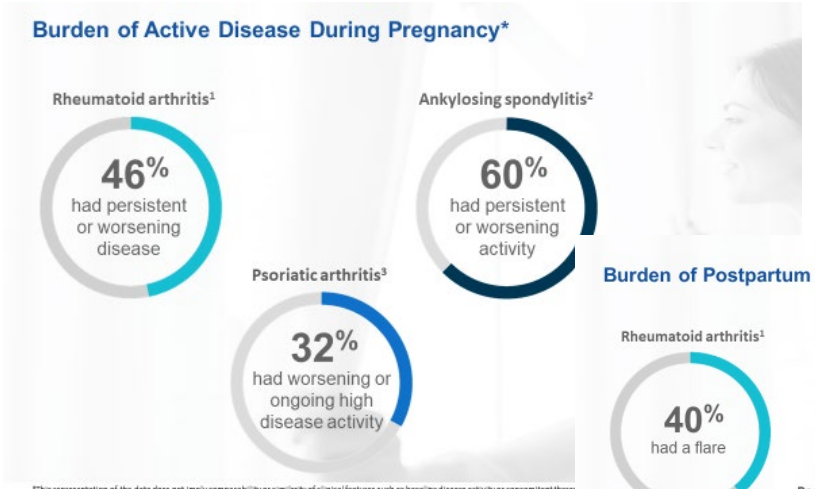
- The information related to certolizumab pegol is included solely as an example of evidence generation.
- There are no controlled studies of certolizumab pegol in pregnant women to demonstrate efficacy or to establish safety.
- This content is not intended to promote certolizumab pegol or to recommend treatment during pregnancy.

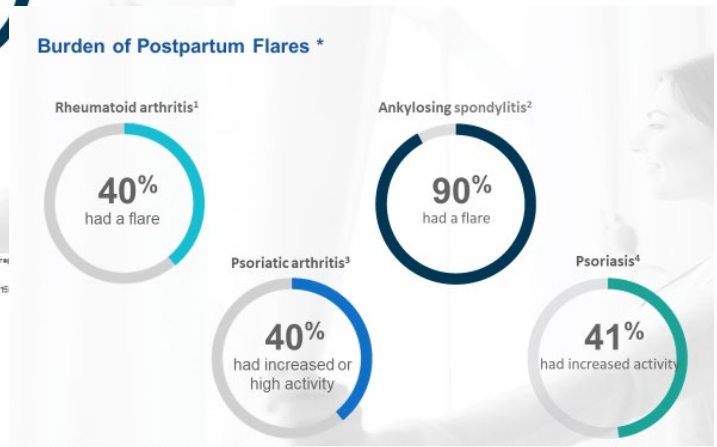
Starting with unmet needs

180 million people living with chronic inflammatory diseases, approximately half of which are women.

17% of patients with CID are within childbearing age (18-45 yrs old)







Ultimate Goal

To generate high-quality evidence as early as possible, empowering women and clinicians with the information they need for decision making during pregnancy

Inspired by patients. Driven by science.

*Chronic inflammatory diseases include Crohn's disease, rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, and PSO

PK in Pregnancy and Placental Transfer Study

CRIB Primary objectives

Transfer of medication across the placenta to infants from mothers


Clinical and epidemiological research

OPEN ACCESS

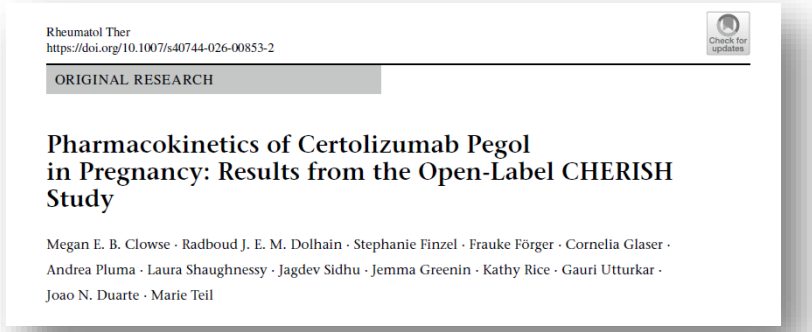
EXTENDED REPORT

Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study

Xavier Mariette,[1] Frauke Förger,[2] Bincy Abraham,[3] Ann D Flynn,[4] Anna Moltó,[5] René-Marc Flipo,[6] Astrid van Tubergen,[7] Laura Shaughnessy,[8] Jeff Simpson,[8] Marie Teil,[9] Eric Helmer,[10] Maggie Wang,[8] Eliza F Chakravarty[11]

CHERISH Primary objectives

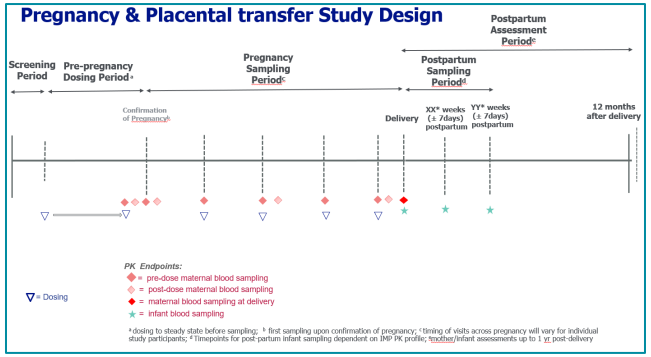
Assess systemic CZP exposure across the course of pregnancy in participants with CIDs


Rheumatol Ther
https://doi.org/10.1007/s40744-026-00853-2

ORIGINAL RESEARCH

Pharmacokinetics of Certolizumab Pegol in Pregnancy: Results from the Open-Label CHERISH Study

Megan E. B. Clowse · Radboud J. E. M. Dolhain · Stephanie Finzel · Frauke Förger · Cornelia Glaser · Andrea Pluma · Laura Shaughnessy · Jagdev Sidhu · Jemma Greenin · Kathy Rice · Gauri Utturkar · Joao N. Duarte · Marie Teil

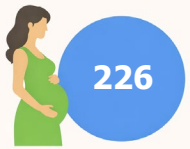


Protocol simulation with patients and hospital

Collaboration with patient, OBs, neonatologists, pediatricians

Integrating evidence across life cycle: PV publications

2015



Pregnancy Outcomes in Subjects Exposed to Certolizumab Pegol

Megan E.B. Clowse, Douglas C. Wolf, Frauke Förger, John J. Cush, Amanda Golembesky, Laura Shaughnessy, Dirk De Cuyper, and Uma Mahadevan

ABSTRACT. ***Objective.*** To provide information on pregnancy outcomes in women receiving certolizumab pegol (CZP).

Methods. The UCB Pharma safety database was searched for pregnancies through to September 1, 2014. Reports for maternal and paternal CZP exposure were included and outcomes examined, and data on CZP exposure, pregnancy, comorbidities, and infant events were extracted by 2 independent reviewers. Concomitant medications and disease activity were reviewed for clinical trial patients.

625 reported exposed pregnancies

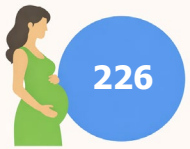
579 reported maternal exposures

339 pregnancies with available outcomes

226 prospective

Integrating evidence across life cycle: PV publications

2015



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2018

ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 9, September 2018, pp 1399–1407
DOI 10.1002/art.40508

Pregnancy Outcomes After Exposure to Certolizumab Pegol

Updated Results From a Pharmacovigilance Safety Database

Megan E. B. Clowse,[1] Angela E. Scheuerle,[2] Christina Chambers,[3] Anita Afzali,[4] Alexa B. Kimball,[5] John J. Cush,[6] Maureen Cooney,[7] Laura Shaughnessy,[7] Mark Vanderkelen,[8] and Frauke Förger[9]

1'600 reported exposed pregnancies

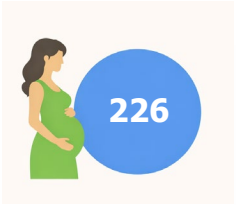
1'541 reported maternal exposures

1'137 prospective reports

528 known outcomes

PK Data Included in label

Integrating evidence across life cycle: PV publications

2015 

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2022 

Therapeutic Advances in Musculoskeletal Disease

Pharmacovigilance pregnancy data in a large population of patients with chronic inflammatory disease exposed to certolizumab pegol

Megan Clowse, Rebecca Fischer-Betz, Catherine Nelson-Piercy, Angela E. Scheuerle, Brigitte Stephan, Marla Dubinsky, Thomas Kumke, Rachna Kasliwal, Bernard Lauwerys and Frauke Förger

5’681 reported exposed pregnancies

5’576 reported maternal exposures

4’234 prospective reports

1’392 known outcomes

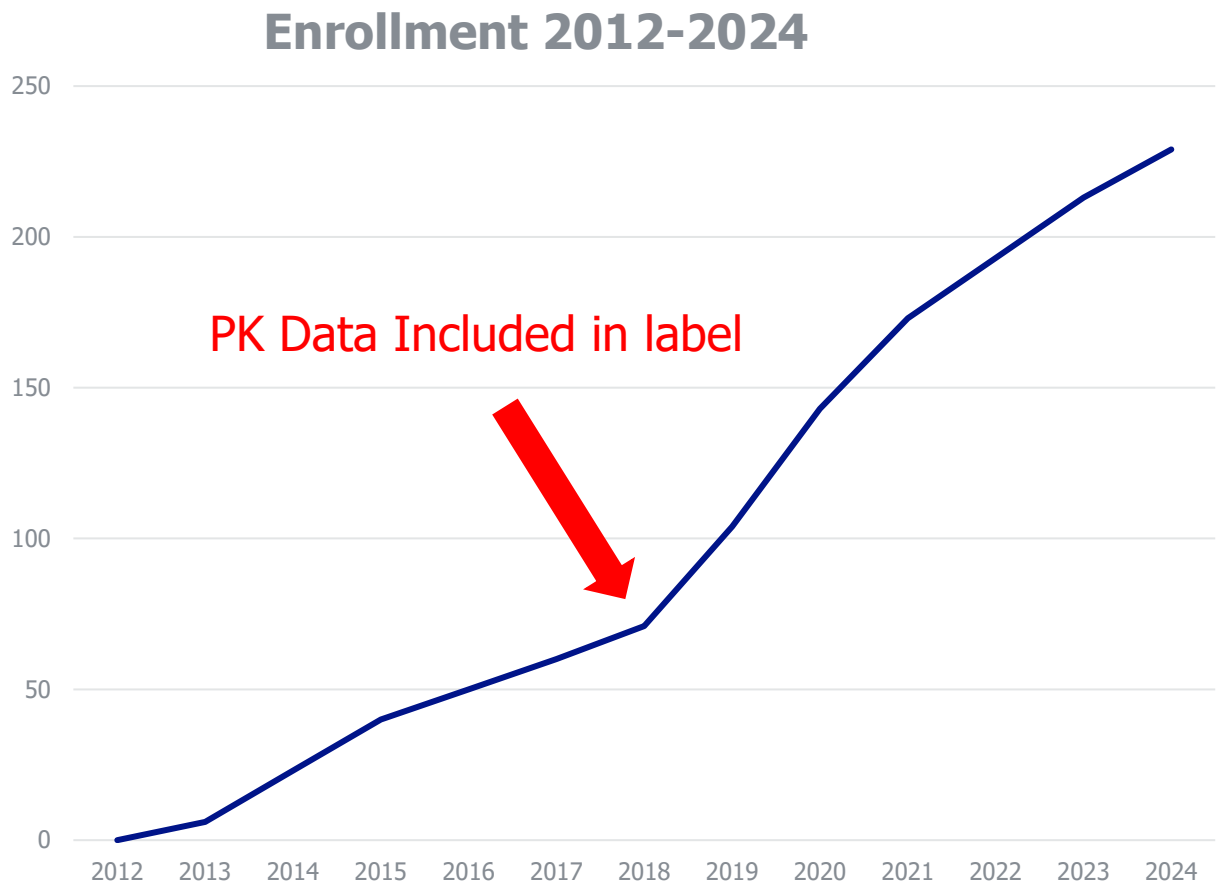
Prospective Pregnancy Registry

A prospective, observational, exposure cohort study of pregnancy outcomes in women in US and Canada: Opened for enrollment - March 2012

CZP Cohort: **CZP exposure** for an approved indication within 12 weeks of LMP and enrolled by 20 weeks gestation, no exposure to other biologics within 5 half-lives prior to LMP

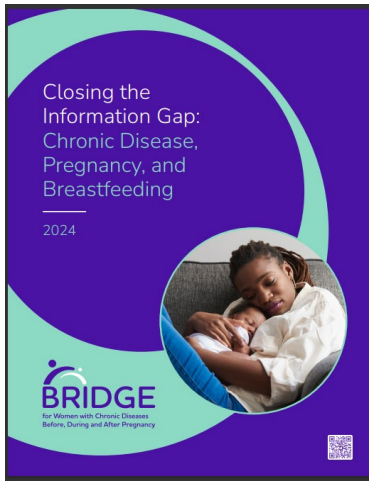
Disease Control Cohort: Diagnosed with a CZP approved indication with **no CZP exposure** during pregnancy but can be exposed to other biological therapy.

Non-Disease Control Cohort: **No CZP approved indications and no exposure** to biological therapy



Conclusion: Optimization of Pregnancy Registries through additional data sources

- **Pregnancy registries are foundational** to pregnancy safety evaluation and **data-informed labeling** can support optimization of registries
- The CZP experience shows how early integration of **non-registry evidence can accelerate learning**
- **Emerging guidance** (e.g. ICH E21) will facilitate the generation of robust data with the appropriate inclusion/retention of pregnant individuals in clinical trials
- **Collaboration** across regulators, industry, clinicians, and patients is critical to best meet patients' needs



Ultimate Goal

To generate high-quality evidence as early as possible, empowering women and clinicians with the information they need for decision making during pregnancy

Thank you

U.S. FOOD & DRUG ADMINISTRATION

BREAK

U.S. FOOD & DRUG ADMINISTRATION

Session 2 Panel Discussion

U.S. FOOD & DRUG ADMINISTRATION

Day 1

Closing Remarks

U.S. FOOD & DRUG ADMINISTRATION

Closing remarks: Day 1

Why are we here?

- Pregnancy is a special time in a woman's life
- Pregnant women deserve to have information to help them understand the safety of medicines and vaccines
- It is not acceptable to wait 10-18 years to obtain the information that is needed to support the safe of use of these therapies when used during pregnancy
- The goal is to bring stakeholders together discuss challenges and opportunities in the development, implementation, and conduct of pregnancy registry studies

Why are we here?

- Over 80% of women surveyed took at least one medication during pregnancy
- Many consulted with HCP's; but other platforms for information are also being consulted; including the internet; social media
- Fear is often behind these decisions
  - Miscarriage
  - Birth defects
  - Neurodevelopmental concerns
- Taking a medication during pregnancy is the NORM
  - It is incumbent upon us as a community to ensure that we have the safety information to support decisions about taking medications during pregnancy
- Important international collaborations are strengthening but there is a need to advance these efforts to increase the availability of clinically useful data to support decision making for providers and their pregnant patients

Session 1: Current State of Pregnancy Registries

- FDA has the authority to issue post-approval pregnancy safety studies under 505(o) of the FD&C
- Types of pregnancy safety studies
  - Pregnancy registries
  - Complementary studies
  - Descriptive pregnancy safety studies
- FDA review of post-approval safety studies
  - 11% of pregnancy registry studies were terminated; generally related to low enrollment
  - Of the pregnancy registries completed, the average time was 11 years

PDUFA VII Commitments

- FDA PDUFA VII Pregnancy Safety Study Framework and Demonstration Projects
- Development of framework about how different types of studies may be optimally used; consistently applied; and provide timely and highest quality evidence for regulatory decision making
  - Several projects underway evaluating different methods of signal detection (signal detection) and signal evaluation (hypothesis testing)
- Results of demonstration projects will inform guidance/MAPP due in 2027
- Specific projects
  - Projects a and c examine signal detection and evaluation for relatively common exposures: valproate and topiramate
  - Project b examines signal detection for relatively low exposures: mycophenolate and leflunomide
  - Project d assessing performance of MCM as a composite outcome in signal detection and evaluation when there is a true risk for some but not all specific malformations
  - Prediction model project: to estimate the magnitude of future exposure at the time of regulatory decision-making
  - Chart review of major congenital malformations

Stakeholder Perspectives

- Healthcare providers: What to do?
- What medicines will give her and her developing fetus the greatest chance for normal pregnancy and infant outcome?
  - Worried about hazards to the baby and the mother
- Multiple considerations: diagnosis, disease activity medications, comorbidities, genetics, social determinants, etc.
- Use of medical databases: did not perform well; unclear medication use (are the prescribed medicines actually being used); inaccurate social determinants, unmeasured disease activity; inaccurate diagnoses
- Local studies: under-powered; variable rigor
- National registries: providers forget because patients are spread thinly; gap between referral and enrollment
- How to increase participation
  - Make it easier: recruitment—few exclusions; remain top of mind; simple screening; enrollment needs to be fast and simple
- Data needs to be rigorous and reliable;
- Data gathering: both from physician and patient; clinically applicable; quick; integrated; and compensated

Stakeholder Perspectives

- National Pregnancy Registry for Psychiatric Medications: Antipsychotic Medication
  - Uses an active control group (patients with psychiatric disease but no exposure to antipsychotic medications)
  - Recruitment: internal and external sources (now using social media)
- Support from industry often based on requirements imposed by FDA; but the registry studies all antipsychotic medications regardless
- How do we practically make these studies sustainable?
- How do we integrate data streams to increase confidence in findings?

- Industry concerns
- What will the uptake of a medication or vaccine be including during pregnancy?
  - Are there alternatives during pregnancy; formulary decisions; payor decisions; international uptake
- How to improve on spontaneous reporting (many more spontaneous reports than enrollment in registry)
- Transcelerate review: 50% reported 5-10 years to accumulate data; 50% reported time greater than 10 years

Multiproduct Pregnancy Registry: Antiretroviral Pregnancy Registry

- Non-consolidated registry efforts are inefficient, costly and unlikely to lead to robust results in a timely manner
- Multi-product, multi-sponsor disease-based registries can address these concerns
- Trust is paramount and requires transparency and oversight by independent advisory committee
- Impact is increased with consistent reporting and publicly available findings
- Closing gaps and overcoming enrollment barriers
  - Lack of awareness
  - Barriers: did not have access to the necessary data to report; uncertain of process to report

Session 1: Panel Discussion

- How do we connect patients/providers more efficiently? How to make it easier?
  - Lack of awareness of registries available in OB/GYN community
  - What is the target HCP audience—maybe it isn't the OB/GYN community?
  - Misunderstanding and difficulty in understanding how to get involved from the patient side
- Potential solutions: No one solution will address this issue
  - Customized HER to provide alerts to the practitioner when a drug is being prescribed to a pregnant woman: pop up fatigues and may not pay attention; could this be linked to patient communication?
  - Institutional involvement or care coordinator; needs a champion within each institution
  - Increase patient-driven enrollment; let patients drive the enrollment
  - Incentivize practitioners: compensation? Board Certification/Maintenance of Certification?
- Incentives that could be considered:
  - Academia: salary support and contributions to manuscripts; but in certain situations may be complicated
  - Patients: Compensation can be useful; obtain information about outcomes of the study
- Removing barriers is as or more important than an incentive: reduce administrative burdens; employ AI tools; make it easy

Session 1: Panel Discussion

- How can Pregnancy Registries be implemented in areas that have historically been underrepresented?
  - Need to be sensitive to potential any potential for coercion
  - Points of contact that could be used (care coordinator); non-traditional ways?
  - Patient support groups; trusted groups
- What are the potential roles of advocacy/patient groups in increasing awareness/enrollment?
  - Can increase awareness, increase socialization; strong collaborators—coordination of communication as well
  - Need to be aware of the potential for misinformation/disinformation
  - Consider partnering with groups to make sure information is accurate
- Communication of data: how and when to communicate the data
  - What thresholds should be considered? Release of information from a separate advisory board? APR uses a threshold for communication at 200 exposures
  - Early sharing should be considered but need to be mindful of impact and confidence in the data
  - If presenting; needs to be presented in a simple and easily understood

Stakeholder Perspectives

- Patient Perspective
  - Concerns: there is a baseline concern already about the health of the baby and health of pregnancy; additional concerns include data breaches, time commitment; no ability to benefit directly from the results
  - Still, these concerns do not preclude interest in many pregnant women
  - It is surprising that so few care providers know about pregnancy registries; how do we educate women about this

Databased on Pregnancy Registries and Integration of Non-registry Sources

- Primary sources of data (designed as research studies)
- Secondary data (designed for other purposes)
  - Safety studies; eternal control; inform registry feasibility; identify patients who can enroll in registries; follow up of pregnancy registry
- Pharmacovigilance: identify dramatic effects for uncommon outcomes
- Pregnancy Registry: identify dramatic effects uncommon or moderate outcomes
- All of these data sources have strengths and limitations
- Use of RWD is dependent upon methods; numbers; and time
  - Methods: ascertainment; reference group and follow up time (who enrolls; who is comparable, and when to enroll)

- Target Trial Emulation: a method to use observational data to provide causal inference
  - Need to ask a causal question; specify the protocol carefully; explicitly describe how each aspect of the targe trial is emulated using observational data
- Database studies improve confidence
- Need to evaluate all data sources including database and pharmacovigilance
- Development of a “comprehensive” pregnancy safety program
  - PK in pregnancy, placental transfer study, pregnancy registry, pharmacovigilance program; complementary database study
  - Need to involve patients, OB/GYNs; neonatologist; pediatricians in designing a coordinated pregnancy safety program
  - Non-registry data can accelerate learning but pregnancy registries are foundational

Session 2: Optimizing Design of Pregnancy Registries in the Context of Totality of Evidence

- Why does it take so long? And what can be done to shorten this time?
  - No universal location to find information
  - Uptake of medicine does take some time; as uptake increases we need to be ready
  - Need better information of patients; direct to patient information and maybe societal changes are needed
  - Are there data that can be generated pre-approval?
  - Engaging patients early can help with both enrollment and with trust in post-marketing; information overload is real—if it can be spread out over a longer period can be helpful
  - Recognize cultural diversity and incorporate this diversity in communication
  - There is a necessary delay—need to identify strategies to decrease the delay
  - What is a rational approach to evidence communication? Need to have clinicians and epidemiologists and communication experts; how do the data tell the story
  - Don't forget the risk of not taking the drug
- Why are the PV data always so different that pregnancy registry numbers?
  - Some issues related to compliance; some related to registries only conducted in North America
  - Short time window from PV identification to getting enrollment into the Pregnancy Registry
  - If the medication is not recommended maybe this may explain some
  - Clinical research coordinators are IMPORTANT!!
  - Need to make better use of advocacy groups and patient groups
  - Enrollment is not the only thing—retention is also important!
  - Technology can be used creatively

Session 2: Optimizing Design of Pregnancy Registries in the Context of Totality of Evidence

- What is the optimal use and integration of all of these data streams?
  - More collaboration between pregnancy registries and experts I large data platforms
  - Pharmacovigilance review in the context of the pregnancy registry—the ability to review both confirmatory information
  - Increase confidence and helping to address limitations for outcomes and for outcomes

Homework

- Consider potential/emerging strategies to overcome challenges tonight so that we can have robust discussion tomorrow
- How to optimize emerging technologies and modern-day communications to improve the conduct of pregnancy registries?
- What is the low hanging fruit? What are the next steps to create sustainable; federated; multiproduct registries? What have the current multi-product registries already taught us?
- What are other novel approaches to leverage other data streams to complement pregnancy registries?