Scientific and Ethical Considerations for the Inclusion of Pregnant Women in Clinical Trials

February 2 & 3, 2021

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

Welcome & Overview | Day 1

Catherine Sewell

U.S. Food and Drug Administration

Remote Participation Instructions

Mute & Slides

- **You have been placed on mute**; speakers can mute/unmute throughout
- We will advance the slide deck, please prompt us to advance

Meeting Information

- #ResearchInPregnancy| Materials—https://healthpolicy.duke.edu/events

Questions & Comments

- Please go on video and use the “raise hand” Zoom option if you’d like to speak, we’ll pass the microphone and you can unmute
- Please feel free to type your question into the Q&A box

Zoom Issues? Please Zoom message Rasheed Willis or email rwillis@newmediamill.com

Meeting Agenda

Day One | Introduction and Preclinical Research

- Session 1: Understanding the Need and Existing Guidance for the Participation of Pregnant People in Clinical Trials
- Session 2: Nonclinical Safety Assessment to Support Clinical Trials Enrolling Pregnant People
- Session 3: Scientific and Ethical Considerations when Designing Clinical Trials that Enroll Pregnant People

Day Two | Approaches to Clinical Trial Design and Conduct and Next Steps to Advance Therapeutic Development

- Case Study: Comparing and Contrasting Clinical Trials Enrolling Pregnant People to Evaluate Treatment for a Chronic Medical Condition and Clinical Trials for a Pregnancy-Related Condition
- Session 4: Challenges and Next Steps

Opening Remarks from FDA

Kaveeta Vasisht

U.S. Food and Drug Administration

FDA Activities Related to Pregnancy and Lactation

Kaveeta P. Vasisht MD, PharmD
Associate Commissioner for Women's Health
Director, Office of Women's Health (OWH)
U.S. Food and Drug Administration
February 2, 2021

U.S. FOOD & DRUG ADMINISTRATION

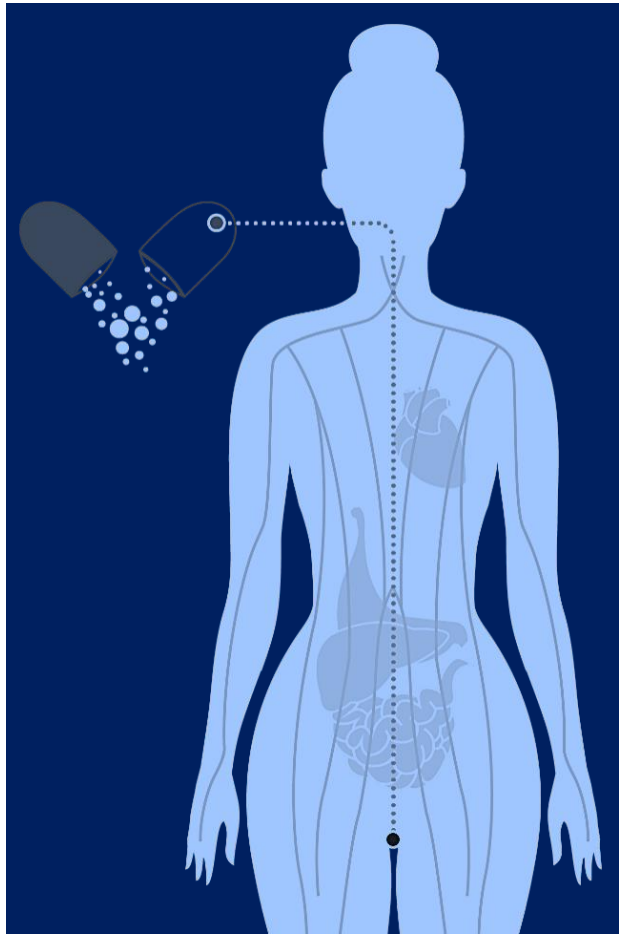
Disclaimer

The views expressed are those of the speaker and do not necessarily reflect official policy of the US FDA.

No official endorsement by the US FDA is intended or should be inferred.

No Conflicts of Interest.

Office of Women's Health Mission



- **Promote the inclusion of women in clinical trials** and the implementation of guidelines concerning the representation of women in clinical trials and the completion of sex/gender analysis
- **Identify** and monitor the progress of **crosscutting** and multidisciplinary women's health initiatives including **changing needs, areas that require study, and new challenges** to the health of women as they relate to FDA's mission
- **Serve** as the **principal advisor to the Commissioner** and other key Agency officials on **scientific, ethical, and policy** issues relating to women's health

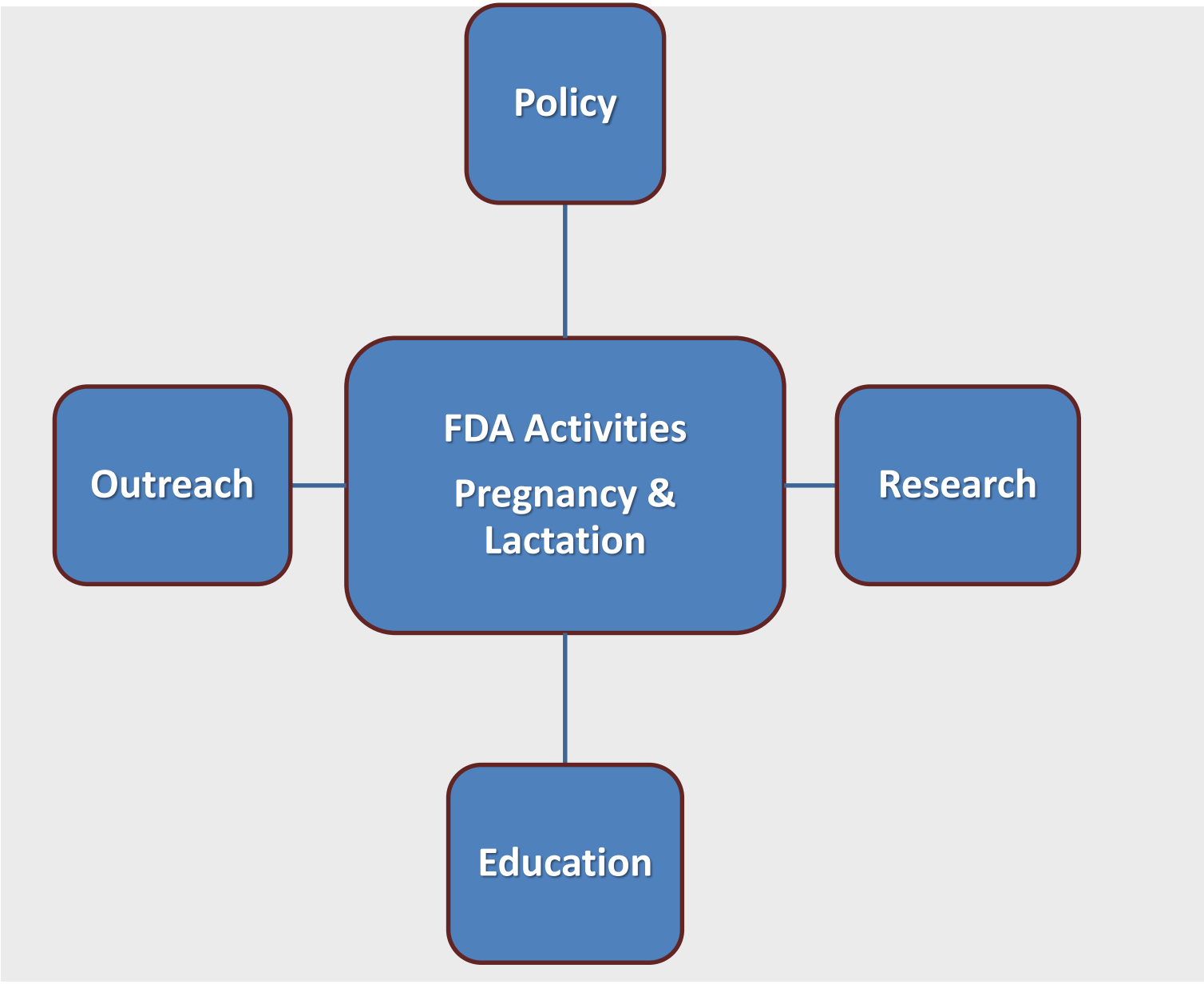
Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

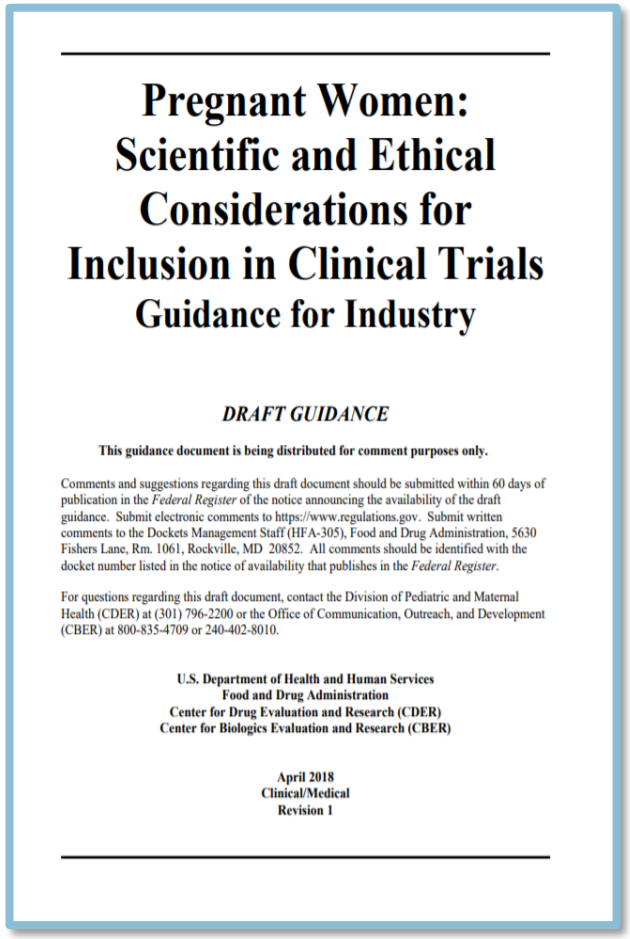
The 21st Century Cures Act P.L. 114-255

- Office of the Commissioner*
- Center for Biologics Evaluation and Research
- Center for Devices and Radiological Health
- Center for Drug Evaluation and Research
- Center for Food Safety and Applied Nutrition
- Center for Tobacco Products
- National Center for Toxicological Research

* Office of Women's Health PRGLAC Task Force Member

- Representation from across FDA
- Provided input prior to each Task Force meeting
- FDA represented on all four Implementation Plan working groups
- Provided input on PRGLAC Report to HHS Implementation Plan Report


Policy
Outreach
FDA Activities
Pregnancy &
Lactation
Research
Education



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

Guidance for Industry

DRAFT GUIDANCE

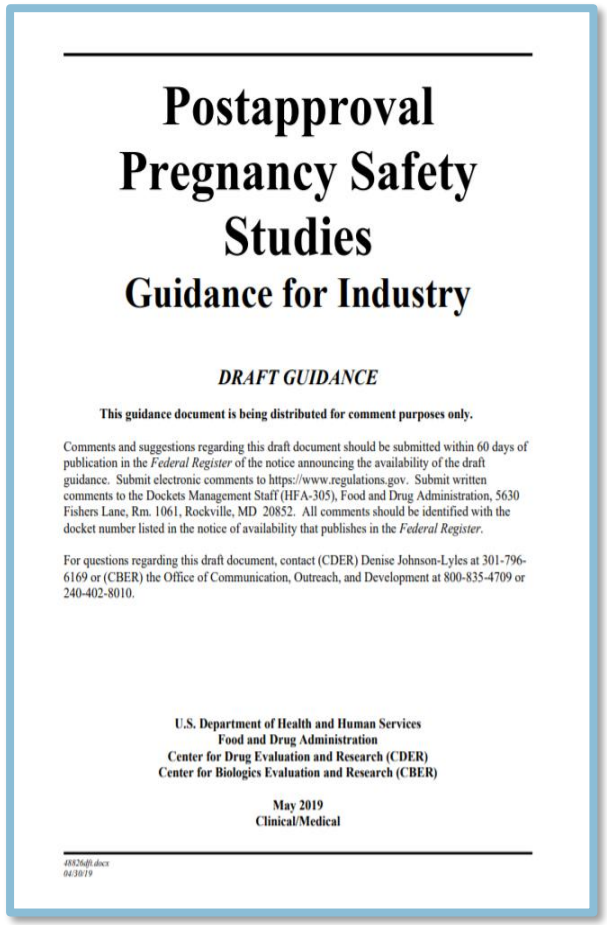
This guidance document is being distributed for comment purposes only.

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

For questions regarding this draft document, contact 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



Postapproval Pregnancy Safety Studies

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

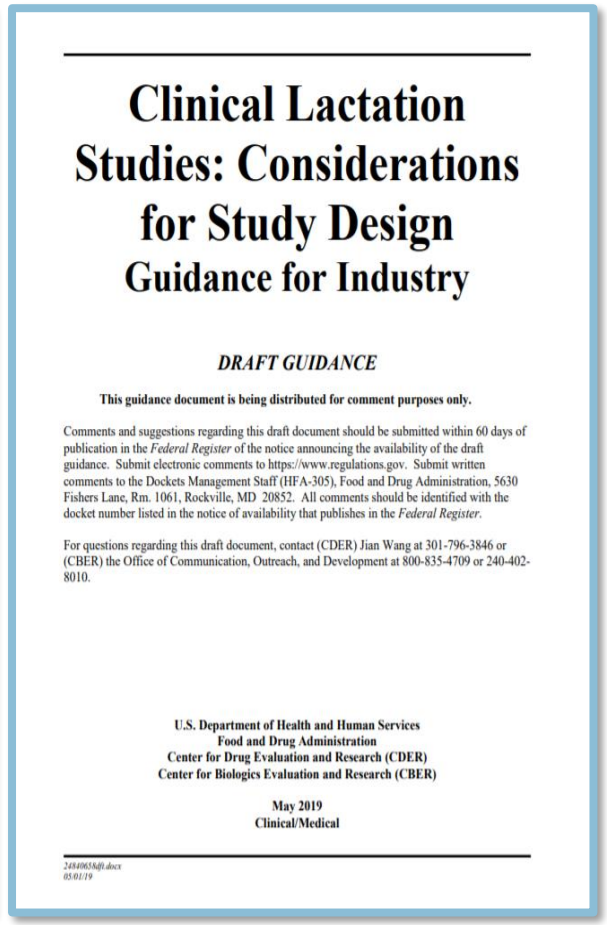
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management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

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

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

May 2019
Clinical/Medical

4882dft.docx
04/30/19



Clinical Lactation Studies: Considerations for Study Design

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

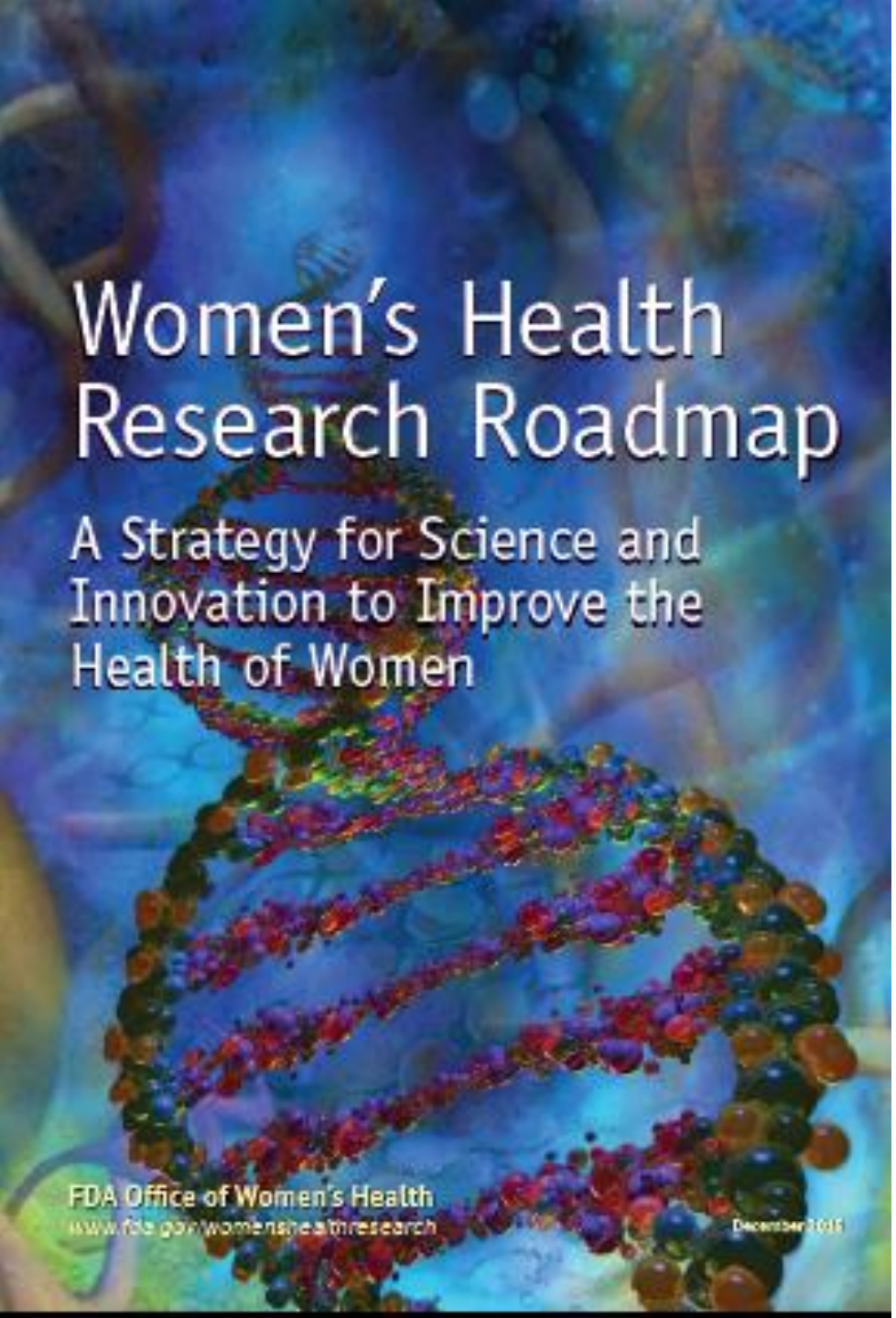
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management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

For questions regarding this draft document, contact (CDER) Jian Wang at 301-796-3846 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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

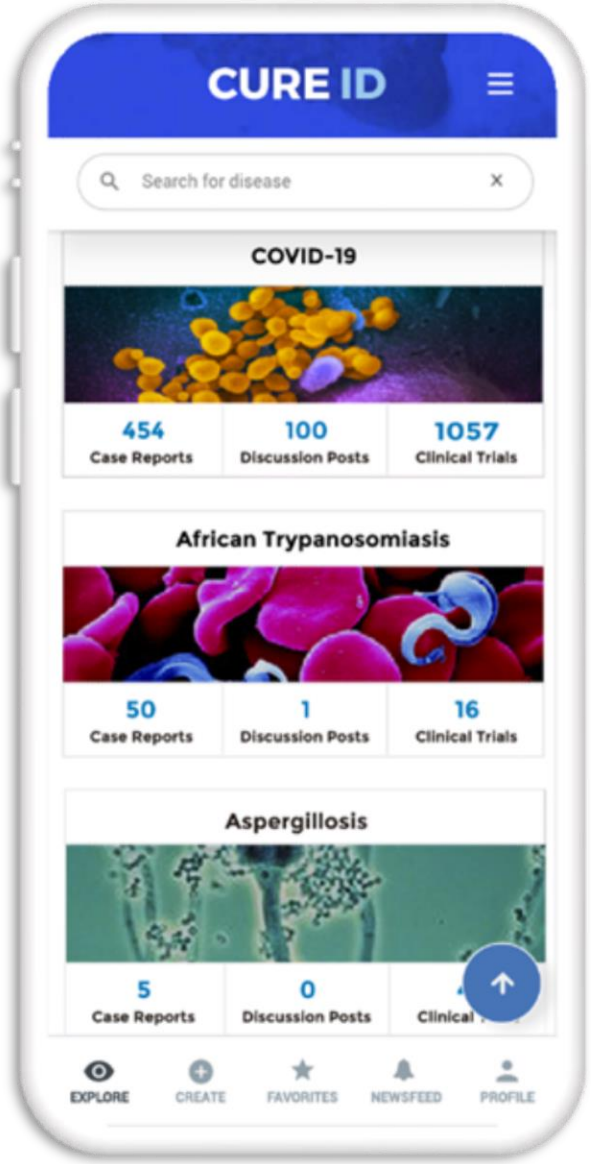
May 2019
Clinical/Medical

2484065&fl.docx
05/01/19



OWH Funded Research in Pregnancy & Lactation

- Assessing real world use of pharmaceuticals among pregnant and lactating women
- Predicting the transfer of breast cancer resistant protein (BCRP) substrates into human milk using in vitro to in vivo extrapolation (IVIVE)
- Pregnancy and Lactation Labeling Rule (PLLR): Health Care Provider Testing to Improve Health Communications Related to Lactation
- Development of an artificially intelligent virtual pregnant woman modeling suite to support regulatory decisions
- Evaluation of women's targeted dietary supplements for labeling compliance and potential contamination, containing live microbes in the US market with special emphasis on pregnant and lactating women
- Model-informed approaches to facilitate dose selection for antimalarial drugs in pregnant women
- Computational framework for assessing xenobiotic disposition and interactions in pregnant women
- Placental Transmission of Zika Virus



CURE ID app:
Reporting novel uses of existing drugs

CURE Pregnancy Treatment Repository

Visit :https://cure.ncats.io/

OWH Pregnancy Registries Webpage

www.fda.gov/pregnancyregistries

- ~120 medical product registries
- Links to drug information
- Patient education resources

FDA Center of Excellence for Perinatal and Maternal Health

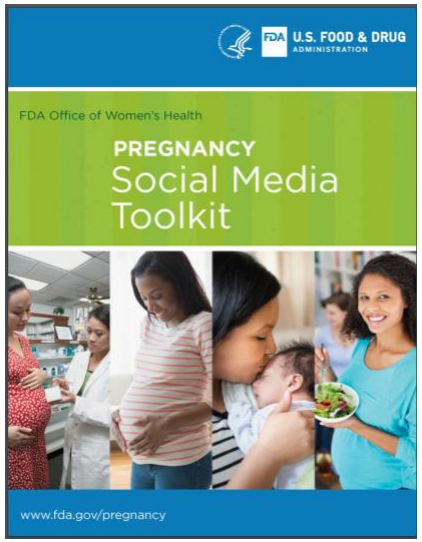
- **FDA Scientists recognized the need for a coordinated effort for research in the perinatal period**, defined to include: maternal, premature, neonatal periods and development throughout childhood.
- PHCE was created to focus on these populations and increase opportunities for collaborations, leveraging research opportunities and support research that applies to the understudied populations of the perinatal period.
- The PHCE Leadership Council and PHCE Liaisons are represented across all FDA.

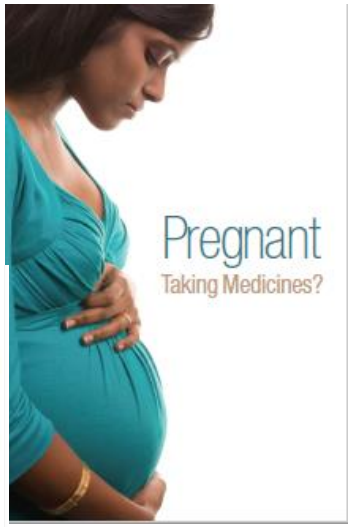
https://www.fda.gov/about-fda/nctr-research-focus-areas/perinatal-and-maternal-research

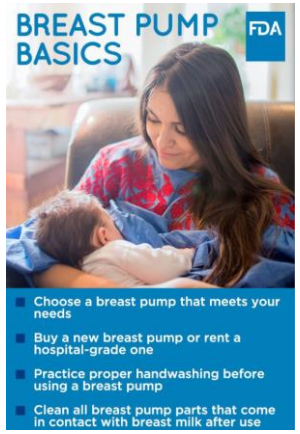
OWH Workshops & Webinars

- The Safety of Asthma Medications During Pregnancy: Research Priorities and Methodology (November 2019)
- COVID-19 and Pregnancy: What We Know (August 2020)
- CBD & Other Cannabinoids Scientific Conference (November 2020)

OWH Pregnancy Resources







www.fda.gov/womenshealthpubs

Stay Connected

twitter.com/FDAWomen

facebook.com/FDA/

fda.gov/consumers/consumer-information-audience/women

www.fda.gov/womens

www.fda.gov/womenshealthresearch

@FDAWomen on Twitter

Session 1: Understanding the Need and Existing Guidance for the Participation of Pregnant People in Clinical Trials

Moderator: Susan McCune, U.S. Food & Drug Administration

Leyla Sahin

U.S. Food and Drug Administration

FDA Perspective on the Inclusion of Pregnant People in Clinical Trials

Leyla Sahin, M.D.
Division of Pediatric and Maternal Health
Center for Drug Evaluation and Research, US FDA

Clinical Trials in Pregnant Women FDA-Duke Margolis Public Meeting 2-2-2021

Disclaimer

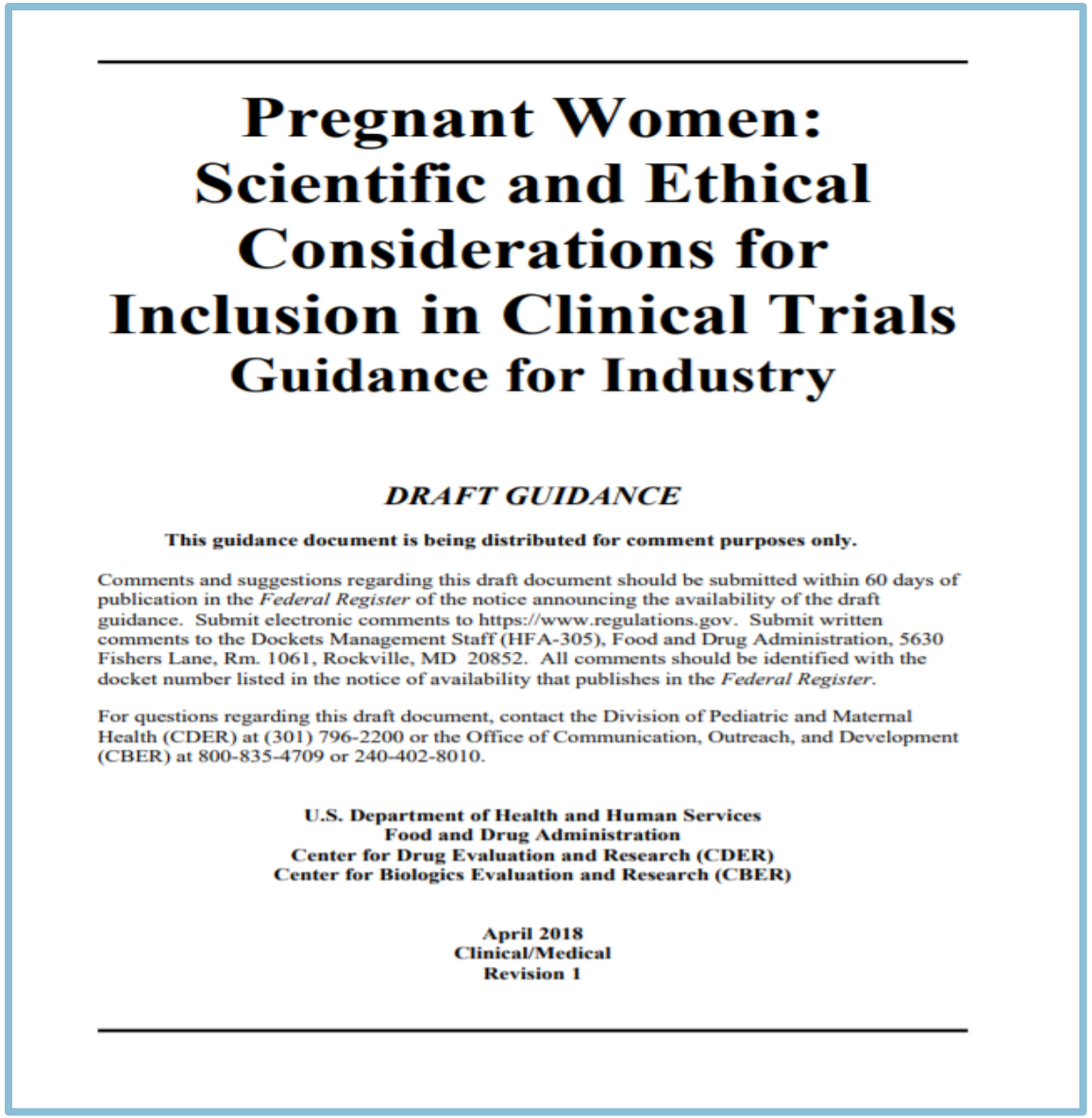
- I do not have any financial disclosures to report
- This presentation represents the views of the speaker, and not the official position of the FDA

Objectives

- Discuss FDA efforts to advance clinical trials in pregnant people
- Review regulatory framework for inclusion of pregnant people in clinical trials
- Discuss FDA efforts to collect data in pregnant and lactating people with COVID-19

FDA perspective

- Committed to advancing research in pregnant and lactating people
  - Data needed to inform labeling and benefit-risk
  - Recent guidance publications
- Regulatory advances
  - Common Rule: has removed reference to pregnant people as “vulnerable”
  - FDA is working to harmonize its regulations with the Common Rule
- Participant in Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)



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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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

For questions regarding this draft document, contact 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

Published
April, 2018

Guidance: Clinical Trials in Pregnant Women

- Ethical and scientific considerations
  - For when to include pregnant women in clinical trials
  - Follows HHS framework of human subject protection regulations
  - Considerations for postmarket vs. premarket setting
  - Women who become pregnant during a trial
- FDA is reviewing public comments

Federal Regulations 45 CFR part 46, subpart B Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research*

- Regulations include 10 specific requirements

1. Where scientifically appropriate, nonclinical studies (including in pregnant animals) and clinical studies have been conducted and provide risk information

*Applies to research conducted or supported by HHS; however, recommended by FDA.

Subpart B 45 CFR 46.204 Requirements for Pregnant Women or Fetuses

2. Prospect of direct benefit to the woman or fetus; if no benefit, the risk to the fetus must be minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

   Minimal Risk (45 CFR 46.102 (j)): "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Subpart B Requirements for Pregnant Women or Fetuses

3. Least possible risk for achieving the objectives
4. Informed consent is obtained as described in subpart A
5. If the prospect of direct benefit is solely for the fetus, then additional consent from the father is needed, unless he is unavailable, incompetent, has temporary incapacity or the pregnancy results from rape or incest

Subpart B Requirements for Pregnant Women or Fetuses

6. Participants are fully informed of the reasonably foreseeable impact of the research on the fetus or neonate
7. For children who are pregnant, assent and permission are obtained
8. No inducements for pregnancy termination
9. Investigators not involved in decisions re: pregnancy termination
10. Investigators not involved in determining the viability of a neonate

Postmarketing vs Premarketing Setting

Considerations:

- All 10 regulatory requirements of 45 CFR 46 Subpart B have to be met
- Risk assessment and benefit considerations may vary depending on the setting
  - amount of data available to inform safety, efficacy, and dosing
  - gestational age
  - seriousness of the disease
  - availability of treatment options

Trials in the Postmarketing Setting

Considerations:

- Have the regulatory requirements been met ?
- Opportunistic Pharmacokinetic (PK) studies: minimal risk
- Intervention trials: is the benefit-risk favorable?

Trials in the Premarketing Setting

- More challenging due to limited safety, efficacy, and dosing information
- Scenario 1: Study participants who become pregnant during a trial

  Considerations to allow continued participation and PK data collection:

  – Are the nonclinical data adequate to support lack of risk?

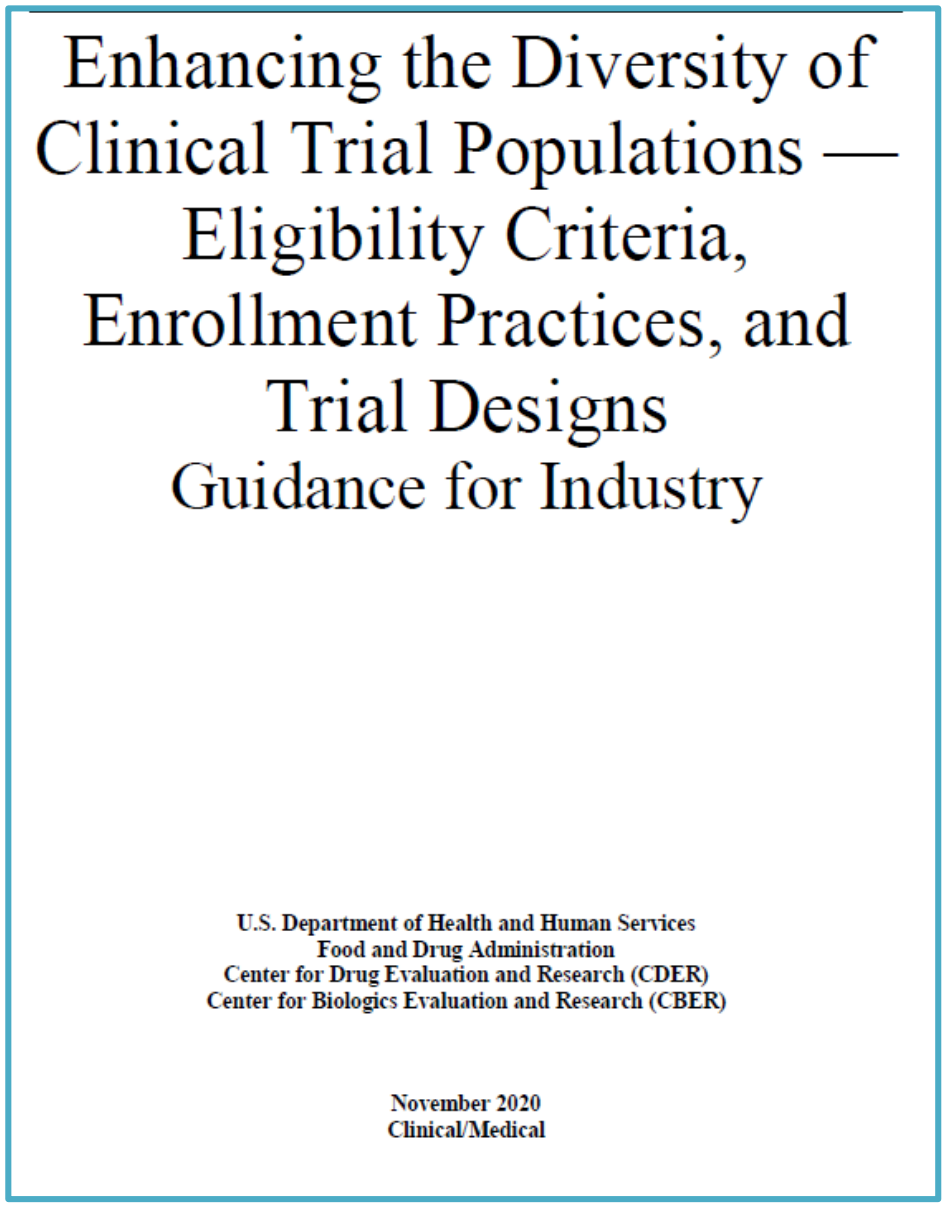
  – Do the benefits of continued treatment outweigh the risks (1. to the fetus, 2. the risk of discontinuation and 3. switching to another drug(s) with potential fetal exposure to an additional drug)
- Unblinding and consent
  – Unblinding for benefit-risk considerations
  – Re-consent as a pregnant participant

Trials in the Premarketing Setting

- Scenario 2: Include in the development plan
  - More challenging
  - Considerations:
    - Timing in drug development
    - Benefit-risk
    - If nonclinical study results not available, consider the inclusion of pregnant people when available

Safety Monitoring of Trial Participants

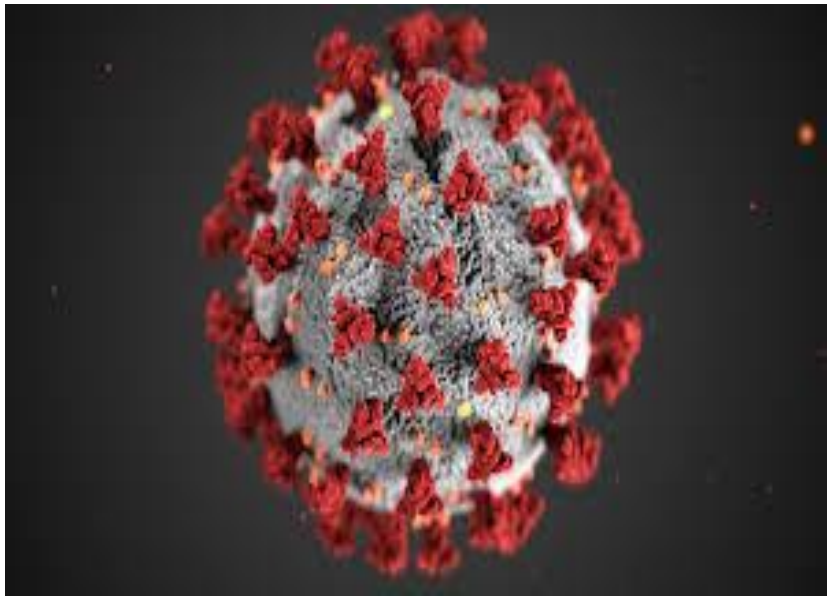
- Consideration for increased safety monitoring
- Cord blood collection at time of delivery
- Pregnancy outcome data
- Follow infant until 1 year of age or longer in a pregnancy registry or other observational study



- Published 11-9-2020
- Women who get pregnant in a trial:
  - Consideration to allow continued participation
  - Do the benefits of continued participation outweigh the risks
  - Consider Pharmacokinetic (PK) data collection to help inform dosing in pregnancy

FDA Advice re: COVID-19

- Guidance 5-2020: Developing Drugs and Biological Products for Treatment or Prevention of COVID-19
  - FDA encourages the enrollment of pregnant and lactating individuals in the phase 3 (efficacy) clinical trials if appropriate
- Guidance 6-2020: Development and Licensure of Vaccines to Prevent COVID-19
  - FDA recommends the early conduct of developmental and reproductive toxicology (DART) studies to allow pregnant women to enroll in clinical trials



Summary

- FDA is committed to advancing clinical trials in pregnant and lactating people
- Regulatory advances are occurring
- Growing consensus on the need to include pregnant and breastfeeding people in clinical research
- Many challenges: discussed in PRGLAC reports
- Time for action: stakeholder collaboration is essential to move forward: federal agencies, industry, academic institutions, clinical trial networks, researchers, IRBs

Thank You

Aaron Pawlyk

National Institutes of Health

Update on Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC): *Implementation*

Aaron C. Pawlyk, Ph.D.

Chief, Obstetric and Pediatric Pharmacology and Therapeutics Branch

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Underrepresented Groups in Research

VIEWPOINT

Improving Public Health Requires Inclusion of Underrepresented Populations in Research

Catherine Y. Spong, MD
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.

Diana W. Bianchi, MD
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.

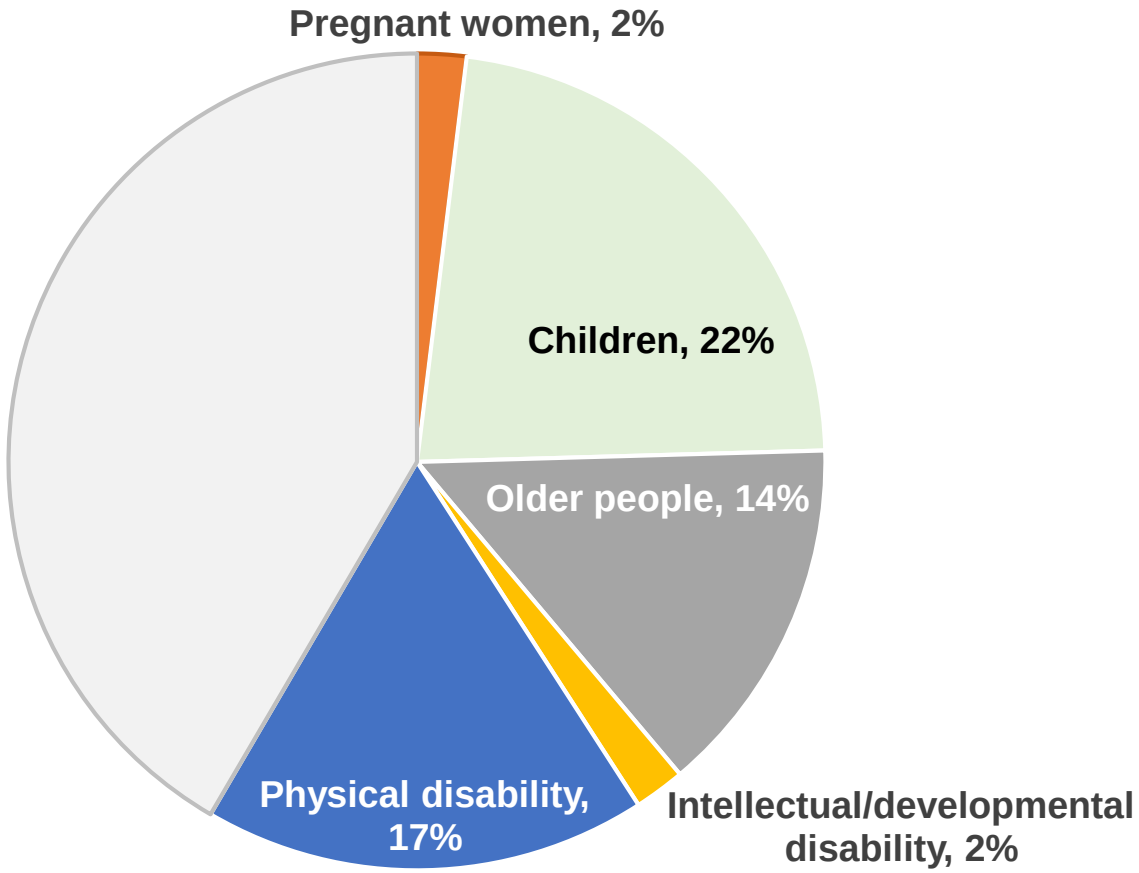
Supplemental content

Advances in genomics have ushered in promising therapies tailored to the individual. Personalized medicine is promoted and has begun to positively influence care. For example, medications such as trastuzumab for the 30% of breast cancers that overexpress *ERBB2* and vemurafenib for patients with late-stage melanoma who carry the V600E variant have been beneficial.[1] Despite these advances, for many sectors of the population—children, older adults, pregnant and lactating women, and individuals with physical and intellectual disabilities—limited evidence-based therapies optimized to their specific medical needs exist. Combined, these groups comprise as much as 58% of the US population (eTable in the Supplement). Research focusing on or at the very least includes members of these groups is critically needed.

Until the initial passage of the Best Pharmaceuticals for Children Act in 2002, pediatric drug doses were based on extrapolation from adults. Importantly, body composition and metabolic processes change as children develop, resulting in different safety and efficacy profiles.[2] Similarly, medication needs change with age cations are often prescribed with minimal evidence to support their use, especially psychotropic drugs with significant adverse effects.

Recently, discussions have arisen about the need for inclusion in research and elimination these gaps. In 2017, the National Institutes of Health (NIH) held a workshop, "Inclusion Across the Lifespan," that highlighted current federal regulations that include protections for "vulnerable populations" (pregnant women, fetuses, neonates, prisoners, and children). Although these regulations were originally designed to protect these individuals, many investigators have called for reconsideration, opting to protect them *through* research, rather than *from* research. Inclusion will likely yield data that will benefit more people.

Many underrepresented populations encounter barriers to participation in research. In a review of 338 phase 3 and 4 NIH-funded actively recruiting studies in Clinicaltrials.gov, explicit exclusion was found in 68% for pregnant women, 47.3% for lactating women, 75.7% for children, 27.8% for older people, 12.4% for those with



Up to 59% of the U.S. population comprises people who typically are not included in research studies (pregnant women, children, older people, and those with intellectual and physical disabilities).

These numbers are approximate to provide a general impact, the numbers do not account for overlap between categories.

Spong CY, Bianchi DW. Improving Public Health Requires Inclusion of Underrepresented Populations in Research. JAMA. 2018;319(4):337–338. doi:10.1001/jama.2017.19138

Pregnancy and Lactation

- 6.3M women become pregnant
  - >90% take at least one medication and 70% use at least one prescription medication
  - 500,000 women have difficulty producing milk
- Concerns re: liability
- Complexity of pregnancy
  - Fetus and placenta change over gestation, timing of exposure
  - Physiologic changes of pregnancy
  - Impact of external factors: obesity, environment
  - Co-existing chronic or acute conditions
- Lactation
  - Benefits of breastfeeding vs. medications in woman
  - Limited assays for assessment of medications in breastmilk

21st Century Cures Act
(Signed December 13, 2016)

SEC. 2041. TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN.

ESTABLISHMENT.—Not later than 90 days after the date of enactment of this Act, the Secretary of Health and Human Services (referred to in this section as the "Secretary") shall establish a task force, in accordance with the Federal Advisory Committee Act…

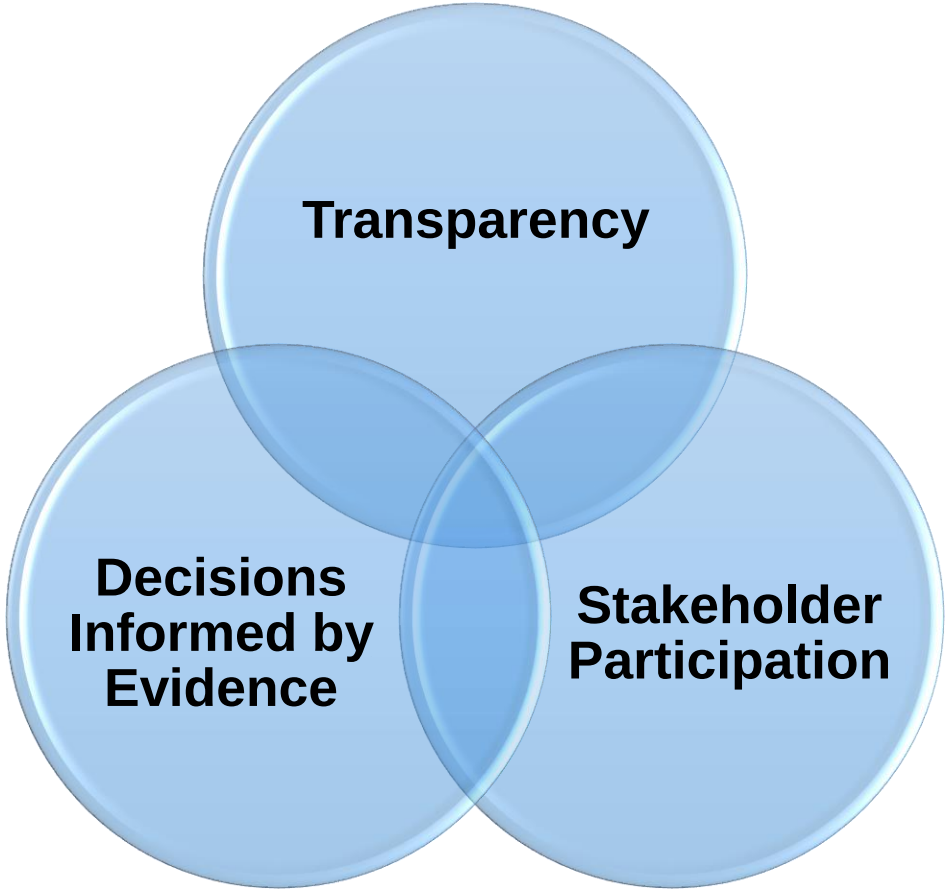
(2) DUTIES.—The Task Force shall provide advice and guidance to the Secretary regarding Federal activities related to identifying and addressing gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies and the collaboration on and coordination of such activities.

At the same time… NICHD Strategic Plan 2020

Goals

1. Identify where NICHD should lead (priorities)
2. Identify where NICHD should partner and collaborate
3. Inform future investments in research, training, and infrastructure

Core Principles



https://www.nichd.nih.gov/about/org/strategicplan

Advancing Safe and Effective Therapeutics and Devices for Pregnant and Lactating Women, Children, and People with Disabilities

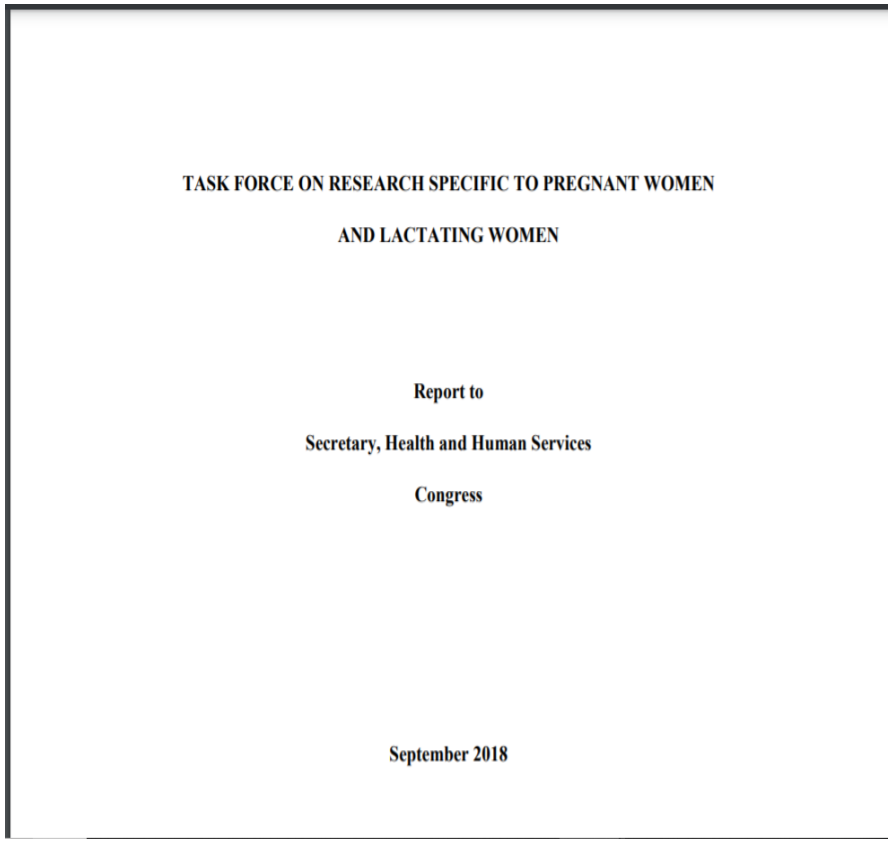
Goal: Lead efforts to develop, test, and evaluate new and existing therapeutics and devices to find safe and effective solutions that **meet the unique needs of pregnant and lactating women, children, and people with intellectual and physical disabilities.**

- Conduct and support foundational research on the development of therapies, including pharmacokinetic, pharmacodynamic, pharmacogenomic, dosing, and formulation studies, to ensure that these treatments meet the needs of pregnant or lactating women, children, and people with disabilities.
- Identify specialized biomarkers, new modeling approaches, and improve outcome measures to support the use of pharmacotherapies and reduce barriers to testing these therapies in pregnant and lactating women, children, and people with intellectual and physical disabilities.
- Support clinical research to test and evaluate therapeutics and medical devices used by pregnant and lactating women, children, and people with intellectual and physical disabilities.
- Use large-scale datasets such as electronic health records, research networks or registries, or other big data approaches—to measure exposure responses to therapy and device use among pregnant and lactating women, children, and people with disabilities.

PRGLAC Report Submitted to HHS Secretary September 2018

15 Recommendations

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


TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN

AND LACTATING WOMEN

Report to

Secretary, Health and Human Services

Congress

September 2018

Next step – Developing a plan to implement these recommendations

PRGLAC Taskforce Working Groups and Recommendations

- 15 overall recommendations
- *September 2018* - Report Submitted to HHS Secretary
- *Next step* – Developing a plan to implement these recommendations

Implementation Plan Submitted to the Secretary August 2020, Posted on PRGLAC Website

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

The 21st Century Cures Act established PRGLAC to advise the Secretary of Health and Human Services (HHS) regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. PRGLAC was tasked with identifying these gaps and reporting its findings back to the Secretary.

Federal members include the directors of NIH, NICHD, the Centers for Disease Control and Prevention, the HHS Office on Women's Health, and the Commissioner of Food and Drugs. Non-federal members include representatives from relevant medical societies, non-profit organizations, and industry.

Advisory Groups

Board of Scientific Counselors (BSC)

National Advisory Child Health and Human Development (NACHHD) Council

National Advisory Board on Medical Rehabilitation Research (NABMRR)

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

Learn More

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

Implementation Suggestions – Likely NIH

- Leverage or expand existing federal programs or networks
- Establish a prioritization process for studying therapeutics used during pregnancy and lactation
- Develop new research tools (e.g. preclinical models – tissue on a chip)
- Expand training in ob/lactation pharmacology
- Consider alternative trial designs, e.g. adaptive
- Create partnerships to accomplish the steps (E.U. ConcePTION)

Implementation Suggestions – Other HHS divisions/Non-government stakeholders

- Require industry to submit study plans to FDA
- Address ethical considerations, liability concerns, and potential research incentives to pursue research (OHRP)
- Foster education and awareness among health care providers and pregnant and lactating women
- Public private partnerships
- Study on liability concerns (NASEM?)
- Some steps would require authorization

PRGLAC: Early Impact

New NIH Reporting Categories

- Pregnancy
- Maternal Health
- Breastfeeding, Lactation, and Breast Milk
- Maternal Morbidity and Mortality

(coming in FY 2020)

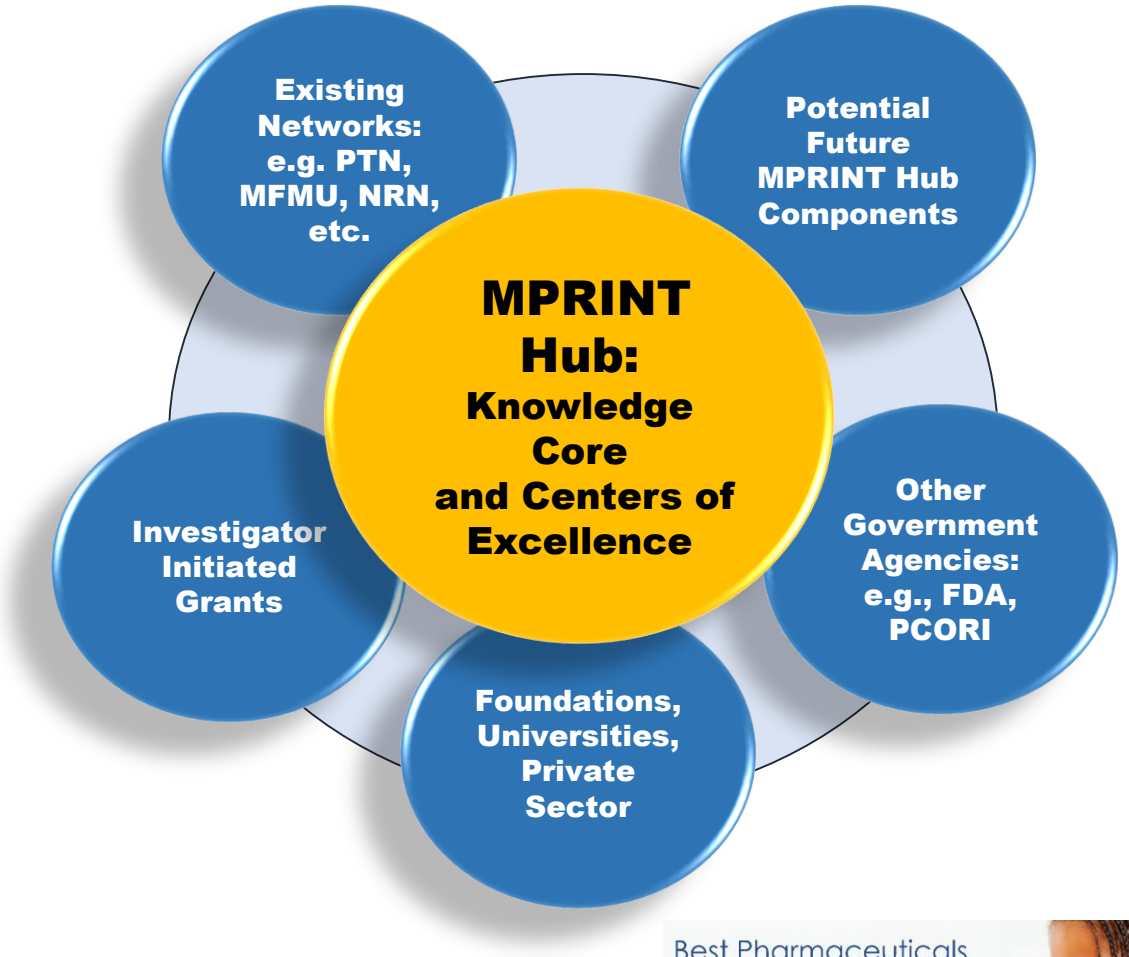
https://report.nih.gov/categorical_spending.aspx

PregSource® Medications Tracker

Maternal and Pediatric Precision in Therapeutics Hub

MPRINT Hub is a service center and science catalyst:

- Provide knowledge and expertise to scientific community
- Serve as a platform for innovative multidisciplinary research
- Synergize with other resources and networks
- Catalyze and accelerate maternal and pediatric therapeutics towards precision medicine



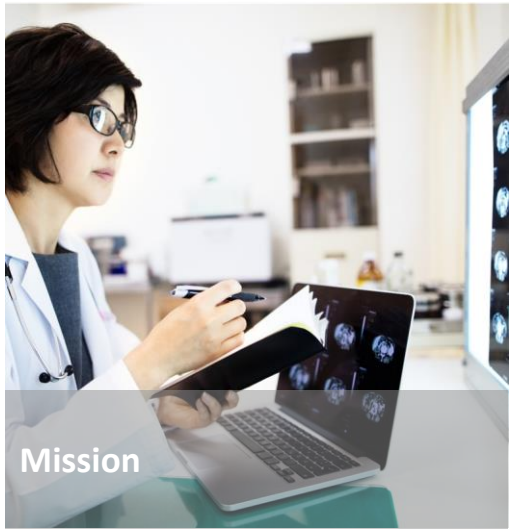
https://www.nichd.nih.gov/about/org/der/branches/opptb/mprint

Public Private Partnership for Qualification of Biomakers for Early Risk Detection of Preeclampsia

FNIH
Foundation for the National Institutes of Health

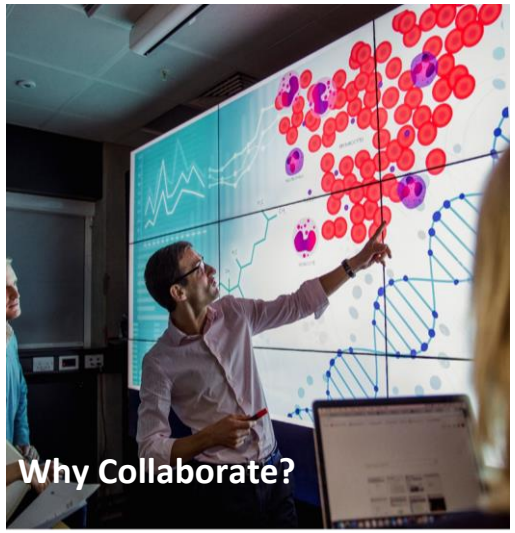
Project under development in the Metabolic Disorders Steering Committee of the FNIH Biomarker Consortium

About the FNIH



The mission of the Foundation for the National Institutes of Health (FNIH) is to support the mission of the NIH. The FNIH creates and leads alliances and public-private partnerships that advance breakthrough biomedical discoveries and improve the quality of people's lives.

The FNIH was created by Congress in 1990 as a not-for-profit charitable organization. The Foundation began its work in 1996 to facilitate groundbreaking research at the U.S. National Institutes of Health (NIH) and worldwide.



- Attract and share resources
- Enable insight and innovation
- Establish standards
- Distribute expertise
- Create consensus
- Drive competitiveness in market
- Disseminate knowledge
- Enhance credibility
- Reduce costs
- Support training & education
- Manage complexity

BIOMARKERS CONSORTIUM FNIH

Thank you!

Jeanne Sheffield

Johns Hopkins Medicine

The Inclusion of Pregnant Women and Breastfeeding Women in Clinical Trials

The Clinician Perspective

Jeanne S. Sheffield, MD
Maternal-Fetal Medicine
Johns Hopkins Medicine

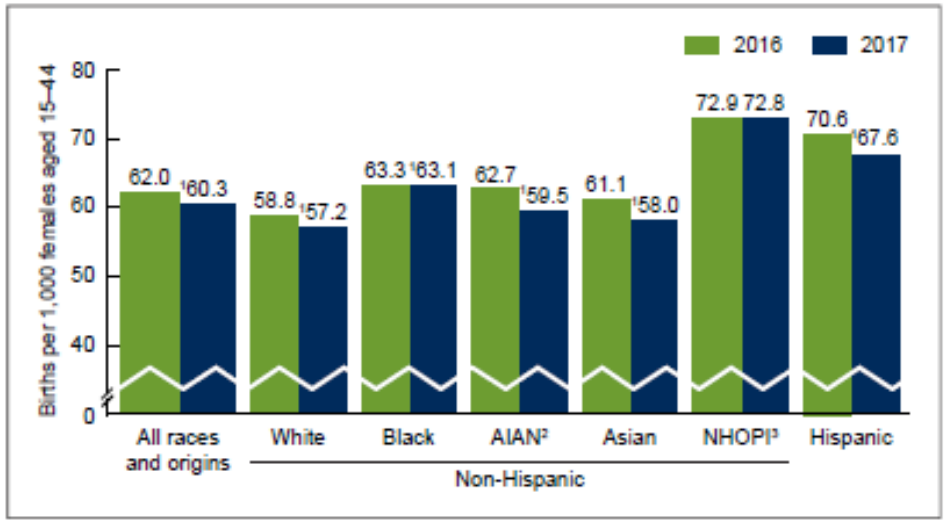
The Health Care Provider:Patient Interaction

- The patient comes to every encounter with the assumption that the physician will be able to accurately diagnose and treat whatever medical issue is present. They also assume that the physician is able to perform a risk:benefit analysis for each therapeutic option and then present the best one to the patient.
  - "Discuss with your physician before starting, taking, etc…."
- Pregnancy compounds this with at least one other patient in the calculations

The Evidence Gap for Pregnant and Lactating Women

- Approximately 6 million women in the United States become pregnant every year with ~ 4 million lives births

Figure 1. General fertility rates, by race and Hispanic origin of mother: United States, 2016 and 2017



¹Significant decline from 2016 ($p < 0.05$).
²AIAN is American Indian or Alaska Native.
³NHOPI is Native Hawaiian or Other Pacific Islander.
NOTES: The general fertility rate is the number of births per 1,000 females aged 15–44. Race groups are single race. Access data table for Figure 1 at: https://www.cdc.gov/nchs/data/databriefs/db318_table.pdf#1.
SOURCE: NCHS, National Vital Statistics System, Natality.

Mitchell et al. Am J Ob/Gyn 2011
Adam et al. Am J Med Genet C Sem 2011
McCormack et al. Front Ped 2014
Wang et al Clin Pharm Ther 2017
Eke et al. NEJM 2019

The Evidence Gap for Pregnant and Lactating Women

- 70-80% take at least one prescription medication during the first trimester and 90% at some point during the pregnancy
  - Average 3 medications/pregnancy and 4 medications/lactation
- 98% of medications have data insufficient to determine teratogenicity risk
- 98% of dosing studies do not include pregnant women

Mitchell et al. Am J Ob/Gyn 2011
Adam et al. Am J Med Genet C Sem 2011
McCormack et al. Front Ped 2014
Wang et al Clin Pharm Ther 2017
Eke et al. NEJM 2019

Pregnancy and Therapeutic Agents

- Prenatal vitamins
- Antiemetic, analgesia and allergy medications
- Medical complications requiring therapy (delaying child-bearing)
  - Diabetes
  - Chronic hypertension
  - Asthma
  - Autoimmune disorders
  - Infectious diseases
  - Heart disease
  - Cancer
  - Seizure disorders
  - GI disorders
  - ……..

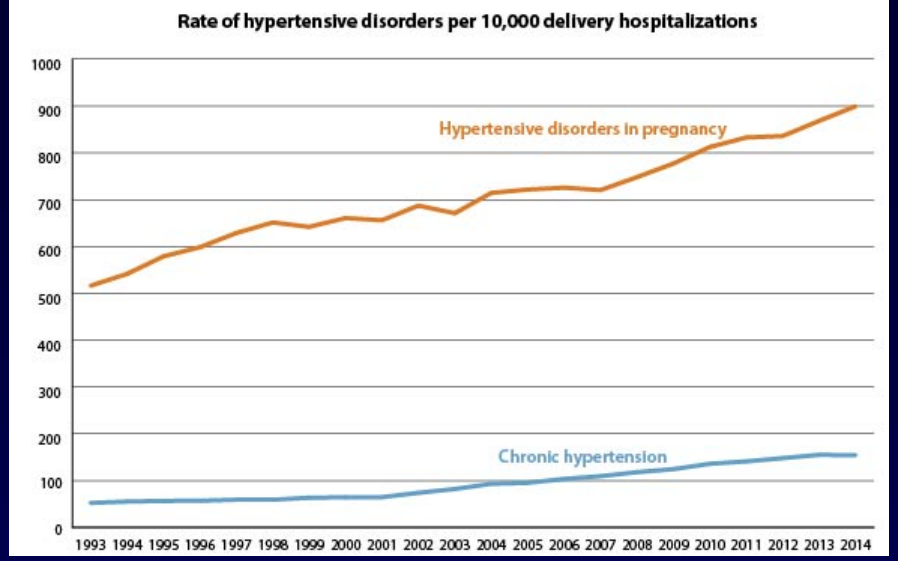
Pregnancy and Therapeutic Agents

- Obstetric complications requiring medications
  - Preterm labor and preterm rupture of membranes, hemorrhage, preeclampsia, stillbirth, labor induction
- Lactation considerations
  - 2003-2012 48% of drugs had no data on breastfeeding and 43% had only animal data (Wang 2017).

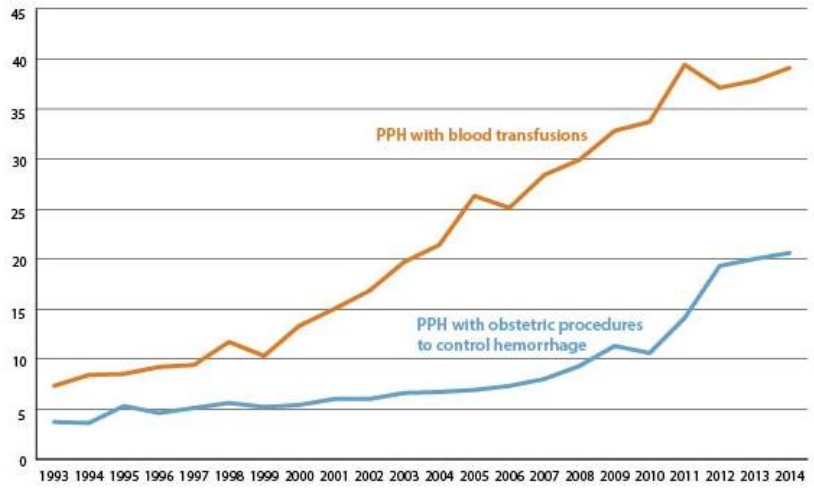
Severe Maternal Morbidity (SMM)

- Physical and psychologic conditions that result from or are aggravated by pregnancy and have an adverse effect on a woman's health
  - SMM affects more than 50,000 women in the US annually and continues to increase
  - Increasing maternal age, obesity, pre-existing chronic medical conditions and Cesarean delivery

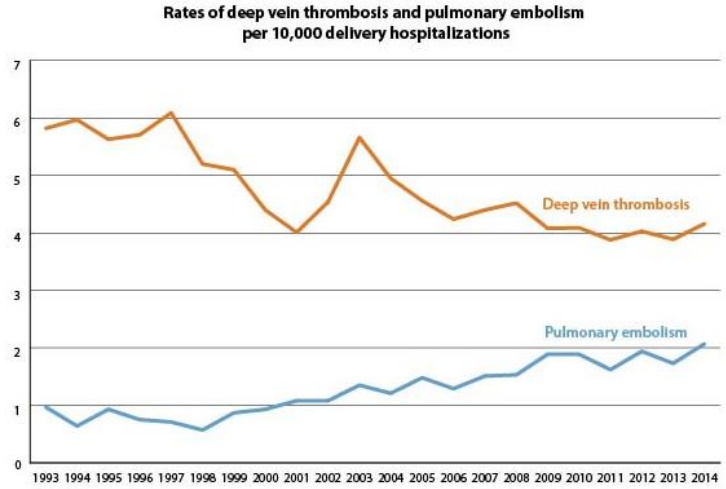
Hypertensive Disorders, 1993-2014



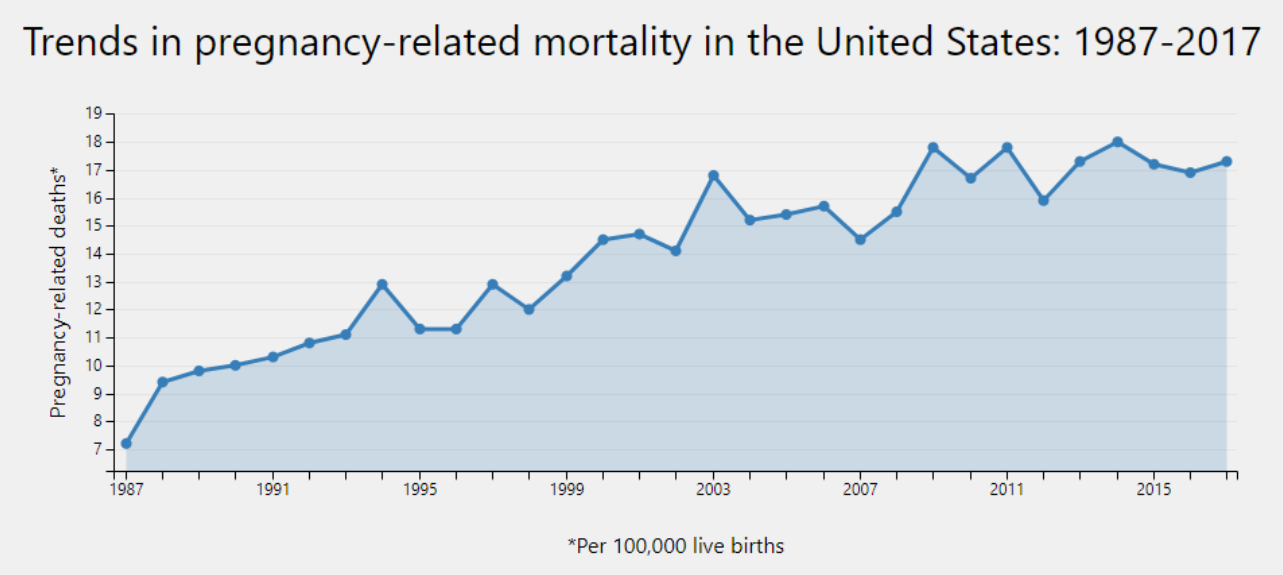
Postpartum Hemorrhage, 1993-2014*



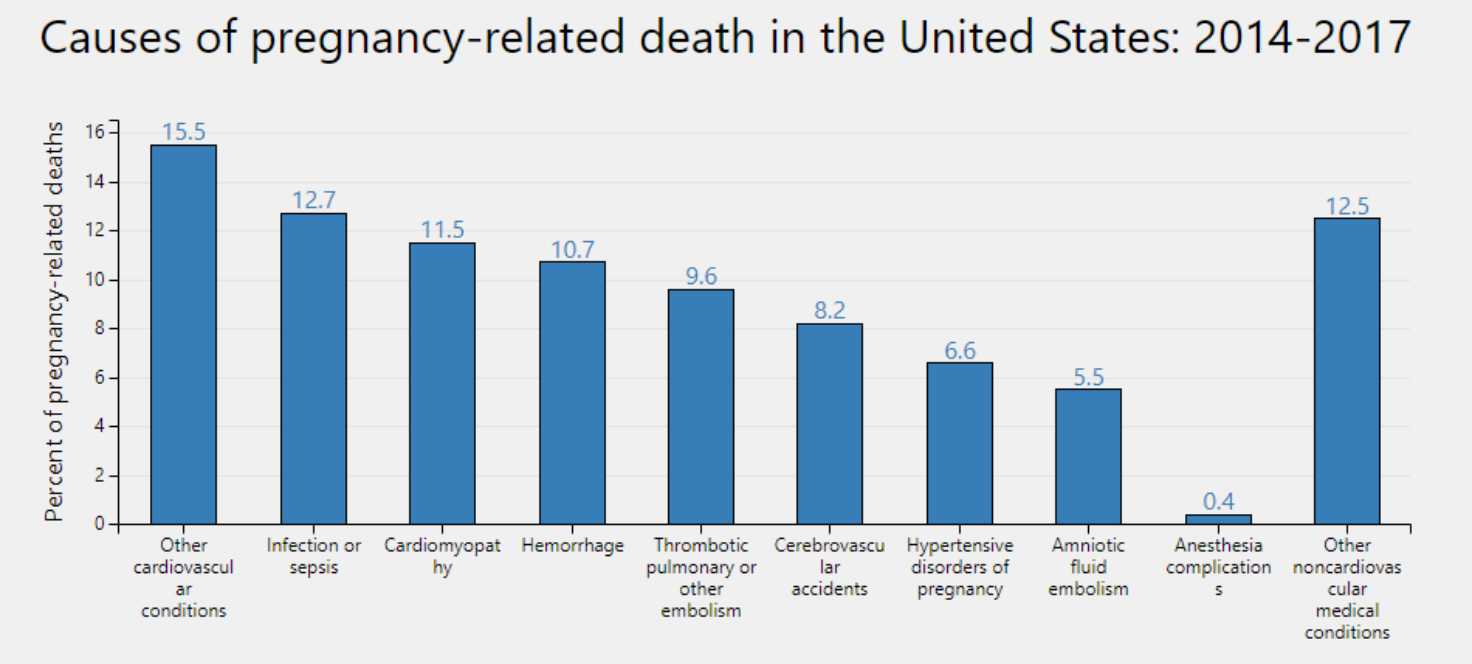
Deep Vein Thrombosis and Pulmonary Embolism, 1993-2014



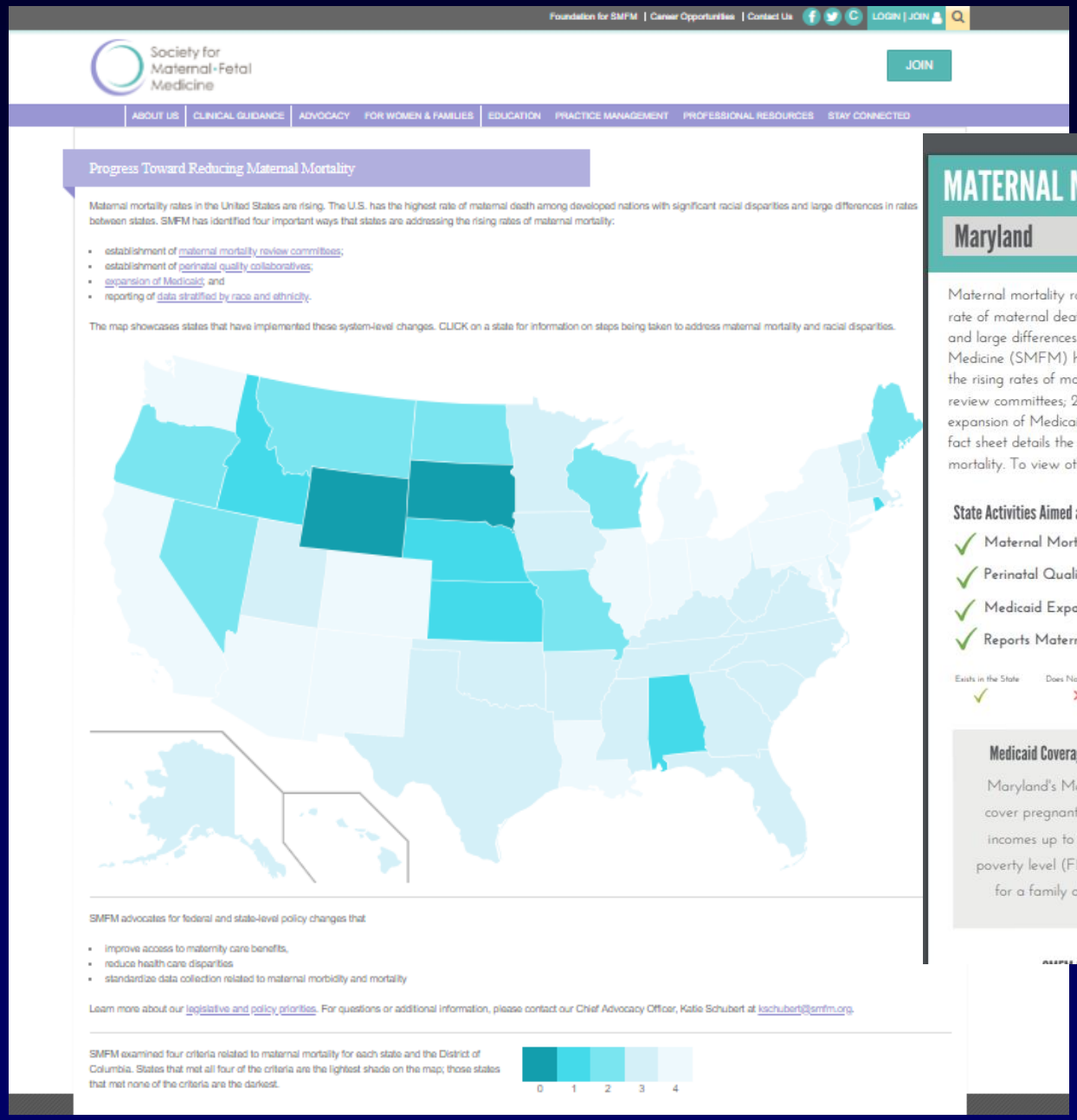
Centers for Disease Control and Prevention

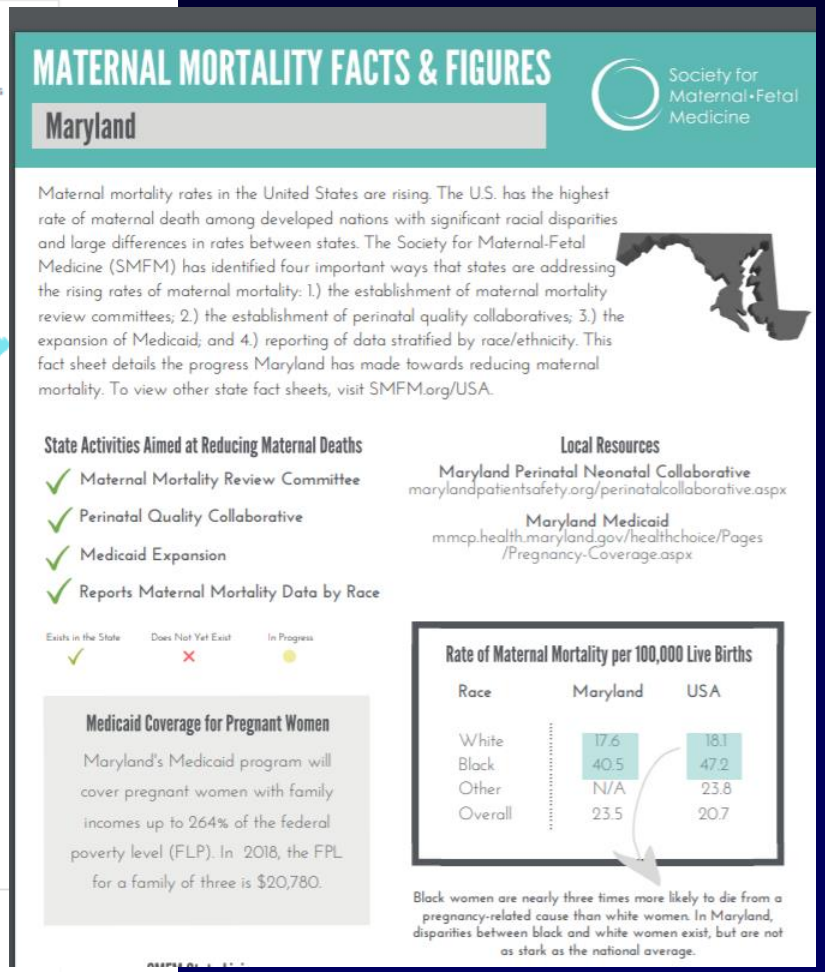


Pregnancy related death = death of a woman while pregnant or within 1 year of the end of a pregnancy from any cause related to or aggravated by the pregnancy or its management.



CDC Pregnancy Mortality Surveillance System





www.smfm.org/usa

Call to Action

For more than a decade, organizations involved in the care for pregnant and lactating women have called the inclusion of pregnant women in clinical research to help address these issues

- Coalition to Advance Maternal Therapeutics (SMFM, ACOG, March of Dimes, AAP)
- ACCP

21st Century Cures Act and PRGLAC

Back to the bedside

- What the clinical care provider needs to know about EVERY medication when caring for a reproductive age woman considering pregnancy and for a pregnant or lactating woman
  - Safety and toxicity data, including teratogenicity risk
  - Dosage information – pre-conception and each trimester including the “fourth”, affects of obesity and medical conditions

Ethical Principles for Pregnant Women and Biomedical Research

"Pregnant women deserve an evidence base for the prevention and treatment of their illnesses equal to others as a matter of justice"

Ethics Working Group on ZIKV Research and Pregnancy 2017

Inclusion or a scientific justification for exclusion

PRGLAC 2019

Altruism

Session 1 Discussion

Discussion Questions:

1. What are the gaps in information on the safety, efficacy, and dosing of drugs used in pregnancy? What are the risks of not having this information? How do we determine the magnitude of benefit that this type of evidence would provide?
2. What have we learned so far from the work undertaken by PRGLAC since its inception in 2016?
3. What are the regulatory barriers to research involving pregnant people?

Session 1: Understanding the Need and Existing Guidance for the Participation of Pregnant People in Clinical Trials

Moderator: Susan McCune, U.S. Food & Drug Administration

Session 2: Nonclinical Safety Assessment to Support Clinical Trials Enrolling Pregnant People

Moderator: Daniel Minck, U.S. Food & Drug Administration

Kimberly Hatfield & Leslie McKinney

U.S. Food and Drug Administration

Nonclinical Safety Assessment to Support Clinical Trials During Pregnancy

Duke Margolis Workshop

Scientific and Ethical Considerations for the Inclusion of Pregnant Women in Clinical Trials

February 2-3, 2021

Kimberly Hatfield, PhD and Leslie McKinney, PhD

U.S. FDA, CDER, Office of New Drugs
Division of Pharmacology/Toxicology – Rare Diseases, Pediatrics, Urology and Reproductive Medicine
~ supporting the Division of Urology, Obstetrics and Gynecology

Objectives

- Explain what types of animal studies are conducted to predict the safety of a drug substance to a developing human in the prenatal period
- Describe the data that support the pregnancy section of the product label
- Discuss what data gaps exist even after the standard reproductive and developmental toxicity studies are completed and what kinds of nonclinical studies might be necessary to support clinical trials in pregnant individuals

Why Conduct Nonclinical Toxicity Studies?

Animal studies to evaluate drug toxicity are mandated

- 1962 Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act (FD&C Act)
  - Response to thalidomide tragedies
  - Demonstration of both the safety and efficacy of marketed drugs
- 21 CFR 312.23(a)(8) – animal toxicology necessary to support first in human clinical trials

Regulations and guidance for how and when to conduct nonclinical studies have been developed over many years

- International guidance (ICH; International Council for Harmonization)
- FDA Guidance (https://www.fda.gov/regulatory-information/search-fda-guidance-documents)

Reproductive/developmental toxicity studies are one part of the total nonclinical assessment of a drug product.

What Do Reproductive and Developmental Toxicity Studies Measure?

Reproductive toxicity

- Structural and functional alterations that affect reproductive competence in sexually mature males and females
    - Male and female fertility
    - Parturition (labor and delivery)
    - Lactation

Developmental toxicity

- Adverse effects on the developing organism (teratogenicity)
    - Mortality
    - Alterations to growth
    - Structural abnormalities
    - Functional impairment

Objective 1

What kinds of animal studies are conducted to predict the safety of a drug substance to a developing human in the prenatal period?

What are the characteristics of a comprehensive nonclinical program?

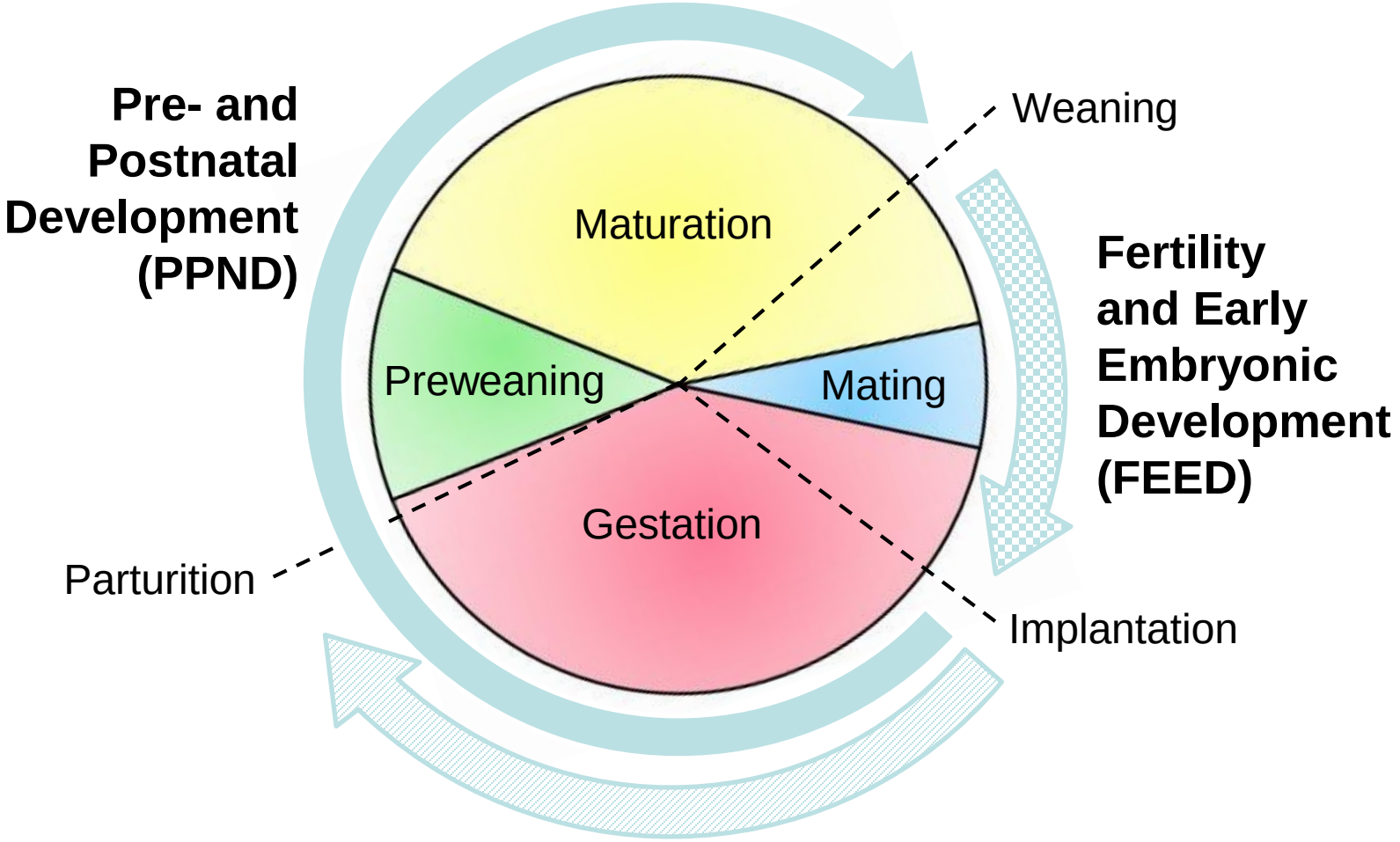
How Do We Evaluate Reproductive & Developmental Toxicity?

- Repeat dose toxicology studies
  - Histopathology evaluation of the reproductive organs
  - Evaluation of estrous/menstrual cycle (extended time in any one stage?)

- Reproductive/developmental toxicology study designs
  - Fertility and early embryonic development (FEED)
  - Embryofetal development (EFD)
  - Pre- and postnatal development (PPND)

Reproductive/Developmental Toxicity Study Design

The reproductive/development cycle is defined by
4 biological phases and is separated into 3 dosing segments

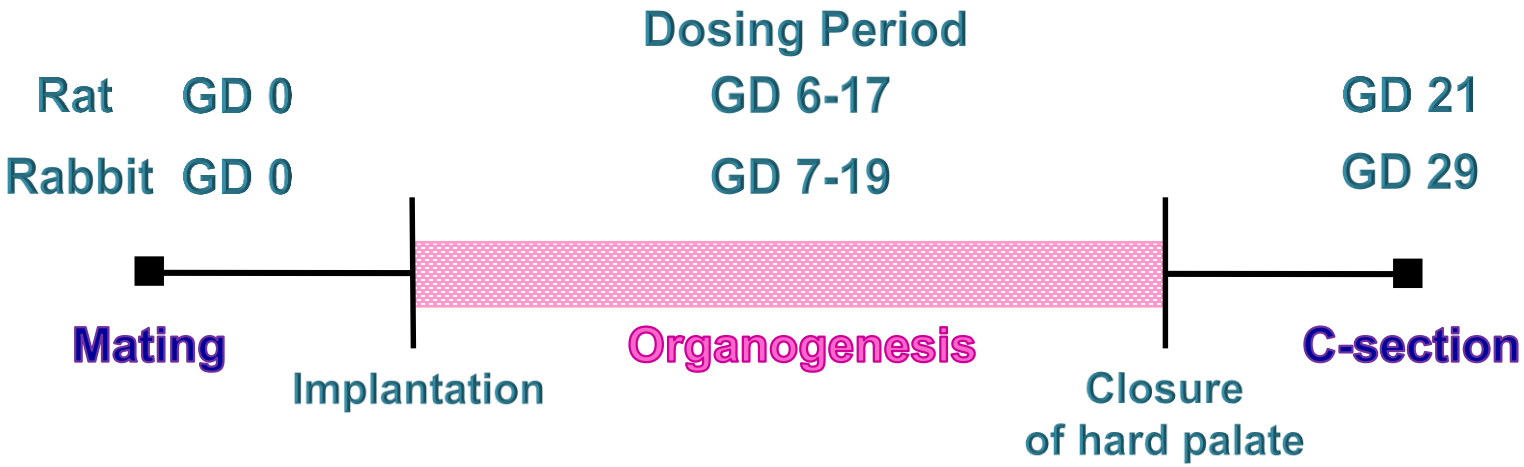


Embryofetal Development (EFD)

Important for drugs that could be used during pregnancy

Evaluated in 2 species: a rodent (usually rat) and non-rodent (usually rabbit)

Dosing occurs from implantation through organogenesis/closure of hard palate



N = at least 16 pregnant females / dose group

- Average litter size of 6 (rabbit) – 12 (rat) → large numbers of offspring to evaluate
  - necessary for level of statistical power
  - to be assured any findings are increased above natural background

Embryofetal Development (EFD) Endpoints Assessed

Maternal health endpoints:

- Body weight changes
- Evaluation of general toxicity to organ systems relative to nonpregnant females

Embryofetal development and other pregnancy parameters:

- Gravid uterine weight
- # fetuses
- Pre- and post-implantation embryofetal loss
- Gross evaluation of the placenta

Fetal health endpoints:

- Altered growth
- Body weight
- Gross evaluation of external, visceral, and skeletal development

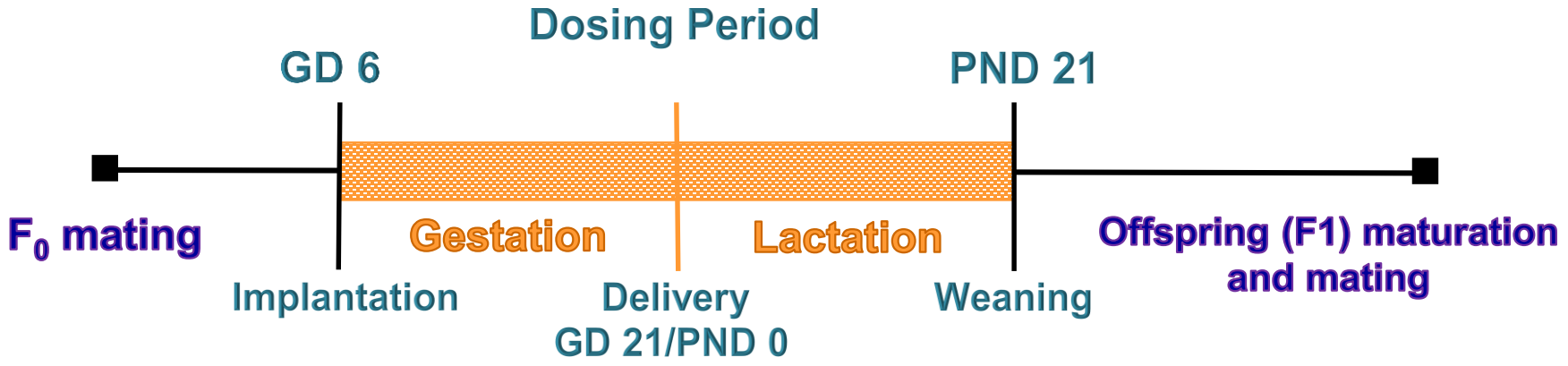
Pre- & Postnatal Development (PPND)

Important for drugs that could be used during pregnancy,
or for those administered during lactation

Evaluated in 1 species: usually rat

Dosing occurs from implantation through end of lactation

One male and one female offspring per litter selected for rearing to adulthood and mating (reproductive competence)



N = at least 16 pregnant females / dose group

Pre- & Postnatal Development (PPND)
Endpoints Assessed

Maternal health and maintenance of pregnancy during treatment:

- Body weight changes
- Duration of pregnancy
- Pregnancy (whole litter) loss
- Live/dead offspring at birth

Offspring (F1 generation) exposed in utero or via lactation:

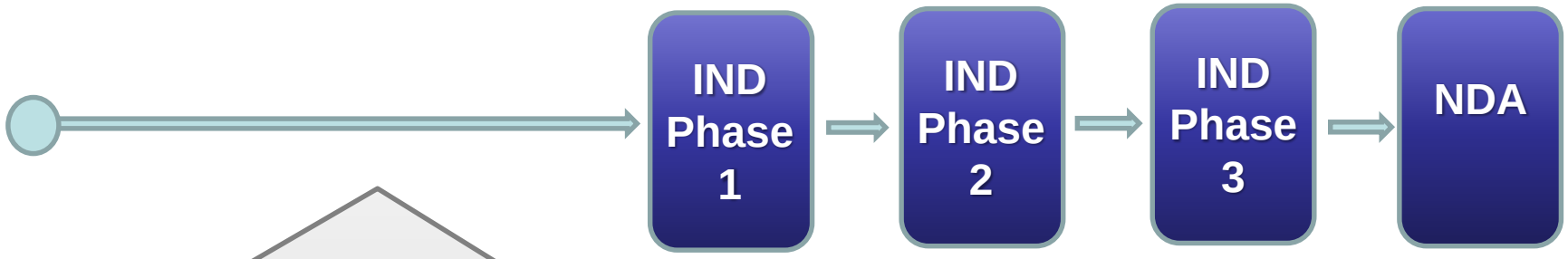
- Body weight
- Pre-/post-weaning survival and growth
- Sexual maturation
- Fertility (reproductive capacity)
- Physical development
- Sensory function/reflexes
- Behavior, learning, memory

Offspring (F2 generation) not exposed

- External exam
- Survival to PND 4-7

Timing of Nonclinical Studies

What nonclinical data do we have *before* evaluating reproductive/developmental toxicity?

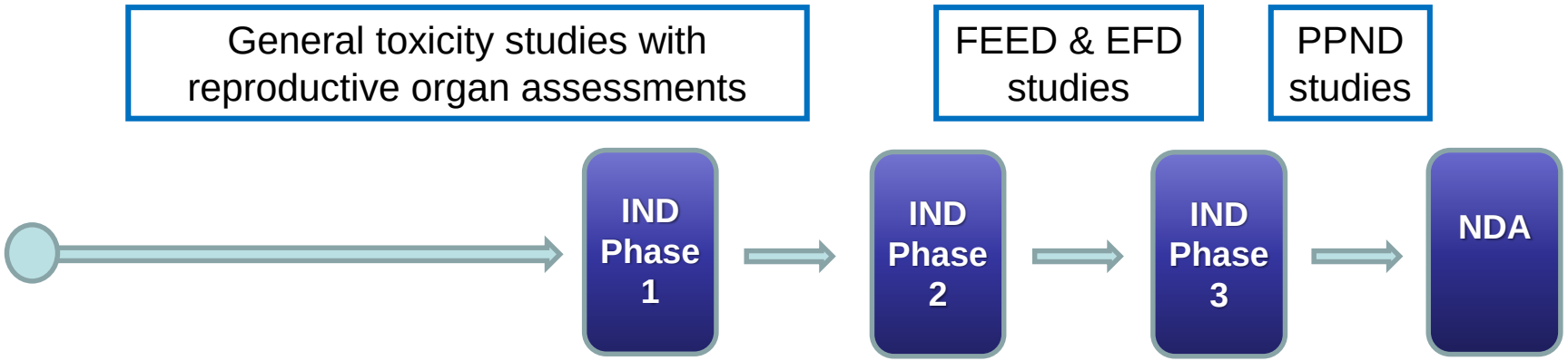


1) Mechanism of action, receptor & organ targets (indication)
2) Absorption / Distribution / Metabolism / Excretion (ADME)
   - How long does the drug stay in the circulation?
   - Does the drug break down to active or toxic metabolites?
3) General toxicity in non-pregnant animals
   - What are the target organs? What are safe doses?
   - Does it affect reproductive organs?
4) Genotoxicity
   - Is the drug a mutagen? Can it damage DNA?

Timing of Reproductive Toxicity Studies – During the IND

Traditional clinical trial

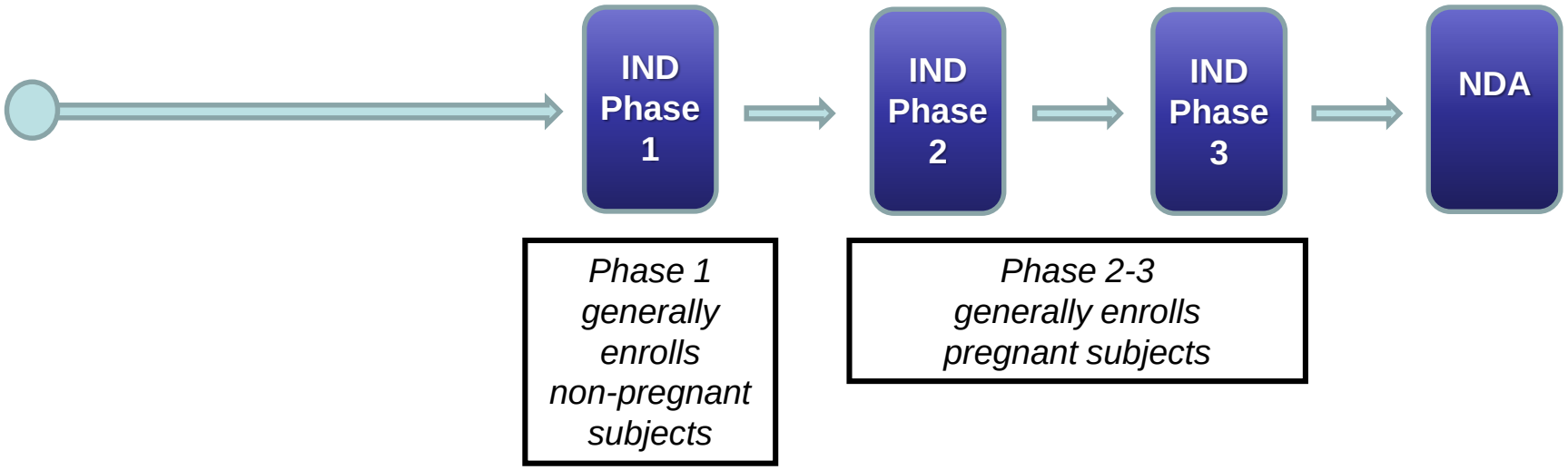
males, postmenopausal individuals, and/or individuals of child bearing potential (with pregnancy testing and contraceptive use):



Timing of Reproductive Toxicity Studies – During the IND

Clinical trial for a <u>pregnancy-specific</u> indication
OR
Clinical trial enrolling pregnant individuals
(treatment population is actively pregnant individuals)

ALL reproductive studies (FEED, EFD, PPND), general toxicity, and genotoxicity
COMPLETE
before pregnant individuals are enrolled



How Do We Extrapolate Animal Findings to Humans?

Repeat Dose, EFD and PPND studies will yield a value for the
dose that produces no toxicity in animals

NOAEL – No Adverse Effect Level

The NOAEL is compared to the recommended human dose:

$$\frac{\textbf{NOAEL}}{\textbf{therapeutic dose in humans}} = \textbf{Multiple of Exposure (MOE)}$$

The larger the MOE number ⟹ the safer the drug

The MOE and the totality of safety information about the drug are used to guide dosing decisions and communicate risk.

Animal Data Guides Risk Assessment

Animal data informs human risk when very limited or no human data are available.

- If **NEGATIVE**, animal data can support further clinical testing
- If **POSITIVE**, animal data can help define a safe human dose range

large MOE ➡ less risk

small MOE ➡ more risk

LIMITATIONS

- Clinical trials can be rejected or modified if:
  - Animal data show potential harm to the fetus that cannot be detected until birth *(non-monitorable toxicity)*
  - Exposure to the fetus cannot be determined
  - Risk / benefit is unfavorable

If human data becomes available over time, it can contribute to the weight-of-evidence to assess safe use.

Objective 2

What nonclinical data support
the pregnancy section of the product label?

How do nonclinical data play a critical role
in FDA's risk / benefit assessment?

Labeling:
Pregnancy and Lactation Labeling Rule (PLLR)

Eliminates Pregnancy Categories (A, B, C, D, X)

Sections 8.1 Pregnancy and 8.2 Lactation include:

- Risk Summary *(for human use)*
- Clinical Considerations *(pertinent info about use during pregnancy, risk of untreated disease)*
- Human Data *(if available)*
- Animal Data *(summary of nonclinical findings of note)*

Section 8.3 Females and Males of Reproductive Potential includes the following subsections * :

- Pregnancy Testing *(when there are recommendations)*
- Contraception *(when there are recommendations)*
- Infertility *(when human or animal data suggest an effect on fertility)*

*omit if not applicable

Labeling Examples

In general, human data are not available for drugs taken during pregnancy, and **animal data** inform the communication of risk to the patient

How are animal studies described in labeling?

How are animal studies used to inform the risk statement for use in pregnant individuals?

Examples of Drugs with Different Risk Profiles for Pregnant Individuals

PREVACID (lansoprazole)

- would be taken episodically during pregnancy for a non-life-threatening indication (GERD)

HUMALOG (fast acting human insulin analog)

- would be taken throughout pregnancy for a life-threatening indication (diabetes)

Disclaimer: The labels presented next are for example only. The presenters do not endorse the use of the drugs discussed in the following labels.

PREVACID
proton pump inhibitor;
gastroesophageal reflux disease (GERD)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published **observational studies** overall **do not indicate** an association of **adverse pregnancy outcomes** with lansoprazole treatment *(see Data).*

In animal reproduction studies, oral administration to rats during organogenesis through lactation at **6.4 times** the maximum recommended human dose (MRHD) produced **reduction in the offspring** in femur weight, femur length, crown-rump length and growth plate thickness (males only) on postnatal Day 21 *(see Data).* These effects were associated with reduction in body weight gain. **Advise pregnant women of the potential risk to a fetus.**

Risk summary describes a developmental finding in animals, but observational human data do not indicate a risk.

Source Data Indicate Fetal Toxicity May Be Secondary to Maternal Toxicity

Animal Data

No adverse effects on **embryo-fetal development (EFD)** occurred in rats and rabbits… at **40 and 16 times** the recommended human dose, respectively).

A **PPND toxicity study in rats with additional endpoints to evaluate bone development** was performed at …**0.7 to 6.4 times** the MRHD….
Maternal effects observed at … **6.4 times** the MRHD….included …**decreased body weight gain and decreased food consumption during gestation.** …… **Body weight of pups was reduced….** Femur weight, femur length, and crown-rump length were reduced…. **The effects on bone parameters were associated with reduction in body weight gain.**

Animal findings can now be put in context and indicate low risk for humans

HUMALOG

fast acting insulin analog; blood sugar management

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The **limited data** with HUMALOG in pregnant women **are insufficient** to inform a drug-associated risk of adverse developmental outcomes. Published studies with insulin lispro … have **not reported ….** major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data).* There are **risks to the mother and fetus associated with poorly controlled diabetes in pregnancy….**

Pregnant rats and rabbits were exposed to insulin lispro in animal reproduction studies during organogenesis. **Fetal growth retardation** was observed in offspring of **rats** at **~3 times** the human dose….**No adverse effects** were observed in offspring of **rabbits** at doses up to **~0.24 times** the human dose…*(see Data).*

Animal data are somewhat equivocal but not strongly negative

Label Describes Risk / Benefit Considerations

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis etc…..

Poorly controlled diabetes increases the fetal risk for major birth defects, …. and related morbidity.

Animal Data

In a **combined fertility and EFD study**, female **rats** were given 0.2, 0.8, and 3 times the human dose, from 2 weeks prior to cohabitation through Gestation Day 19. There were **no adverse effects** on female fertility, implantation, or fetal viability and morphology. However, **fetal growth retardation** was observed at 3X the human dose …..

In an **EFD** study, **rabbits** were dosed at up to 0.2 times the human dose from Gestation Days 7 through 19. There were **no adverse effects** on fetal viability, weight and morphology at any dose.

Physician can use information to balance the potential risk of drug use versus the risk of not controlling the disease

Objective 3

What data gaps exist even after the standard reproductive and developmental toxicity studies are completed?

What other kinds of nonclinical studies might be necessary to support clinical trials in pregnant individuals?

What Are The Limitations of Reproductive / Developmental Toxicity Studies?

Inherent limitations:

- Species differences: rats and rabbits are not humans
- Developmental stages for rat, rabbit and human have different durations
    - e.g. a newborn rat is comparable to a 3rd trimester human

Limitations of study designs:

- Reproductive / developmental studies are observational
- Studies primarily assess:
    - morphological abnormalities
    - physiological functions necessary for growth and survival
    - simple (instinctually driven) behaviors (eating, sleeping, reproduction)

Parameters Not Typically Assessed in Detail by Reproductive / Developmental Studies

Neurodevelopment

- Sensory modalities are not assessed for subtle changes
- Higher order learning and memory are not usually assessed

Immune system development

- No systematic evaluation of immune competence
- The lab environment is ‘clean’

Endocrine system

- Onset of puberty and bone parameters are not usually assessed
- Puberty can be evaluated in a juvenile animal study

Additional Nonclinical Testing Can Be Conducted To Evaluate Risk

Fetal exposure

- Placental transfer
- Tissue concentrations (drug / metabolite) in the fetus

Effects on specific systems

- Are certain organ systems vulnerable?
- Developmental studies
    - Brain and behavior
    - Immune challenge
    - Endocrine function

Labels that include results from extra testing

- Duloxetine (Cymbalta) includes extra neurobehavioral evaluation of offspring

CYMBALTA

SNRI; anxiety, depression, nerve pain

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

…… Data from published literature and a postmarketing retrospective cohort study… **did not find a ….. risk for major birth defects or other developmental outcomes…**

In rats and rabbits treated with duloxetine **during the period of organogenesis**, ….fetal weights were decreased but there was **no evidence of developmental effects at doses up to 3 and 6 times**, respectively, the MRHD. When duloxetine was administered to **rats** throughout gestation and lactation, pup weights at birth and pup survival to 1 day postpartum were decreased at 2 times the MRHD. At this dose, **pup behaviors consistent with increased reactivity…..were observed**. Post-weaning growth was not adversely affected.

Drug mechanism of action led to extra neurobehavioral evaluation of pups.

Studies Outside of the Standard Battery Can Provide Specifics to Inform Risk

Animal Data

When duloxetine was administered to pregnant **rats** throughout gestation and lactation, the **survival** of pups to 1 day postpartum and **pup body weights** at birth and during the lactation period **were decreased** at a dose **~2 times the MRHD**.

Furthermore, **behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity** were observed.

- **Labels can describe extra testing that has been done, and be reassuring if no major findings are observed.**
- **However, extrapolation of behavioral studies to humans can be hard.**

Decision Process – Proposed Clinical Trial in Pregnant Individuals

Review team integrates ALL information and results from BOTH nonclinical and clinical studies

Are animal findings relevant to humans?

Can we estimate fetal drug exposure?

- How is the drug absorbed? Tissue distribution? Metabolism?
- Is the fetus exposed? How much compared to the mother?
- How long and during which trimester is the fetus exposed?
- Can the fetus metabolize the drug?
- Could the fetal brain be exposed?
- Are there toxicities that could affect the fetus more than the mother?

FDA subject matter experts can be consulted for additional input and guidance

Fictional Case Study

- Small Innovative Drug Company is developing “Wonder Drug” for a Serious Adult Disease.
- Animal studies revealed that Wonder Drug has cardiac toxicity – at very high doses (30X the proposed therapeutic dose).
- **Phase 1 clinical trials are allowed to proceed** and no cardiotoxicity is observed at the therapeutic dose.
  - **Wonder Drug fails in Phase 2 due to lack of efficacy.**

- Small Innovative Drug Company doesn’t give up on the drug.
- **Further research shows** Wonder Drug might be effective for prevention of pre-term labor.
- The company designs a Phase 2 trial to enroll pregnant individuals who have had one previous pre-term delivery.
  - Treatment proposed starting at 18 weeks of pregnancy and throughout gestation at the therapeutic dose already shown to be safe in adults.

Fictional Case Study

Can Small Innovative Drug Company show that Wonder Drug is also safe for the fetus?

- Previous animal work in the rat had shown that Wonder Drug crosses the placental barrier, indicating that fetuses can be exposed.
- Embryofetal development (EFD) studies in the rat and rabbit showed dose-dependent fetal loss. At very high doses, Wonder Drug caused **maternal heart damage that may have contributed to fetal loss**.
- But even at lower doses that didn't affect the pregnant females, there was still a **low incidence of fetal loss**, raising the question of whether the drug was affecting cardiac development.
- The no effect level for fetal loss was **10X** the therapeutic level.

Is this margin enough to be sure of safety?

Or put another way –
Is fetal loss a sensitive enough endpoint?

Fictional Case Study

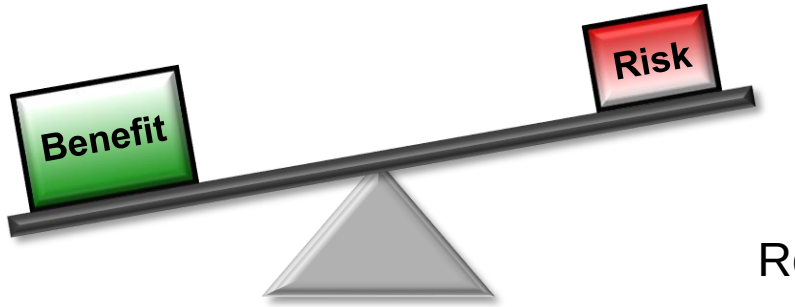
How can the company proceed?

- At this juncture, **communication with the FDA** would be helpful, to determine what kind of safety data are needed.
- Additional animal data should be obtained. But what kind?
- A PPND study is still needed.
  - The company can add additional endpoints on to the study design to determine whether there is organ toxicity that might have been missed in the EFD study (e.g. histopathology of fetal organs).
  - A no effect level for cardiotoxicity to the fetus can then be established.
- **Once the dose-dependence of these specialized endpoints is determined, it would be possible to set a safe dose in humans based on the multiple of exposure.**

It All Comes Down to BENEFIT vs RISK

Questions to consider

- How serious is the indication for the mother? For the fetus?
- Is the benefit certain?
- Is the population that would benefit well-defined?
- If the drug is toxic to the fetus, is it monitorable? Is it reversible?
- If the mother is NOT treated, will her condition be a risk to her fetus?



CONCLUSION

Reproductive / developmental toxicity studies
in animals provide essential information
for the clinician to use to make a treatment decision
and to inform the patient of risk

Reference to Guidance

- ICH-S5(R3) - Detection of Toxicity to Reproduction for Human Pharmaceuticals (Feb 2020)
- Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (July 2020)
- Reproductive and Developmental Toxicities -- Integrating Study Results to Assess Concerns (Sept 2011)
- Guidance for Industry: Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations (June 2015)
- ICH-M3(R2) - Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (Jan 2010)
- ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (May 2012)

ICH Guidance: https://www.ich.org/page/safety-guidelines

FDA Guidance: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Session 2 Discussion

Discussion Questions:

1. If a nonclinical safety signal is observed, are clinical trials in pregnant people likely to be prohibited? What additional information could FDA rely on to inform the risk? What is needed for an optimal discussion of benefit versus risk that could lead to inclusion of pregnant people in trials when a nonclinical safety signal is observed?
2. If a nonclinical safety signal is not observed, are clinical trials in pregnant people generally considered safe to proceed? What additional information does FDA rely on to inform the potential risk?
3. It seems that a comprehensive nonclinical reproductive toxicity assessment needs to be completed and reviewed by FDA prior to conducting any clinical trial investigating therapeutics in pregnant people. This may be beyond the ability of a small research laboratory to accomplish or delay starting early clinical trials. Are there any exceptions to this drug development pathway or is there a way to conduct nonclinical studies in parallel with clinical trials?

Session 2: Nonclinical Safety Assessment to Support Clinical Trials Enrolling Pregnant People

Moderator: Daniel Minck, U.S. Food & Drug Administration

Break—15 Minutes

We are still live. Please mute your audio.

Session 3 will begin at 2:30 pm.

Session 3: Scientific and Ethical Considerations when Designing Clinical Trials that Enroll Pregnant People

Moderator: Susan McCune, U.S. Food & Drug Administration

Christine Nguyen

U.S. Food and Drug Administration

Prescription Drug Use in Pregnancy: Information Needed

Christine P. Nguyen, M.D.
Division of Urology, Obstetrics, and Gynecology
Center for Drug Evaluation and Research, U.S. FDA

Clinical Trials in Pregnant Women FDA-Duke Margolis Meeting
February 2, 2021

Disclaimer

- I do not have any financial disclosures to report.
- This presentation represents the views of the speaker and not the official position of the FDA.
- Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the speaker or the FDA.

Objectives

To Understand:

- Prescribing information needed to ensure safe and effective drug use
- Available evidence in drug label to guide use in pregnant people
- Gaps in information for pregnant people

Prescription (Rx) Drug Label

- Contain a summary of the essential information needed for the safe and effective (intended) use of the drug
- Be informative and accurate
- Be based on human data, whenever possible
- Not be promotional, false or misleading
- Be updated when necessary

Certain Key Categories in Rx Drug Label*

Drug Imagine

Indication (s)	• Hypertension • Asthma
Dose/Dose Regimen	• Hypertension – 10 mg once daily • Asthma – 20 mg as needed, not to exceed 20 mg/day
Safety	• Contraindications • Warnings & Precautions, Adverse Reactions
Efficacy	• Hypertension – Clinical Trials for Hypertension • Asthma – Clinical Trials for Asthma
Pregnancy	• No more letter category (ABCDX) • Summaries of available safety information

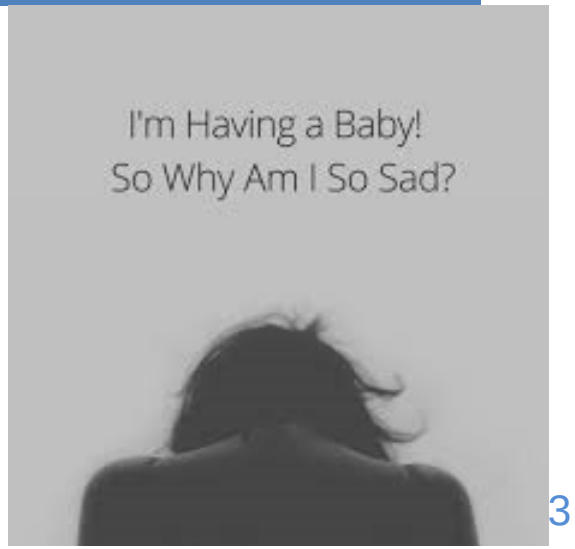
*Not inclusive list

Different Types of Drug Use

On-Label	Off-Label	Investigational
• Drug: Approved • Indication: Approved	• Drug: Approved • Indication: Unapproved	• Drug: Unapproved • Indication: Unapproved

Approved Drug for Approved Indication

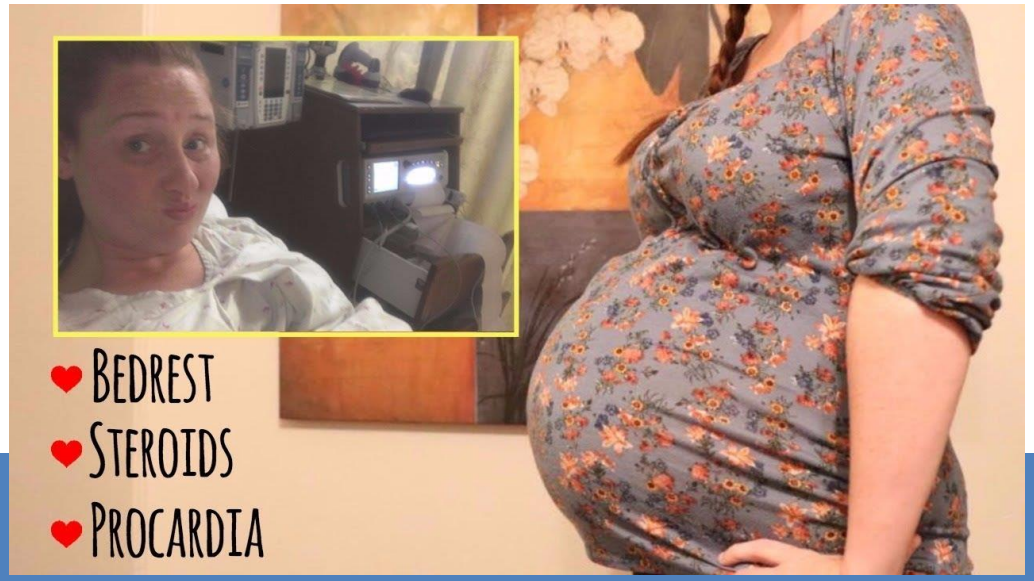
“ON-LABEL”



On-Label Use: Asthma

Drug Imagine

Approved Indication	• Yes - asthma
Dose/Dose Regimen	• Asthma: 20 mg as needed, not to exceed 20 mg/day • Potential Gap: Dose/dose regimen throughout pregnancy
Safety	• General safety generally applied to pregnant person • ?Safety for obstetrical outcomes, for Fetus/Neonate/Child
Efficacy	• Efficacy for asthma generally applied to pregnant person
Pregnancy	• No more letter category (ABCDX) • Summaries of available safety information



Approved Drug for Unapproved Use

"OFF-LABEL"

Off-Label Use: Preterm Labor

Drug Imagine

Approved Indication	• Hypertension • Asthma
Dose/Dose Regimen	• Hypertension: 10 mg once daily • Asthma: 20 mg as needed, not to exceed 20 mg/day • ?Dose/dose regimen for preterm labor
Safety	• Some ability to generalize to pregnant person • ?Safety for obstetrical outcomes, for Fetus/Neonate/Child
Efficacy	• ?Evidence of efficacy for preterm labor
Pregnancy	• No more letter category (ABCDX) • Summaries of available safety information

Unapproved Drug

INVESTIGATIONAL

Investigational Use: ME-2 for Severe Influenza

Approved Indication	• None
Dose/Dose Regimen	• Unknown
Safety	• Unknown
Efficacy	• Unknown
Pregnancy	• ?Nonclinical data • Human data - none

Summary

- Key information necessary for effective & safe treatment
  - Condition treated
  - Dose
  - Efficacy
  - Safety (maternal, obstetrical, fetal/neonatal/child)
- Potential to apply certain information from non-pregnant people, depending on the type of use
- Other information must be obtained from pregnant people – sources of data vary depending on the nature of the information needed

Thank You

Cathy Spong

University of Texas Southwestern Medical Center

Maggie Little

Georgetown University

Christina Bucci-Rechtweg

Novartis Pharmaceuticals Corporation

Cynthia Gyamfi-Bannerman

Columbia University Medical Center

How do we apply ethical and scientific principles to the different trial designs to meet the trial's objectives?

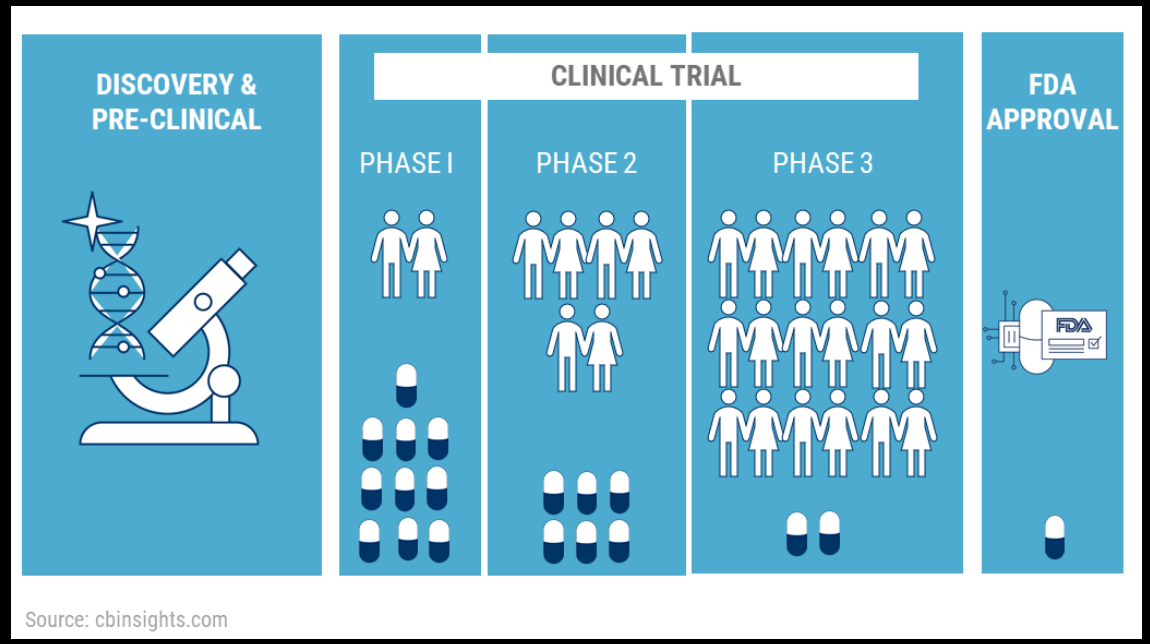
Columbia University
PRETERM BIRTH PREVENTION CENTER

Cynthia Gyamfi-Bannerman, MD, MS
Vice Chair for Faculty Development
Ellen Jacobson Levine and Eugene Jacobson Professor of OBGYN
Director, Maternal Fetal Medicine Fellowship Program
PI, NICHD MFMU—Columbia Center
Columbia University Irving Medical Center

Disclosures

- NICHD/NHLBI funding
- Grant from Hologic to study PTB
- NY Sera Advisory Board Participant

Clinical Trials and Pregnant People



Source: cbinsights.com

- 2 broad categories
  - Interventions to improve pregnancy outcomes
    - Preterm birth
    - Preeclampsia
    - Intrahepatic cholestasis of pregnancy
  - Interventions for common medical conditions that co-exist with pregnancy
    - Hypertension
    - Diabetes
    - COVID-19

NICHD MFMU Origins

- Obstetrical management, especially for high-risk patient, had often adopted practices without objective evaluation

- To address the need for well-designed clinical trials in maternal fetal medicine, the NICHD established the MFMU Network in 1986

MFMU Centers 2016-2021

Brown University

Case Western Reserve University

Columbia University

Northwestern University

The Ohio State University

University of Alabama — Birmingham

University of North Carolina — Chapel Hill

University of Pennsylvania

University of Pittsburgh

University of Utah

University of Texas — Galveston

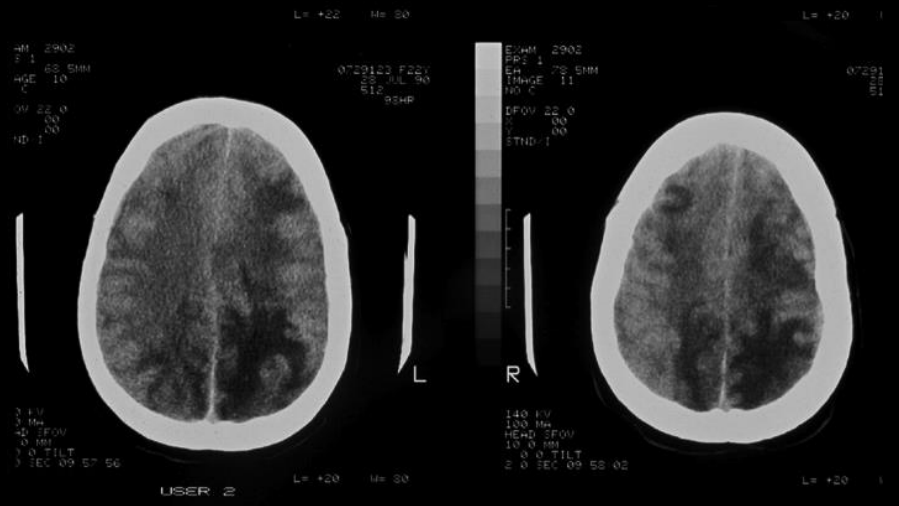
University of Texas — Houston

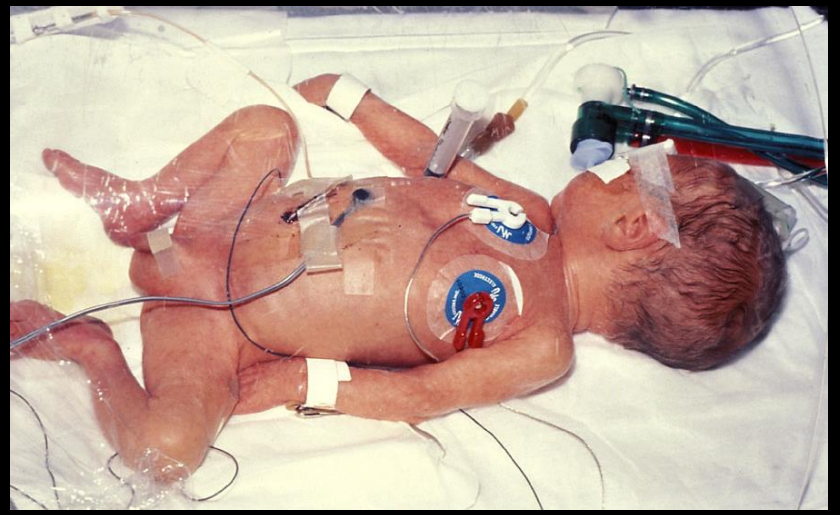
MFMU Network

- ***ONLY*** federally funded obstetric clinical trials research network
- The MFMU Network conducts clinical studies to improve maternal, fetal and neonatal health with greatest priority given to randomized trials
- The aim is to:
  - Reduce morbidity to mom and baby, related to preterm birth, fetal growth abnormalities & maternal complications
  - Address maternal mortality
  - Provide rationale for evidence-based, cost-effective, obstetric practice

Pravastatin for the Prevention of Preeclampsia in High-Risk Women: A Pilot Study

Obstetric-Fetal Pharmacology Research Units (OPRU) Network
The National Institute of Child Health and Human Development





Primary Research Question

- What are the **Pharmacokinetic** properties and maternal and fetal **safety** profiles of **pravastatin** when used as a prophylactic daily treatment in pregnant women at high risk of preeclampsia?

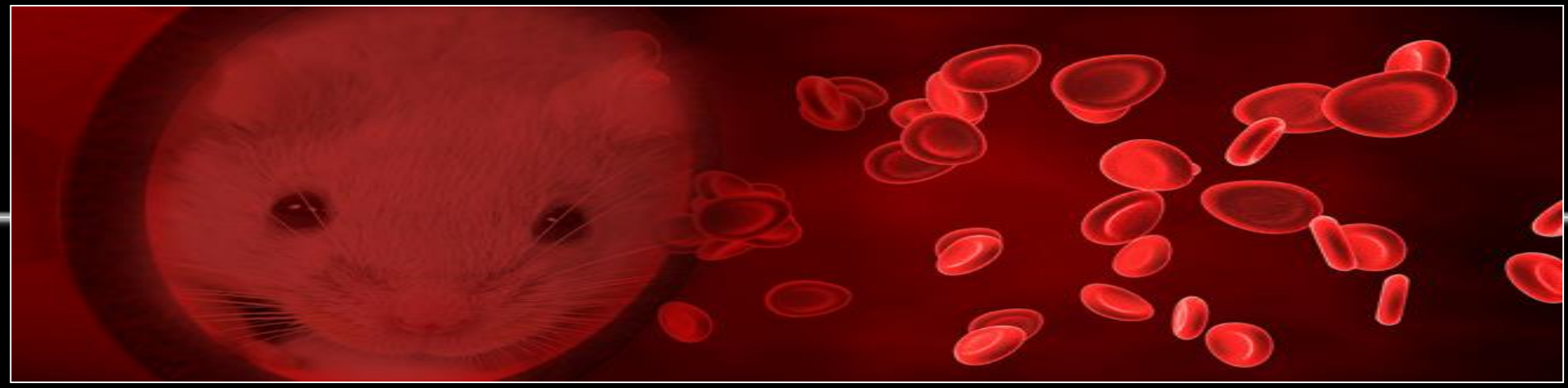
ClinicalTrials.gov

NCT01717586

opru
Obstetric-Fetal Pharmacology Research Units Network

Results – Maternal Outcomes

	Placebo (N=10)	Pravastatin (N=10)
Preeclampsia	4 (40)	0
Mild	1	0
Severe features	3	0
GHTN	1	1
Highest BP mm Hg		
Systolic	152.4 ± 23.1	144.2 ± 18.4
Diastolic	96.8 ± 17.1	91.8 ± 16.1
GA at delivery, weeks	36.7 ± 2.1	37.7 ± 0.9
Indicated PTD < 37 wks	5 (50)	1 (10)
	RR 0.17, 95% CI (0.02-1.11)	
Length of hospital stay	4 [3 - 7]	3 [3 - 4]



A Randomized Controlled Trial of Pravastatin for the Prevention of Preeclampsia in High Risk Women

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

NIH National Heart, Lung, and Blood Institute

How the MFMU has changed lives

- The *Eunice Kennedy Shriver* NICHD is named after JFK's sister
- His first son, Patrick Bouvier, died of respiratory distress in 1963
  - He was 35 weeks

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antenatal Betamethasone for Women at Risk for Late Preterm Delivery

C. Gyamfi-Bannerman, E.A. Thom, S.C. Blackwell, A.T.N. Tita, U.M. Reddy, G.R. Saade, D.J. Rouse, D.S. McKenna, E.A.S. Clark, J.M. Thorp, Jr., E.K. Chien, A.M. Peaceman, R.S. Gibbs, G.K. Swamy, M.E. Norton, B.M. Casey, S.N. Caritis, J.E. Tolosa, Y. Sorokin, J.P. VanDorsten, and L. Jain, for the NICHD Maternal–Fetal Medicine Units Network*

Published April, 2016

Society for Maternal·Fetal Medicine

SMFM Statement

smfm.org

Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

A single course of betamethasone is recommended for pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.

How do we apply ethical principles?

- Informed consent
- Publicize trials to allow participation of those potentially eligible
- Close monitoring for safety and SAEs
- It would be unethical not to study promising interventions in eligible pregnant individuals

How do we apply ethical and scientific principles to the different trial designs to meet the trial's objectives?

Columbia University
PRETERM BIRTH PREVENTION CENTER

Cynthia Gyamfi-Bannerman, MD, MS
Vice Chair for Faculty Development
Ellen Jacobson Levine and Eugene Jacobson Professor of OBGYN
Director, Maternal Fetal Medicine Fellowship Program
PI, NICHD MFMU—Columbia Center
Columbia University Irving Medical Center

Kathryn Schubert

Society for Women's Health Research

Session 3 Discussion

Discussion Questions:

1. What information regarding drug therapy is typically needed and can only be obtained in pregnant people?
2. What are the ethical considerations and scientific considerations for enrolling pregnant people in clinical trials, what are some of the major challenges?
3. Discuss principles, such as the severity of the condition, unmet need, benefits, risks, and uncertainties that support enrolling pregnant people in clinical trials. This should include the risks of an untreated condition and the value of the information that could be obtained with research. Discuss timing of enrollment and when to stop a trial in pregnancy.
4. How do we apply ethical and scientific principles to the different trial designs to meet the trial's objectives?
5. What strategies could be used to advance the culture of including pregnant people in research?

Session 3: Scientific and Ethical Considerations when Designing Clinical Trials that Enroll Pregnant People

Moderator: Susan McCune, U.S. Food & Drug Administration

Day 1 Adjournment

Scientific and Ethical Considerations for the Inclusion of Pregnant Women in Clinical Trials

February 2 & 3, 2021

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

Welcome Back & Day 1 Summary | Day 2

Catherine Sewell

U.S. Food and Drug Administration

Remote Participation Instructions

Mute & Slides

- **You have been placed on mute**; speakers can mute/unmute throughout
- We will advance the slide deck, please prompt us to advance

Meeting Information

- #ResearchInPregnancy | Materials—https://healthpolicy.duke.edu/events

Questions & Comments

- Please go on video and use the “raise hand” Zoom option if you’d like to speak, we’ll pass the microphone and you can unmute
- Please feel free to type your question into the Q&A box

Zoom Issues? Please Zoom message Rasheed Willis or email rwillis@newmediamill.com

Meeting Agenda

Day One | Introduction and Preclinical Research

- Session 1: Understanding the Need and Existing Guidance for the Participation of Pregnant People in Clinical Trials
- Session 2: Nonclinical Safety Assessment to Support Clinical Trials Enrolling Pregnant People
- Session 3: Scientific and Ethical Considerations when Designing Clinical Trials that Enroll Pregnant People

Day Two | Approaches to Clinical Trial Design and Conduct and Next Steps to Advance Therapeutic Development

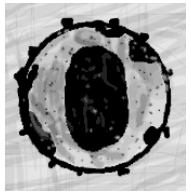
- Case Study: Comparing and Contrasting Clinical Trials Enrolling Pregnant People to Evaluate Treatment for a Chronic Medical Condition and Clinical Trials for a Pregnancy-Related Condition
- Session 4: Challenges and Next Steps

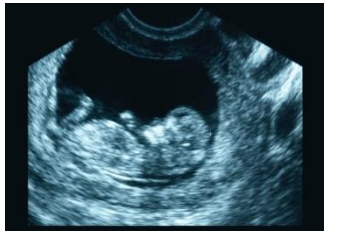
Case Study: Comparing and Contrasting Clinical Trials Enrolling Pregnant People to Evaluate Treatment for a Chronic Medical Condition and Clinical Trials for a Pregnancy-Related Condition

Moderator: Marta Wosińska, Duke-Margolis Center for Health Policy

Lynne Mofenson

Elizabeth Glaser Pediatric AIDS Foundation





Potential New Approaches on When and How to Study Antiretroviral Drugs in Pregnancy

Scientific and Ethical Considerations for the Inclusion of Pregnant Women in Clinical Trials
February 2-3, 2021

Lynne M. Mofenson, M.D.
Senior HIV Technical Advisor
Elizabeth Glaser Pediatric AIDS Foundation

Elizabeth Glaser Pediatric AIDS Foundation
Until no child has AIDS.

Disclosures

- I do not have any financial disclosures to report.

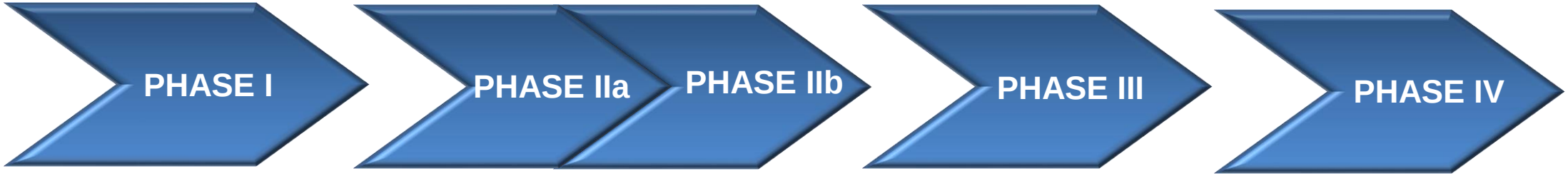
The “Usual” Situation for Use of Drugs in Pregnancy

The “Usual” Situation for Use of Drugs in Pregnancy

- One picture to sum it up:

→New drugs are already approved and marketed years before any studies in pregnant people conducted (if any are conducted at all).

Outline of Typical Clinical Trial Drug Development Phases



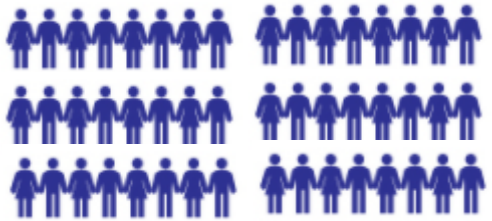
Non-Pregnant

Pharmacokinetics, safety, tolerability

Pharmaco-dynamics, dose range

Definitive dose, preliminary efficacy

Efficacy, comparison to standard of care



Post-market approval surveillance, safety, rare events

Drug Development Phases: Current Timing of Pregnancy Studies

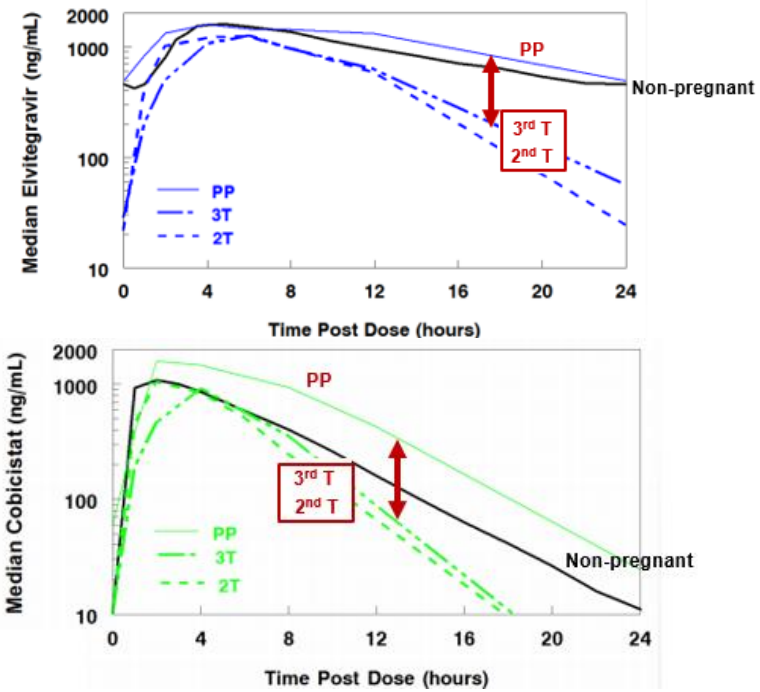
	PHASE I	PHASE IIa	PHASE IIb	PHASE III	PHASE IV
Non-Pregnant	Pharmacokinetics, safety, tolerability	Pharmaco-dynamics, dose range	Definitive dose, preliminary efficacy	Efficacy, comparison to standard of care	Post-market approval surveillance, safety, rare events
Pregnant, Current Status of Studies	**Not included**	**Not included**	**Not included**	**Rarely included**	**Post-licensure:** → **PK in pregnancy study *may or may not* be done** → **Comparison of efficacy in pregnancy with standard *may* or *may not* be done** → **Safety surveillance *may or may not* be done**

So – Then When We First Begin to Study Drugs in Pregnancy is Post-Drug Approval

- Dose/safety/efficacy in non-pregnant persons (hopefully including women) is already established.
- However, there remains lack of clarity about dose and optimal use in pregnancy.

Importance of Studying Drugs in Pregnancy Post-Drug Approval

- Need: to establish safe and effective dose in pregnancy
  - Example of why important: P1026s/PANNA PK studies enroll pregnant people already receiving ARV drugs at recommended dose; studies show **elvitegravir and cobicistat levels are significantly decreased in late pregnancy**



Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV

Jeremiah D. Momper[a], Brookie M. Best[a], Jiajia Wang[b], Edmund V. Capparelli[a], Alice Stek[c], Emily Barr[d], Martina L. Badell[e], Edward P. Acosta[f], Murli Purswani[g], Elizabeth Smith[h], Nahida Chakhtoura[i], Kyunghun Park[a], Sandra Burchett[j], David E. Shapiro[b], Mark Mirochnick[k], for the IMPAACT P1026s Protocol Team

Clinical Infectious Diseases

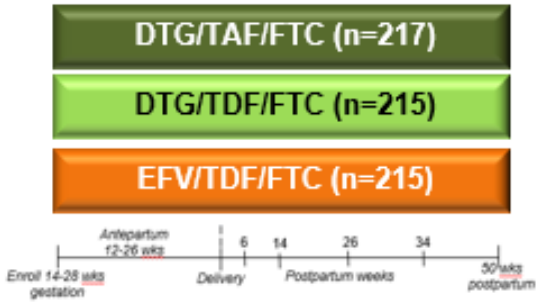
BRIEF REPORT

Clinically Significant Lower Elvitegravir Exposure During the Third Trimester of Pregnant Patients Living With Human Immunodeficiency Virus: Data From the Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNAnt women (PANNA) Network

Vera Bukkems,[1] Coca Necsoi,[2] Carmen Hidalgo Tenorio,[3] Coral Garcia,[3] Jürgen Rockstroh,[4] Caroline Schwarze-Zander,[4] John S. Lambert,[5,6,7] David Burger,[1] Deborah Konopnicki,[2] and Angela Colbers[1]; for the Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNAnt women (PANNA) Network

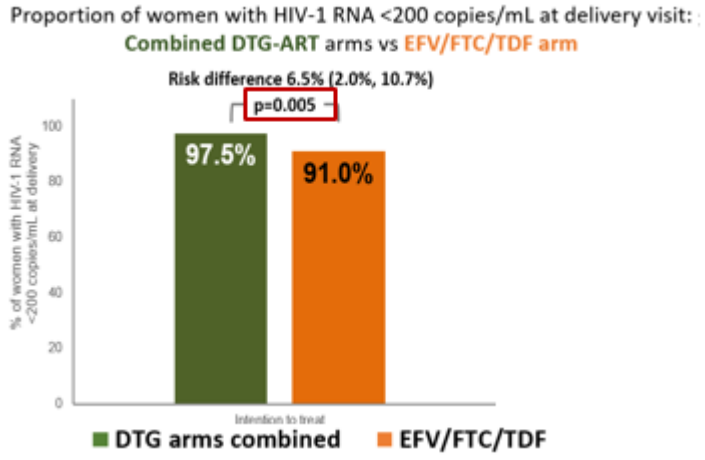
Importance of Studying Drugs in Pregnancy Post-Drug Approval

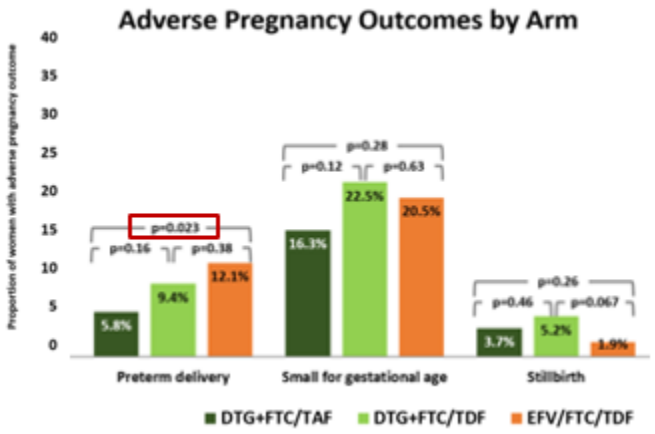
- Next (after PK data): Determine safety/efficacy in pregnancy
  - VESTED model – compare viral efficacy and safety (including pregnancy outcome) in pregnancy between approved regimens for non-pregnant people.

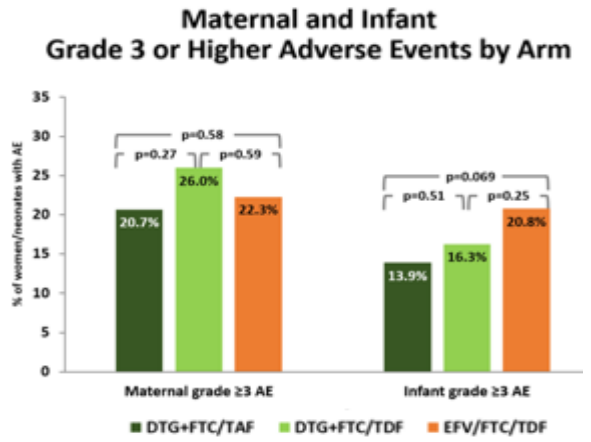


→DTG **superior** viral efficacy to EFV and similar safety.

→TAF safe in pregnancy, with less preterm delivery than EFV and similar safety to other regimens.







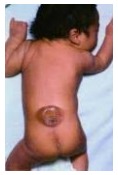
Importance of Studying Drugs in Pregnancy Post-Drug Approval

- And need: Pharmacovigilance for rare adverse events like birth defects
  - Tsepamo model – birth surveillance in HIV+ women on different ART regimens preconception vs during pregnancy and uninfected women in Botswana.
    - Possible ↑ neural tube defects with preconception DTG vs preconception non-DTG, preconception EFV, or HIV-uninfected.

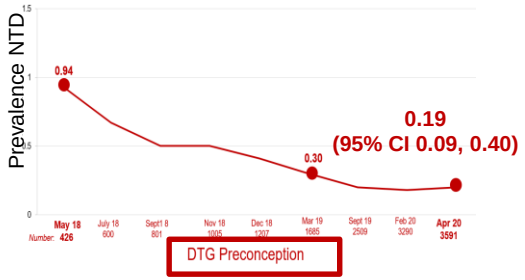
The NEW ENGLAND JOURNAL of MEDICINE

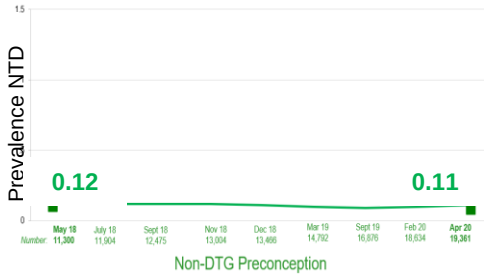
Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana

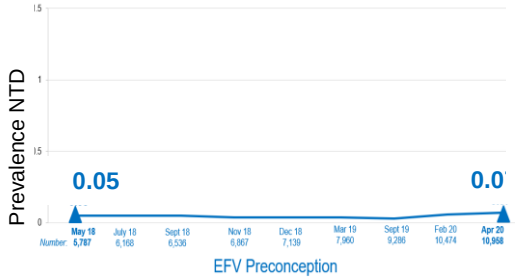
Rebecca Zash, M.D., Lewis Holmes, M.D., Modiegi Diseko, B.P.H., Denise L. Jacobson, Ph.D., M.P.H., Sean Brummel, Ph.D., Gloria Mayondi, B.Sc., Arielle Isaacson, B.A., Sonya Davey, M.Phil., Judith Mabuta, Mompati Mmalane, M.D., Tendani Gaolathe, M.D., M. Essex, D.V.M., Ph.D., Shahin Lockman, M.D., Joseph Makhema, M.B., B.S., and Roger L. Shapiro, M.D., M.P.H.

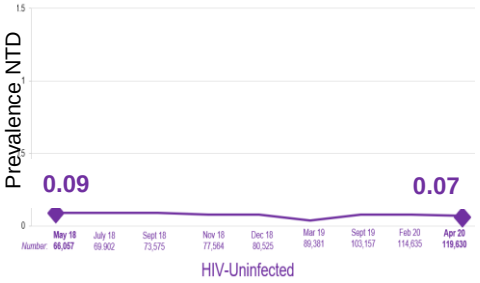


Open spinal bifida
(Copp & Greene, 2016, Encyclopedia of Life Sciences, John Wiley)



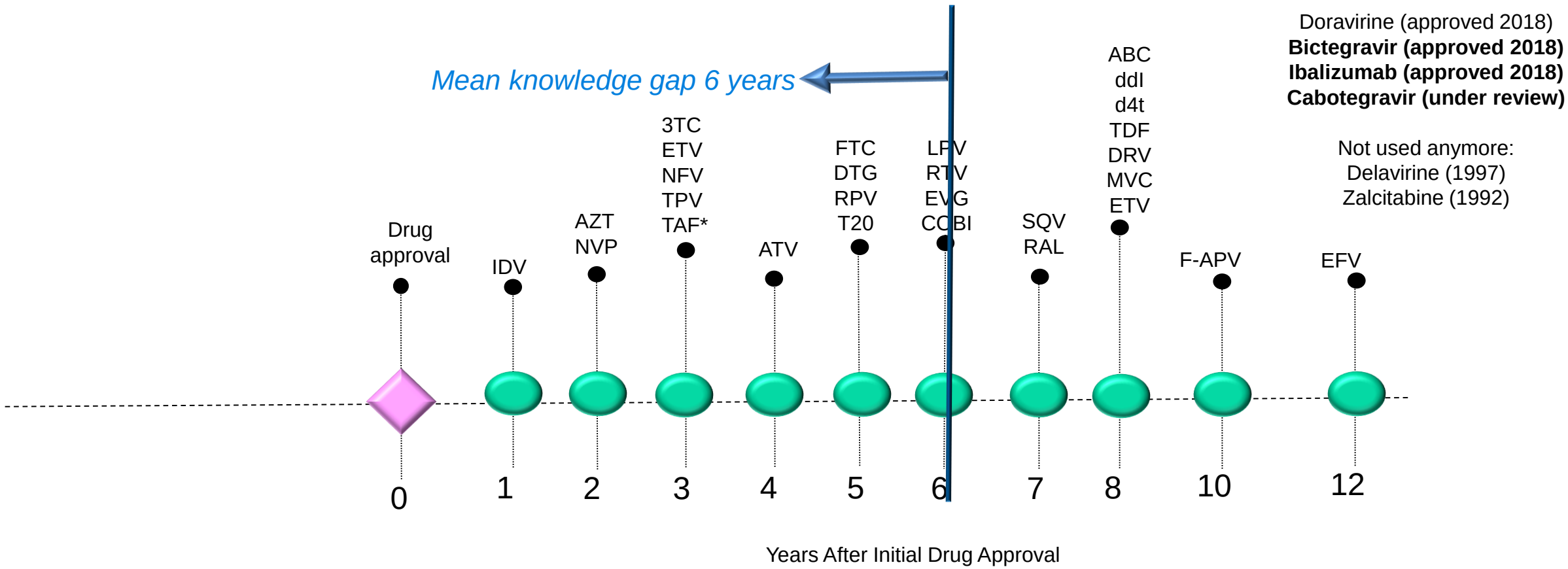






Time from FDA Drug Approval to First Published Pharmacokinetics and Safety ARV Data in Pregnancy

modified from: Colbers A et al. Clin Infect Dis 2019;69:1254-8.



No published data

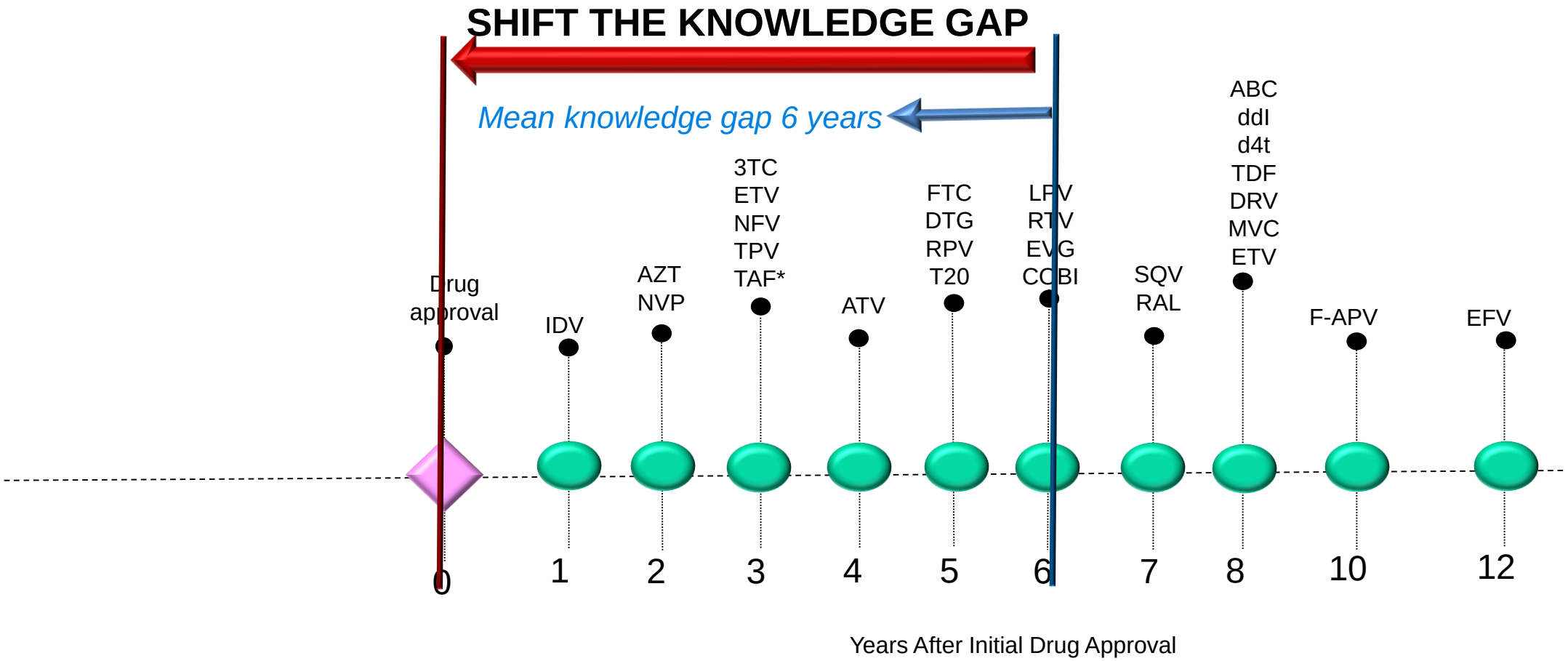
Doravirine (approved 2018)
Bictegravir (approved 2018)
Ibalizumab (approved 2018)
Cabotegravir (under review)

Not used anymore:
Delavirine (1997)
Zalcitabine (1992)

Time from FDA Drug Approval to First Published Pharmacokinetics and Safety ARV Data in Pregnancy

modified from: Colbers A et al. Clin Infect Dis 2019;69:1254-8.

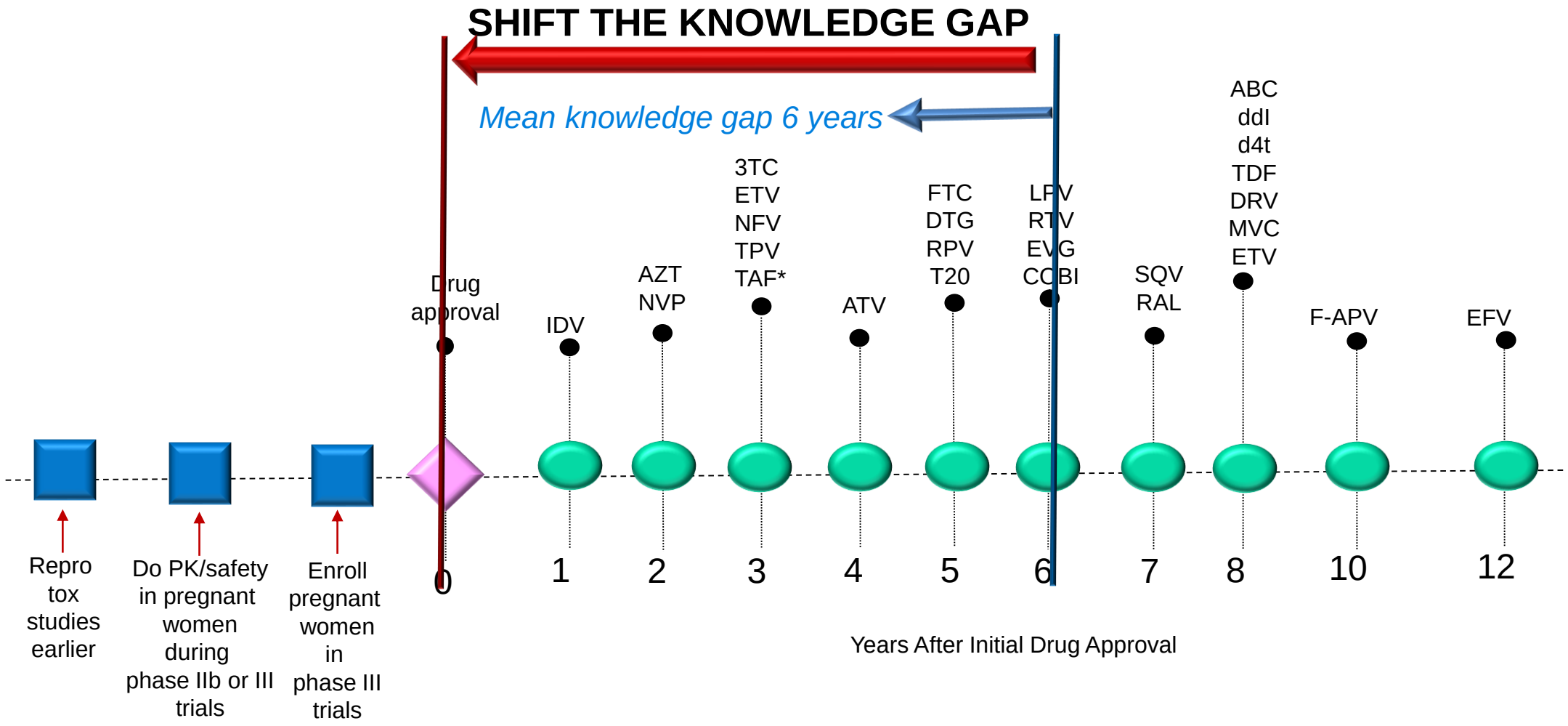
Goal: Shift the Knowledge Gap for Drugs in Pregnancy



Time from FDA Drug Approval to First Published Pharmacokinetics and Safety ARV Data in Pregnancy

modified from: Colbers A et al. Clin Infect Dis 2019;69:1254-8.

Goal: Shift the Knowledge Gap for Drugs in Pregnancy



Principles for Clinical Drug Trials in Pregnancy

Roes KCB et al. Trials 2018;19:123

- Generally, planning a “first ever” PK/safety trial in pregnant women is warranted only if:
  - 1) preclinical repro-tox data don’t demonstrate severe adverse effects and
  - 2) drug dose and safety is sufficiently established in non-pregnant population (phase I/IIb data).
  - Also usually want 3) some evidence efficacy in non-pregnant persons (e.g., phase IIb data) before exposing large numbers of pregnant women.

Proposed Framework for Conducting Pregnancy Drug Studies

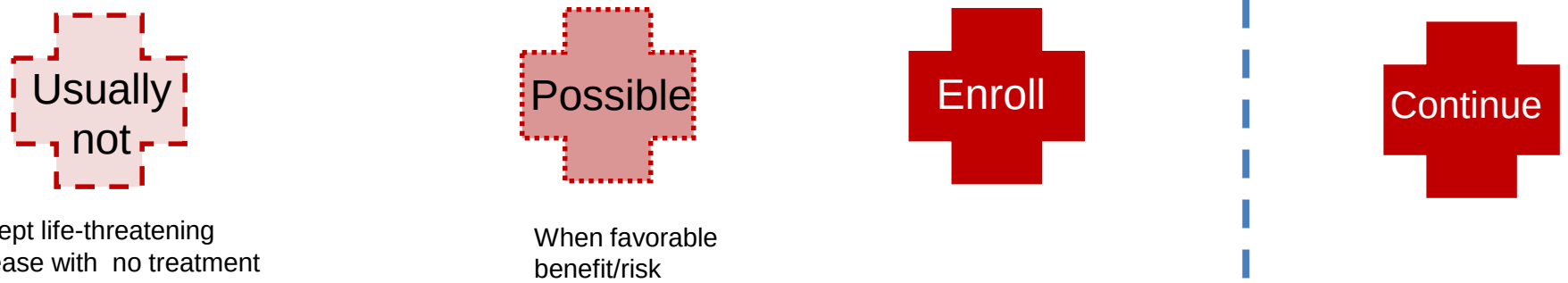
Non-Pregnant	Pharmacokinetics, safety, tolerability	Pharmaco-dynamics, dose range	Definitive dose, efficacy	Efficacy, comparison to standard of care	Post-market approval surveillance, safety, rare events
Pregnant, Current Status of Studies	Not included	Not included	Not included	Rarely included	Post-licensure: Phase I pregnancy study may or may not be done; surveillance may or may not be done
Pregnant, <u>Proposed</u> Approach to Studies	Usually not		Possible	Enroll	Continue

Except life-threatening disease with no treatment (e.g., Ebola)

When favorable benefit/risk

Proposed Framework for Conducting Pregnancy Drug Studies

Non-Pregnant	Pharmacokinetics, safety, tolerability	Pharmaco-dynamics, dose range	Definitive dose, efficacy	Efficacy, comparison to standard of care	Post-market approval surveillance, safety, rare events
Pregnant, Current Status of Studies	Not included	Not included	Not included	Rarely included	Post-licensure: Phase I pregnancy study may or may not be done; surveillance may or may not be done
Pregnant, <u>Proposed</u> Approach to Studies	*Repro-tox studies* →				

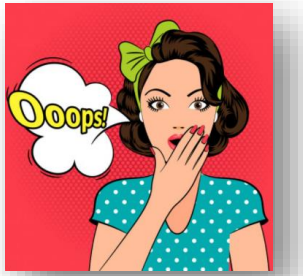


→ **Key to this is earlier pre-clinical repro-toxicity study completion**

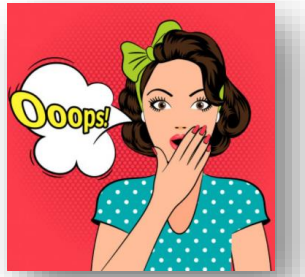
Questions Related to Preclinical Repro-Toxicity Data

- **When** in drug development should pre-clinical repro-tox data be obtained and which issues need to be addressed, to move this step earlier?
- **How** to interpret the preclinical data – for example, if adverse findings with high doses/levels are not seen with lower dose resulting in human therapeutic levels.
- **How** should pre-clinical repro-tox data be used to help decide:
  - When it is appropriate to permit women who become pregnant during a Phase I-III trial to consent to stay on study drug and gather PK/safety data
  - When it is appropriate to enroll pregnant women in a trial of a new ARV, and in which trimester
  - What later surveillance (pharmacovigilance) should be designed, to capture outcomes of potential concern based upon repro-tox data

While Trials in Women of Childbearing-Potential Require Contraception – These Women Still Become Pregnant -



While Trials in Women of Childbearing-Potential Require Contraception – These Women Still Become Pregnant -

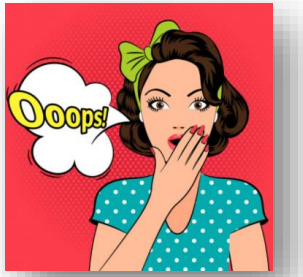


- Partners PrEP Trial

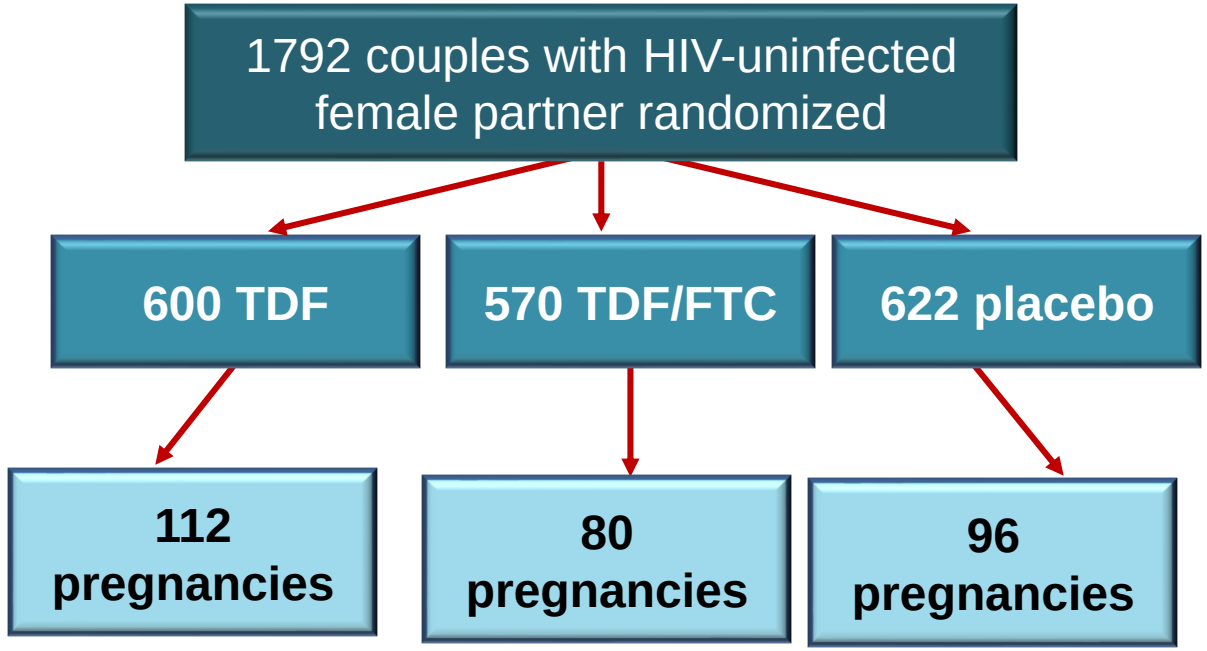
PARTNERS PrEP STUDY

  - **Excluded pregnant** or breastfeeding people or those intending pregnancy.
  - Provided contraceptive counseling & free contraceptives (55% used)
  - Monthly pregnancy testing
  - If pregnant, **discontinued drug for duration of pregnancy and breastfeeding**

While Trials in Women of Childbearing-Potential Require Contraception – These Women Still Become Pregnant -



- Partners PrEP Trial
  - **Excluded pregnant** or breastfeeding people or those intending pregnancy.
  - Provided contraceptive counseling & free contraceptives (55% used)
  - Monthly pregnancy testing
  - If pregnant, **discontinued drug for duration of pregnancy and breastfeeding**



16% became pregnant on study

Did f/u for pregnancy outcome,
no difference outcomes PrEP vs controls

Questions Related to Women Becoming Pregnant in Phase I-III Trials Conducted in Non-Pregnant Adults

- When should there be a protocol requirement for contraception to enroll into a trial and if so what choice for contraception?
- What needs to happen, for the default position to become that participants may consent to stay on study drug and on study if they become pregnant in a trial, unless adverse preclinical repro-tox or other data suggest otherwise?
- If allowing to stay on study drug, how can we best incorporate PK/safety studies into the ongoing trial to obtain data in pregnancy?

Missed Opportunities
HIV Prevention in Women with CAB-LA

HPTN 084
Long-acting Injectable For the Epidemic

ABC NEWS 7 November 2020

Study finds long-acting shot helps women avoid HIV infection

A new study suggests a shot of an experimental medicine every two months works better than daily pills to help keep women from catching HIV

Great news for women!

The New York Times 9 November 2020

Shot to Prevent H.I.V. Works Better Than Daily Pill in Women

Missed Opportunities
HIV Prevention in Women with CAB-LA

abc NEWS 7 November 2020

Study finds long-acting shot helps women avoid HIV infection

A new study suggests a shot of an experimental medicine every two months works better than daily pills to help keep women from catching HIV

Great news for women!

who are not pregnant or breastfeeding or planning pregnancy

The New York Times 9 November 2020

Shot to Prevent H.I.V. Works Better Than Daily Pill in Women

HPTN 084 protocol: **"There is no requirement to exclude women of reproductive potential from clinical trials of CAB based on reprotoxicity findings available to date**. Given the limitations of the data and because animal studies are not always predictive of the human situation ***women of reproductive potential are required to adopt highly reliable means of contraception during participation and throughout long term follow up phases of studies following exposure to CAB LA***."

Missed Opportunities
HIV Prevention in Women with CAB-LA

abc NEWS 7 November 2020

Study finds long-acting shot helps women avoid HIV infection

A new study suggests a shot of an experimental medicine every two months works better than daily pills to help keep women from catching HIV

Great news for women!

who are not pregnant or breastfeeding or planning pregnancy

The New York Times 9 November 2020

Shot to Prevent H.I.V. Works Better Than Daily Pill in Women

HPTN 084 protocol: **"There is no requirement to exclude women of reproductive potential from clinical trials of CAB based on reprotoxicity findings available to date**. Given the limitations of the data and because animal studies are not always predictive of the human situation ***women of reproductive potential are required to adopt highly reliable means of contraception during participation and throughout long term follow up phases of studies following exposure to CAB LA*.**"

"….Because CAB and CAB LA are investigational agents, **women may not enroll if they are pregnant or desire to become pregnant**. Receipt of study product by participants requires use of an effective method of contraception…Participants should be encouraged to delay pregnancy for at least 48 weeks following discontinuation of IM dosing."

Missed Opportunities
HIV Prevention in Women with CAB-LA

abc NEWS 7 November 2020

Study finds long-acting shot helps women avoid HIV infection

A new study suggests a shot of an experimental medicine every two months works better than daily pills to help keep women from catching HIV

Great news for women!

who are not pregnant or breastfeeding or planning pregnancy

The New York Times 9 November 2020

Shot to Prevent H.I.V. Works Better Than Daily Pill in Women

HPTN 084 protocol: **"There is no requirement to exclude women of reproductive potential from clinical trials of CAB based on reprotoxicity findings available to date**. Given the limitations of the data and because animal studies are not always predictive of the human situation ***women of reproductive potential are required to adopt highly reliable means of contraception during participation and throughout long term follow up phases of studies following exposure to CAB LA*.**"

"….Because CAB and CAB LA are investigational agents, **women may not enroll if they are pregnant or desire to become pregnant**. Receipt of study product by participants requires use of an effective method of contraception…Participants should be encouraged to delay pregnancy for at least 48 weeks following discontinuation of IM dosing."

"…Regardless of the randomization assignment or point in the study, all pregnant participants will be placed on open-label TDF/FTC for the duration of the pregnancy. **No participant with a recognized pregnancy will be administered CAB, CAB LA, or CAB LA placebo**."

Missed Opportunities
HIV Prevention in Women with CAB-LA

- Pre-clinical repro-tox: not teratogenic rats/rabbits. In rats only, high dose (1000 mg/kg/d – 28-times higher than maximal human dose) had ↑ stillborn (2.9% CAB vs 0.7% control) and neonatal death at d 2-4 (10.2% vs 0.7%). No differences from controls at 0.5 mg/kg/d or 5 mg/kg/d dose.

Missed Opportunities
HIV Prevention in Women with CAB-LA

- Pre-clinical repro-tox: not teratogenic rats/rabbits. In rats only, high dose (1000 mg/kg/d – 28-times higher than maximal human dose) had ↑ stillborn (2.9% CAB vs 0.7% control) and neonatal death at d 2-4 (10.2% vs 0.7%). No differences from controls at 0.5 mg/kg/d or 5 mg/kg/d dose.

CROI Conference on Retroviruses and Opportunistic Infections

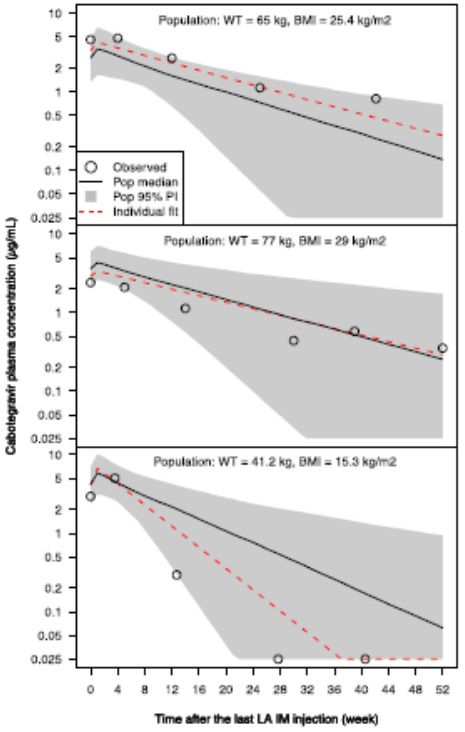
CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS
Boston, Massachusetts
March 8–11, 2020

Table 2. Summary of Confirmed Pregnancy Following CAB Exposure

Participant # (age range, years)	Past obstetric history	CAB exposure	Pregnancy outcome
1 (20-30)	None	CAB LA	Live birth (38 weeks) – no congenital anomaly reported
2 (30-40)	No pre-term and 2 full-term	CAB LA	Live birth (38 weeks) – no congenital anomaly reported
3 (20-30)	2 full-term normal births	CAB LA	Live birth (38 weeks) – no congenital anomaly reported
4 (20-30)[a]	1 prior spontaneous miscarriage	CAB LA	Live birth
5 (20-30)	1 normal live birth	CAB LA	Induced abortion at 10 weeks (non-medical reason)
6 (30-40)	2 full-term normal births	CAB LA	Induced abortion at 5 weeks (non-medical reason)
7 (30-40)	1 normal full-term birth, 3 pre-term (2 elective abortion, 1 stillbirth)	CAB LA	Induced abortion at 7 weeks (non-medical reason)
8 (30-40)	2 normal live births and 1 induced abortion	CAB LA	Induced abortion at 6 weeks GA (non-medical reason)
9 (20-30)[b]	2 full-term normal births, 1 stillbirth, 1 spontaneous abortion	CAB LA	Spontaneous abortion at 1 week GA
10 (30-40)	2 full-term pregnancies and 2 induced abortions	CAB oral	Medical abortion at 7 weeks GA
11 (40-50)	2 full-term pregnancies (normal births), 3 spontaneous abortions	CAB oral	Spontaneous abortion at 9 weeks GA
12 (20-30)	1 premature birth and 1 spontaneous abortion	CAB oral	Induced abortion at 7 weeks GA (medical reason)
13 (30-40)	2 previous pregnancies	CAB oral	Possible early miscarriage at 1-2 weeks GA

- What data in pregnancy?
  - 13 pregnancies
    - 1 miscarriage
    - 8 abortions (most elective)
    - 4 births with no problems
  - PK in 3 pregnant women after stop CAB – rate of decline during PK tail was similar to non-pregnant women.

Figure 1. Maternal CAB PK Tail Following CAB LA Discontinuation Throughout Pregnancy and Post-Partum



Missed Opportunities

→Will pregnant women – a high risk group for HIV acquisition in high prevalence settings – be excluded from being able to receive this drug because of limited data in pregnancy – despite high efficacy?

→Will women who become pregnant while receiving CAB be told they have to stop drug because of limited data in pregnancy and breastfeeding?

→Could this situation have been avoided by doing studies in pregnancy during the phase III study, which after all was being conducted in (and CAB targeted for use by) women?

Questions Related to Enrolling Pregnant Women into Clinical Trials

- How much (and which) safety and efficacy data are needed in non-pregnant adults, prior to enrolling pregnant women into new drug trials?
- How do we prioritize certain drugs for study in pregnancy? For example:
  - Availability (or lack thereof) of alternative treatment/prevention agents
  - Magnitude of potential health benefits for the individual woman and fetus
  - Likelihood of widespread use of the agent in young women
- What alternative trials designs would facilitate safety, speed and efficiency?
- What pregnancy-related evaluations would need to be included in phase III study enrolling pregnant women? Include interim pregnancy-related analyses with early stopping rule for pregnancy subgroup regarding safety?

Potential Designs to Include Pregnant Women in Pre-Approval Drug Trials

Women who become pregnant on study should be allowed to remain on drug/on study with consent in most cases

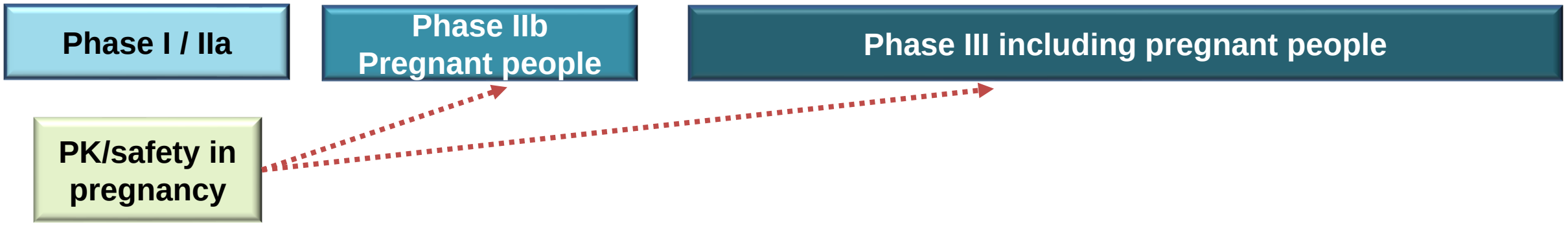
Phase I / IIa

Phase IIb

Phase III

Potential Designs to Include Pregnant Women in Pre-Approval Drug Trials

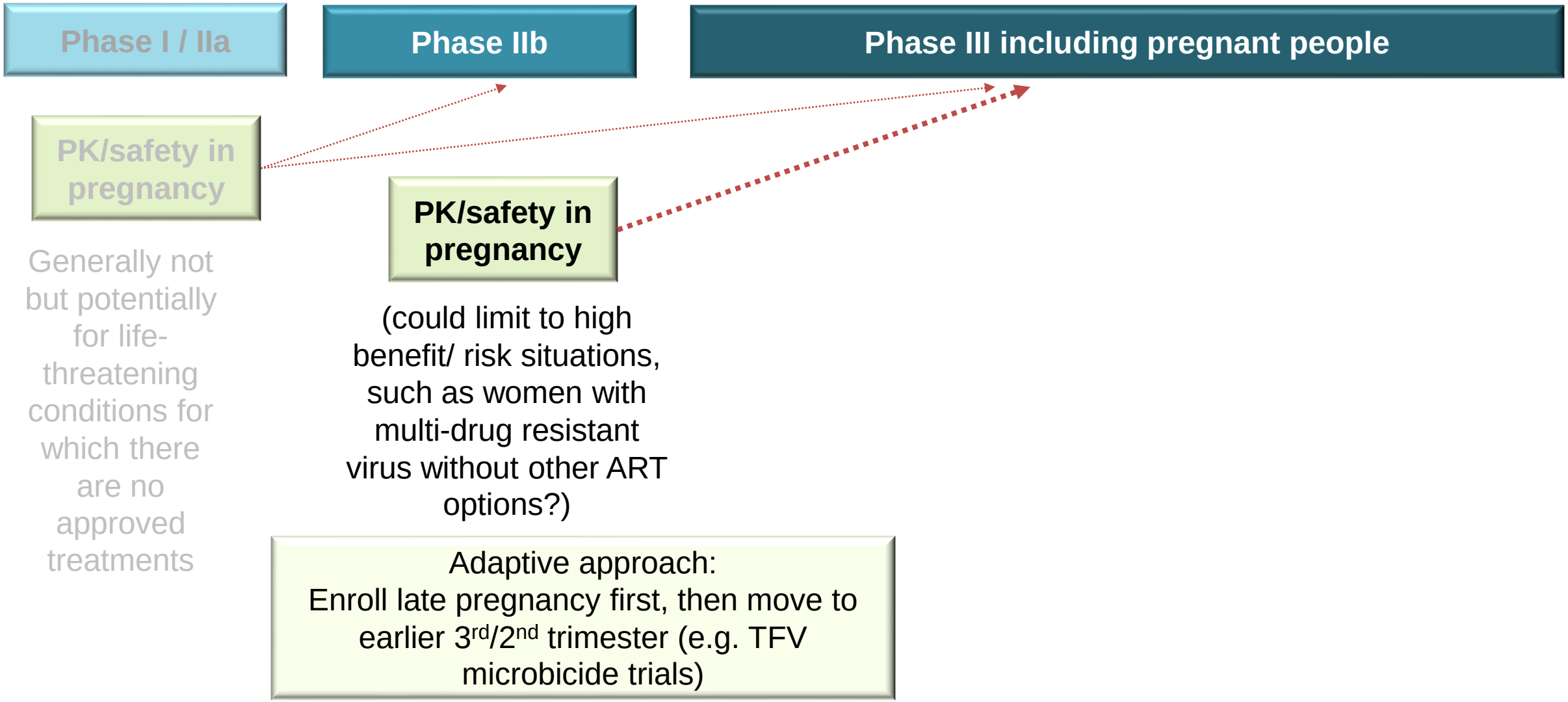
Women who become pregnant on study should be allowed to remain on drug/on study with consent in most cases



Generally not but potentially for life-threatening conditions for which there are no approved treatments

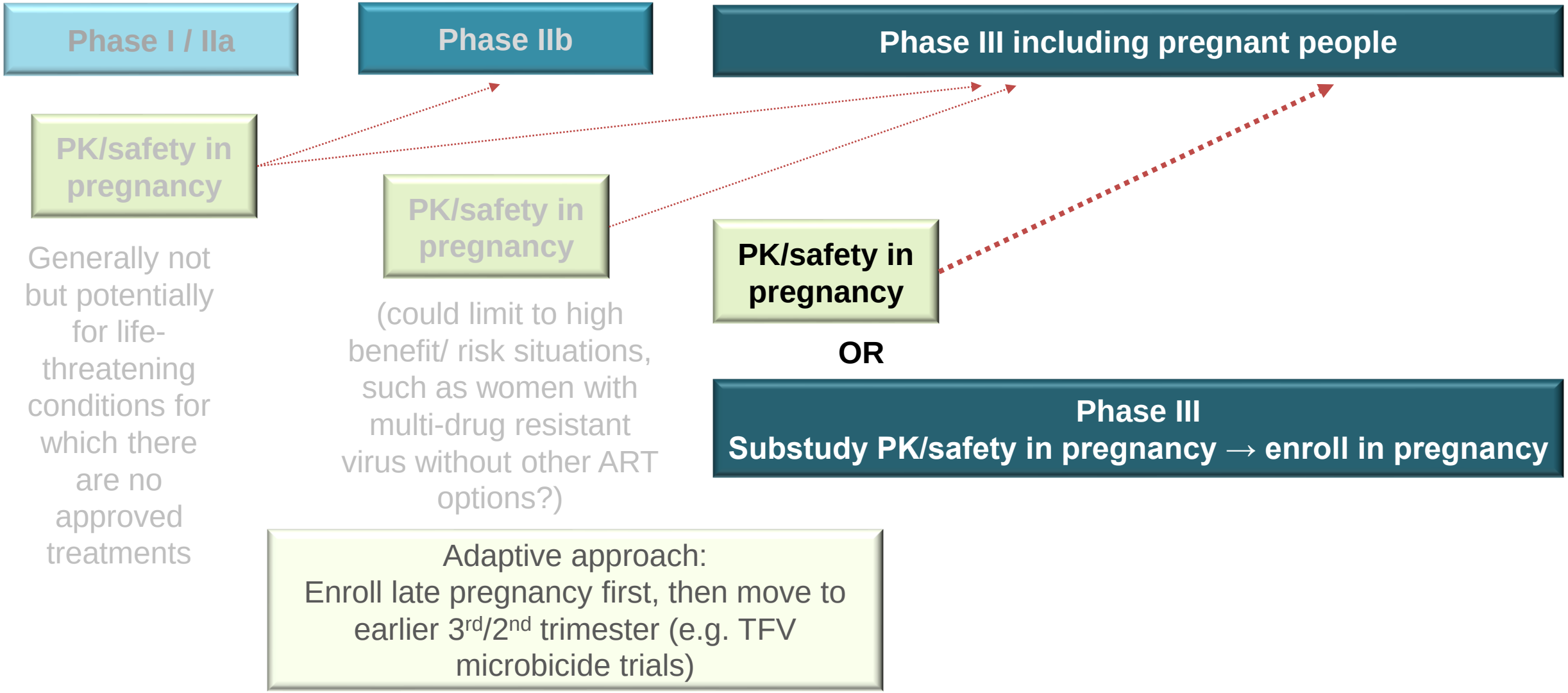
Potential Designs to Include Pregnant Women in Pre-Approval Drug Trials

Women who become pregnant on study should be allowed to remain on drug/on study with consent in most cases



Potential Designs to Include Pregnant Women in Pre-Approval Drug Trials

Women who become pregnant on study should be allowed to remain on drug/on study with consent in most cases



Historic Perspective on Drug Use in Pregnancy

- One picture to sum it up:

Historic Perspective on Drug Use in Pregnancy

- One picture to sum it up:

→ *Lessons learned:* As new drugs are developed for treatment & prevention of HIV (and other significant diseases occurring in pregnancy), studies in pregnant & breastfeeding people are critical and need to be conducted early – ideally before approval - for promising drugs.

Historic Perspective on Drug Use in Pregnancy

- One picture to sum it up:

- Update:

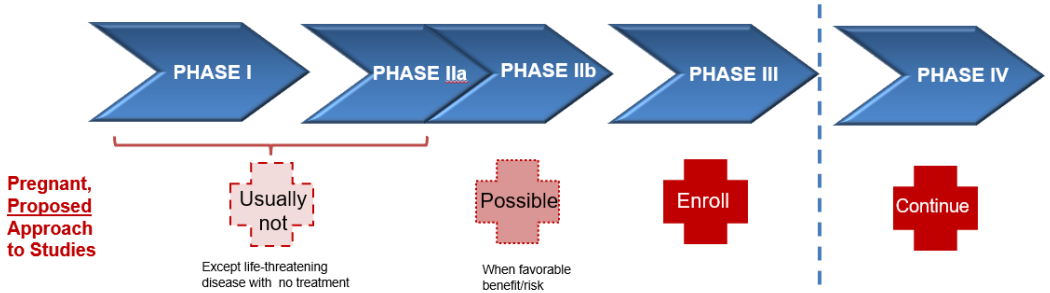
→ *Lessons learned:* As new drugs are developed for treatment & prevention of HIV (and other significant diseases occurring in pregnancy), studies in pregnant & breastfeeding people are critical and need to be conducted early – ideally before approval - for promising drugs.

Historic Perspective on Drug Use in Pregnancy

- One picture to sum it up:

→ *Lessons learned:* As new drugs are developed for treatment & prevention of HIV (and other significant diseases occurring in pregnancy), studies in pregnant & breastfeeding people are critical and need to be conducted early – ideally before approval - for promising drugs.

- Update:



→ Data on PK, safety, and efficacy of new drugs in pregnancy are available at time of new drug approval.

Thanks to Elaine Abrams and Shahin Lockman for input into this talk

and

THANK YOU for your attention!

Catherine Sewell

U.S. Food and Drug Administration

Clinical Case Study:
Fetal Growth Restriction

Day Two
Scientific and Ethical Considerations for the Inclusion of Pregnant Women in Clinical Trials

Catherine Sewell, MD, MPH
Division of Urology, Obstetrics and Gynecology, US FDA

Disclaimer

- I do not have any financial disclosures to report.
- This presentation represents the views of the speaker and not the official position of the FDA.
- Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the speaker or the FDA.

Fetal Growth Restriction (FGR)

- Prevalence: up to 10% of pregnancies globally
- Estimated fetal weight (EFW) <10th percentile for gestational age (GA) [ACOG*], ultrasound EFW or abdominal circumference (AC)<10%ile [SMFM‡]
- Measurement of fundal height (limited by obesity and leiomyomas)
- Ultrasound⁎—if confirms <10%ile for gestational age, add amniotic fluid index (AFI) and umbilical artery (UA) dopplers (absent or reverse end-diastolic flow), fetal anatomy
  - Lack of consensus regarding terminology, etiology, and diagnostic criteria
  - Difficulty in differentiating between the fetus that is constitutionally small and growing appropriately, and the small fetus that is not fulfilling its growth potential because of an underlying pathologic condition

*American College of Obstetricians and Gynecologists
‡Society for Maternal Fetal Medicine
⁎biparietal diameter, head circumference, abdominal circumference, femur length

Fetal growth restriction. ACOG Practice Bulletin No. 204. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;133:e97–109.
Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction. Society for Maternal-Fetal Medicine. AJOG 2020 Oct;223(4):B2-B17.

Etiology of FGR

- Medical conditions
- Multiple gestation
- Teratogen exposure
- Infectious diseases
- Genetic and structural disorders
- Placental disorders and umbilical cord abnormalities

Fetal growth restriction. ACOG Practice Bulletin No. 204. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;133:e97–109.

Current or Past Studies in FGR

Title	Conditions	Design	Interventions	Outcomes
Transplacental aspirin therapy for early onset fetal growth restriction, JHU (NCT04557475)	FGR requiring delivery prior to 32 weeks	Randomized, parallel assignment, open label	Aspirin (ASA) two tablets daily with dinner vs. standard of care (SOC)	Number of fetuses delivered for non-reassuring fetal status prior to 32 weeks Secondary: Change UA dopplers, AFI, fetal heart rate decels, biophysical profile score, GA at delivery, birthweight (BW) %ile at delivery, placental weight at delivery
Treatment of Intrauterine Growth Restriction with Low Molecular Weight Heparin, Fundació Sant Joan de Déu, Spain (NCT03324139)	IUGR at <32 weeks at diagnosis and doppler with absent/reverse flow	Randomized, blinded parallel assignment	Low molecular weight heparin 3500 IU/2 ml daily of Bemiparina SC vs. placebo injection of sodium chloride, maximum of 13 weeks	Efficacy in the prolongation of gestation, reducing neonatal morbidity, reducing thrombotic and ischemic placental lesions, effect on pro-angiogenic and anti-inflammatory profile
L-arginine in Treatment of Intrauterine Growth Restriction, Ain Shams University, Egypt (NCT03321292)	20-40 years old with fetus with IUGR from 28 weeks, no systemic disease in pregnant person	Randomized, single blind parallel assignment	L-arginine 1000 mg and ASA 75 mg vs. ASA 75 mg	BW, Apgar, AFI, UA doppler
The Dutch STRIDER (Sildenafil TheRapy In Dismal Prognosis Early-onset Fetal Growth Restriction), Amsterdam (NCT02277132)	18-50 years old with FGR of likely placental origin	Randomized, blinded, parallel assignment	Sildenafil 25 mg orally three times daily vs. placebo	Intact neonatal survival until term age, fetal growth velocity by ultrasound, age-adequate performance on the two year Bayley scales of infant development, preeclampsia/HELLP, fetal ultrasound and doppler studies, placental growth factor
Antenatal Allopurinol in Intrauterine Growth Restriction UMC Utrecht (NCT00346463)	30-36 weeks with FGR and abnormal UA dopplers	Randomized, blinded, parallel assignment	Allopurinol	Free radical production, fetal parameters, postponement of birth, morbidity including long term neurodevelopmental outcome, mortality, pharmacokinetics (PK)

Current or Past Studies in FGR

Title	Conditions	Design	Interventions	Outcomes
Omega 3 plus vaginal progesterone on birthweight of intrauterine growth-restricted fetuses, Assiut University, Egypt (NCT04161989)	20-35 years old between 28-30 weeks with singleton pregnancy with idiopathic asymmetrical intrauterine growth restriction	Randomized, parallel assignment, open label	Omega 3 capsule (1000 mg fish oil plus 100 mg wheat germ oil) vs. Omega 3 plus capsule and Prontogest 400 mg vaginal suppository	Mean BW, EFW, time of delivery
Pentaerithrityl tetranitrate (PETN) for secondary prevention of intrauterine growth restriction, Jena University Hospital, Germany (NCT03669185)	Age 18 and older between 19 0/7 and 22 6/7 weeks with abnormal UA doppler	Randomized, blinded, parallel assignment	Pentalong 1 tablet twice daily vs. placebo for a maximum of 133 days	Number of participants who develop FGR, severe morbidity, perinatal death, abruption, birth weight, delivery before 30 and 34 weeks, delivery between 34-37 weeks admission to neonatal ICU, rate of intraventricular hemorrhage (IVH), mortality
Melatonin to Prevent Brain Injury in Unborn Growth Restricted Babies Monash University, Australia (NCT01695070)	18-45 year old with FGR fetus at 23 0/7 to 34 0/7 weeks	Open label	Melatonin 4 mg tablet orally twice daily	Oxidative stress in umbilical artery (measure malondialdehyde and 8-isoprostane), maternal venous serum, doppler studies, placental oxidative stress, GA at birth, composite neonatal outcome
Impact of Antioxidant Juice Intake on Brain Injury and Placental Pathology in Infants with IUGR, Brigham and Women's (NCT04394910)	People carrying fetuses with a diagnosis of IUGR in the third trimester	Randomized, blinded, parallel assignment	Pomegranate juice 8 oz daily vs. placebo juice	Infant brain injury assessed on term-equivalent MRI, total and regional infant brain volumes, diffusion tensor imaging measures Secondary: cognitive, motor and language neurodevelopment, compliance with juice regimen, placental weight, incidence of preeclampsia, GA at delivery, incidence of resuscitation at delivery, cord gas

Current Clinical Context for FGR

Criterion	Fetal Growth Restriction
Nature of the Disease (serious, life-threatening?)	Serious Potentially life-threatening for the fetus/neonate
Unmet medical need (treatment not addressed adequately by available therapy)?	Yes
Treatment options available?	No. Therapies being studied, but little evidence
Timing for initiation of intervention and duration of intervention	Depends on when FGR arises, other signs which could dictate timing of delivery
Benefit for the pregnant person? The fetus? Both?	Benefits to fetus: prevent fetal death in utero, preterm birth and associated complications, neurodevelopmental delay/deficiency, early neonatal death Consider implications of subpart B—need consent of both parents
Potential harm to pregnant person or fetus or both?	Potential toxic effect of drug on fetus/neonate e.g. persistent pulmonary hypertension in newborn, fetal/neonatal death or Potential toxicity in pregnant person: bleeding, headaches

Current Clinical Context: Drugs Currently Used for FGR

Approval Status	Drugs	Potential Sources of Data
Approved	None approved for this indication Approved drugs currently used/being studied for FGR: • Aspirin • Low molecular weight heparin (enoxaparin, dalteparin)	• Nonclinical data (embryofetal development, pre-and postnatal development) • Premarket and postmarket safety in nonpregnant people can support safety in pregnant person • Postmarketing data on use in pregnancy—are they relevant to the clinical development program at hand (time frame drug used, long-term outcomes on safety, dosing, ? Efficacy) • Dose-finding: doses approved for nonpregnant uses have not been evaluated in pregnancy
In development	None	• Proof of concept (animal model) • Nonclinical data • Safety/tolerability in healthy, nonpregnant people • Dose selection • Small study in pregnant people with FGR: dosing, pharmacokinetics (PK), safety, preliminary efficacy • Target population for inclusion: benefit-risk: early second trimester, people with previous FGR affecting pregnancy or with medical conditions

THE FIELD IS WIDE OPEN…

Hypothetical Trial of an Already Approved Drug
“NormoGrowth”
for the New Indication of Treatment of FGR

Animal Toxicology Data for “NormoGrowth” for FGR

Approval Status	Data Needed for Approved Drug and Drug in Development
Approved: “NormoGrowth”	• Pharmacology (mechanism of action, receptor binding, specificity, safety pharmacology) • PK (absorption, distribution, metabolism, excretion) • Repeat dose animal studies that cover the intended duration of treatment, and evaluate a dose range • Toxicokinetics (to predict drug exposure in humans, inform a start dose, calculate safety margins) • Genotoxicity studies • Reproductive and developmental studies (fertility and early embryofetal development, embryofetal development, pre- and postnatal development)
Drug in development	

Dose of “NormoGrowth”

Approval Status	Data Needed
Approved	• Cannot extrapolate PK information due to the continuum of physiologic changes in pregnancy • PK/(pharmacodynamics(PD), preliminary safety studies of NormoGrowth in pregnant people—consider risk to fetus • Opportunistic PK studies of NormoGrowth in pregnant people already taking the drug for another indication • Phase 2 and 3 for efficacy and safety of selected doses
Contrast with a new drug in development	• Dose selection studies in non-pregnant people—but can’t extrapolate to pregnant people • Small study in pregnant people with FGR for dosing, PK/PD, preliminary safety • Phase 2 and 3 for efficacy and safety of selected doses

Study Design for "NormoGrowth" for FGR

Study Design Elements	Considerations
Randomized blinded controlled clinical trial of NormoGrowth + standard of care compared with placebo + standard of care alone Vs. open label single arm of NormoGrowth	Randomized 1:1 Standard of care = surveillance, ultrasound/Doppler velocimetry, amniotic fluid volume assessment, fetal testing
Inclusion Criteria	People carrying a pregnancy with FGR FGR defined as: EFW<10th percentile for gestational age? Other criteria: UA dopplers with absent or reverse end-diastolic flow?
When to start NormoGrowth?	When FGR first diagnosed—20-27 weeks (second trimester?) Criteria for FGR? Consider: FGR alone or with other factors? UA dopplers? Hypertensive disorder? Depends on cause of FGR…
Duration of use of NormoGrowth	Until delivery? Fetal death? Uncertainty surrounding the optimal management and timing of delivery

Study Design for "NormoGrowth" for FGR

Study Design Elements	Considerations
Fetal/Neonatal Outcomes	BW Fetal growth UA dopplers AFI/placenta Fetal or neonatal death Major neonatal morbidity Neurodevelopmental outcomes in early childhood Potential for fetal toxic exposure GA at delivery (surrogate endpoint?)
Outcomes for Pregnant Person in Study of NormoGrowth	Preeclampsia/HELLP

Discussion Questions

1. How do the clinical context and study objectives impact the design of a trial (for example, how do clinical investigators consider the clinical context and study objectives when choosing whether to implement a single arm or placebo controlled study)?
2. What effects do the physiologic changes throughout pregnancy have on drug metabolism and how does that affect the study design? How do considerations related to the duration of treatment and trimester of pregnancy (e.g. vulnerability of the fetus) affect the study design?
3. How does the condition influence potential endpoints/outcomes we consider for the pregnant person, neonate, and older infant?

Shahin Lockman

Harvard University

Some perspectives based upon experience with HIV clinical treatment trials in pregnancy

- Many pregnant people desire opportunity to take part in research and express benefits
  - Feasible to enroll pregnant people into clinical trials
- Contraceptive requirement for clinical trials enrollment sometimes seen as coercive
- Plan pregnancy trials well in advance & employ efficient approaches, to shorten timelines
- Study design:
  - Adverse pregnancy outcomes = key outcome (variable by location, population, time)
  - Design to minimize chance of adverse outcomes unrelated to study
  - Plan thoughtful communications strategy, involving stakeholders throughout
  - Need framework for prioritizing agents for pregnancy trials (and trial size/design and timing)

Susan Kindig

Eli Lilly and Company

Anne Lyerly

University of North Carolina, Chapel Hill

Yodit Belew

U.S. Food & Drug Administration

Case Study Discussion

Discussion Questions:

1. How do the clinical context and study objectives impact the design of a trial (for example, how do clinical investigators consider the clinical context and study objectives when choosing whether to implement a single arm or placebo controlled study)?
2. What effects do the physiologic changes throughout pregnancy have on drug metabolism and how does that affect the study design? How do considerations related to the duration of treatment and trimester of pregnancy (e.g. vulnerability of the fetus) affect the study design?
3. How does the condition influence potential endpoints/outcomes we consider for the pregnant person, neonate, and older infant?

Case Study: Comparing and Contrasting Clinical Trials Enrolling Pregnant People to Evaluate Treatment for a Chronic Medical Condition and Clinical Trials for a Pregnancy-Related Condition

Moderator: Marta Wosińska, Duke-Margolis Center for Health Policy

Break—10 Minutes

We are still live. Please mute your audio.

Session 4 will begin at 1:40 pm.

Session 4: Challenges and Next Steps

Moderator: Marta Wosińska, Duke-Margolis Center for Health Policy

Kathryn Schubert

Society for Women's Health Research

Christina Bucci-Rechtweg

Novartis Pharmaceuticals Corporation

Cynthia Gyamfi-Bannerman

Columbia University Medical Center

Karim Calis

National Institutes of Health

Leslie Meltzer Henry

University of Maryland Francis King Carey School of Law

Lynne Yao

U.S. Food and Drug Administration

Session 4 Discussion

Discussion Questions:

1. What current resources exist to assist clinical investigators in obtaining feedback on the robustness of their nonclinical and clinical data prior to proceeding with IND submissions for clinical trials enrolling pregnant people?
2. What are the priority conditions impacting pregnant people that should be addressed first? What are the short term and long term goals of clinical trial conduct and therapeutic development in these areas?
3. How can industry, academia, regulatory stakeholders and, NIH best collaborate to make progress in therapeutic development for conditions impacting pregnant people? What are the opportunities for public-private partnership to drive this work forward?
4. What are the greatest challenges and what are potential solutions to the conduct of clinical trials during pregnancy?
5. How do we foster education and awareness about available resources, requirements, and options for participating in clinical research [for researchers, healthcare providers and pregnant people]?

Session 4: Challenges and Next Steps

Moderator: Marta Wosińska, Duke-Margolis Center for Health Policy

Closing Remarks & Meeting Adjournment

Marta Wosińska,

Deputy Director, Duke-Margolis Center for Health Policy

Thank You!

Contact Us

healthpolicy.duke.edu

Subscribe to our monthly newsletter at
dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW, Suite 500
Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

Follow Us

DukeMargolis

@DukeMargolis

@DukeMargolis

Duke Margolis