

# Ethics, Research and Pregnancy

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THE UNIVERSITY  
of NORTH CAROLINA  
at CHAPEL HILL

PHASES  
PREGNANCY + HIV/AIDS  
SEEKING EQUITABLE STUDY

# CDC Health Advisory




**PREGNANT PEOPLE** with symptomatic COVID-19 have a

**70%**  
**INCREASED RISK OF DEATH.**

COVID-19 during pregnancy increases the risk for adverse pregnancy and neonatal outcomes, including preterm birth and admission of the baby to an intensive care unit.

**ONLY 31%**  
of pregnant people have been vaccinated against COVID-19

**GET VACCINATED.**  
**FIND A COVID-19 VACCINE NEAR YOU.**  
**VACCINES.GOV**



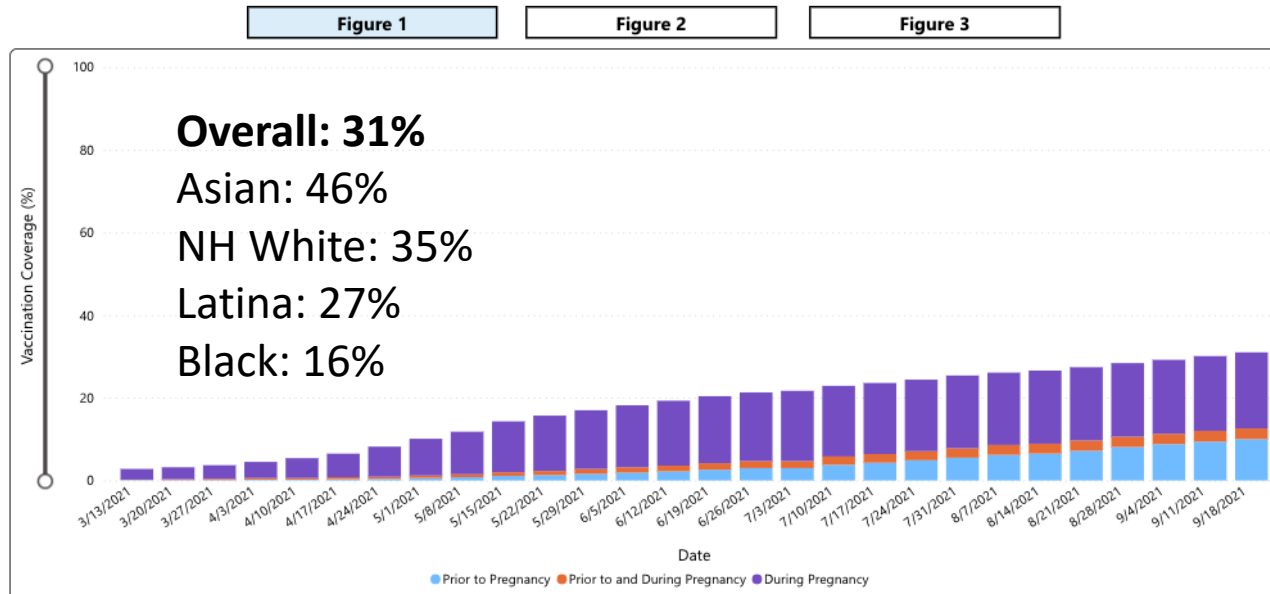
September 29<sup>th</sup>, 2021

CDC recommends **urgent action** to increase Coronavirus Disease 2019 (COVID-19) vaccination among people who are pregnant, recently pregnant (including those who are lactating), who are trying to become pregnant now, or who might become pregnant in the future. CDC **strongly recommends COVID-19 vaccination either before or during pregnancy** because the benefits of vaccination outweigh known or potential risks.

# COVID and pregnancy: vaccination, outcomes

COVID-19 vaccination among pregnant people aged 18-49 years overall, by race/ethnicity, and date reported to CDC - Vaccine Safety Datalink,\* United States

**Figure 1: Percent of Pregnant People Aged 18–49 Years Fully Vaccinated with COVID-19 vaccine Prior to and during Pregnancy, by Timing of Vaccination and Date Reported to CDC – Vaccine Safety Datalink\*, United States**  
December 14, 2020 – September 18, 2021



\*Vaccination coverage\* represents the total number of pregnant people (denominator as of September 18, 2021 = 189,986) who were fully vaccinated, including both doses of the Pfizer-BioNTech or Moderna vaccines or a single dose of the Johnson & Johnson's Janssen vaccine; \*prior to pregnancy\* represents total number of pregnant people who were fully vaccinated prior to pregnancy, including both doses of the Pfizer-BioNTech or Moderna vaccines or a single dose of the Johnson & Johnson's Janssen vaccine; \*prior to and during\* pregnancy represents total number of pregnant people who received one dose of the Pfizer-BioNTech or Moderna vaccines prior to pregnancy and one during pregnancy; \*during pregnancy\* represents total number of people who received both doses of the Pfizer-BioNTech or Moderna vaccines or a single dose of the Johnson & Johnson's Janssen vaccine during pregnancy.

Last update: September 18, 2021  
 Data source: Vaccine Safety Datalink.

- Cases: 125,250
- Deaths: 161
- 97% of hospitalized are unvaccinated

## Mississippi health officials plea for vaccination after 'significant' number of COVID-19 fatalities in pregnant women

*The eight women who recently died were unvaccinated, health officials said.*

By [Meredith Deliso](#)  
 September 10, 2021, 4:57 PM • 5 min read



# Vaccines authorized - December 2019

## ***F.D.A. Clears Pfizer Vaccine, and Millions of Doses Will Be Shipped Right Away***

An initial shipment of about 2.9 million doses of the vaccine will be sent around the United States over the next week.

## ***F.D.A. Authorizes Moderna Vaccine, Adding Millions of Doses to U.S. Supply***

The Food and Drug Administration authorized a second coronavirus vaccine for emergency use, clearing the way for millions more Americans to be immunized next week.

# Priority Groups for Vaccination (ACIP)

- Phase 1a: **Health care workers** and long-term care facility residents
- Phase 1b: Persons aged  $\geq 75$  years and **frontline essential workers**
- Phase 1c: Persons aged 65-75 years, persons aged **16-64 years with high risk medical conditions (including pregnancy)**, and other essential workers



➤ **Pregnant people represented across priority groups**

# ACOG Practice Advisory, December 2020

- Vaccines available under EUA **have not been tested in pregnant women**, no pregnancy-specific data
- COVID-19 **vaccines should not be withheld** from pregnant individuals who meet criteria for vaccination based on ACIP-recommended priority groups.
- Pregnancy testing should not be a requirement prior to receiving any EUA-approved COVID-19 vaccine.



# World Health Organization

- **January 27, 2021**

- **WHO recommends not to use mRNA-1273 in pregnancy**, unless the benefit of vaccinating a pregnant woman outweighs the potential vaccine risks, such as in health workers at high risk of exposure and pregnant women with comorbidities placing them in a high-risk group for severe COVID-19.
- Information and, if possible, counselling on the lack of safety and efficacy data for pregnant women should be provided. WHO does not recommend pregnancy testing prior to vaccination."

- **January 29, 2021**

- While pregnancy puts women at higher risk of severe COVID-19, very little data are available to assess vaccine safety in pregnancy.
- Nevertheless, based on what we know about this kind of vaccine, we don't have any specific reason to believe there will be specific risks that would outweigh the benefits of vaccination for pregnant women.
- For this reason, those pregnant women at high risk of exposure to SARS-CoV-2 (e.g. health workers) or who have comorbidities which add to their risk of severe disease, **may be vaccinated in consultation** with their health care provider.

- WHO recommends vaccination in pregnant women **when the benefits of vaccination to the pregnant woman outweigh the potential risks.**

# COVID-19 and pregnancy

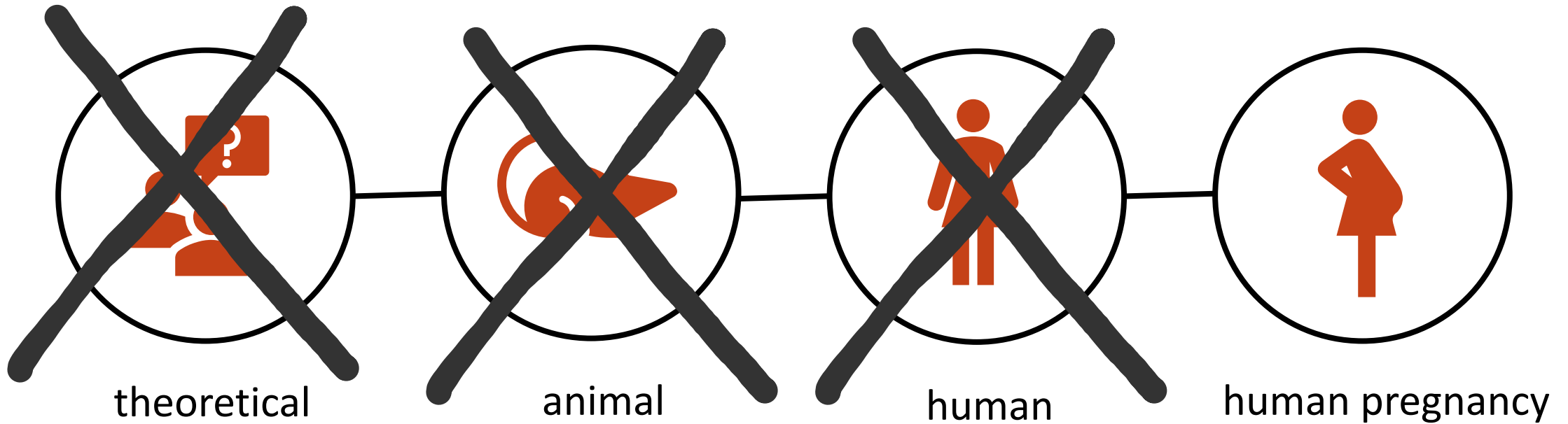
- Increased risk for severe illness
- Increased risk associated with comorbidities
- Increased risk for ICU admission
- Increased risk for mechanical ventilation
- Increased risk for preterm birth
- Increased risk for death
- Black and Hispanic individuals bear disproportionate burden of infection, morbidity and death





# Assessing vaccine risk and pregnancy

**Authorized mRNA vaccines:**



MEDICAL DISPATCH

# THE CORONAVIRUS VACCINE PRESENTS A DILEMMA FOR PREGNANT WOMEN

*Vaccine trials have excluded the pregnant population, even though women of reproductive age make up a majority of frontline workers.*

By Anna Louie Sussman

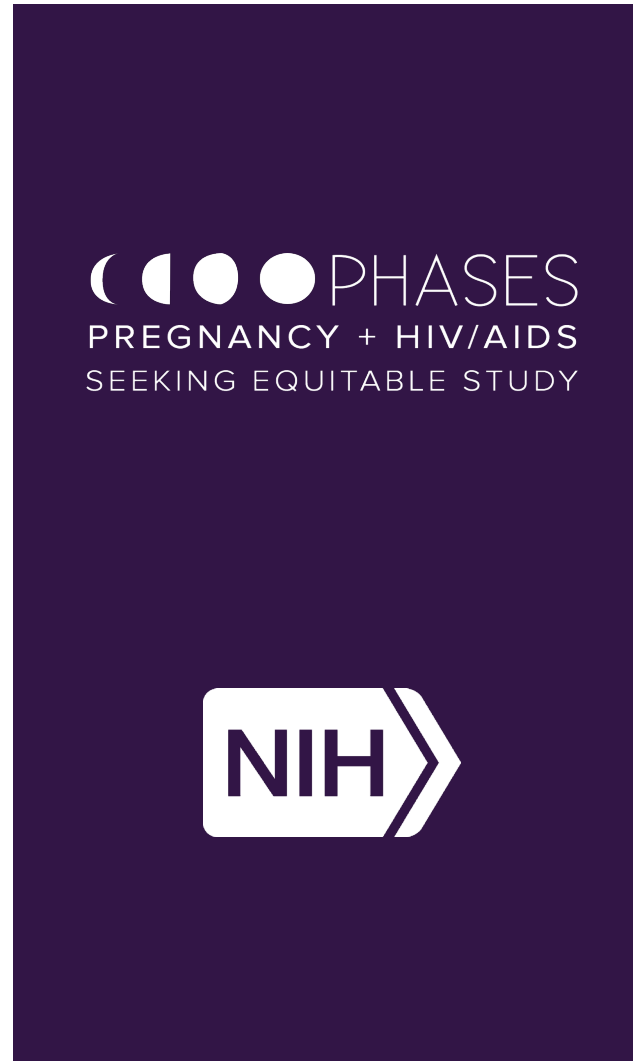
February 1, 2021

# The journey toward ethical inclusion



Toward the Responsible Inclusion of  
Pregnant Women in Medical Research

THE SECOND WAVE INITIATIVE



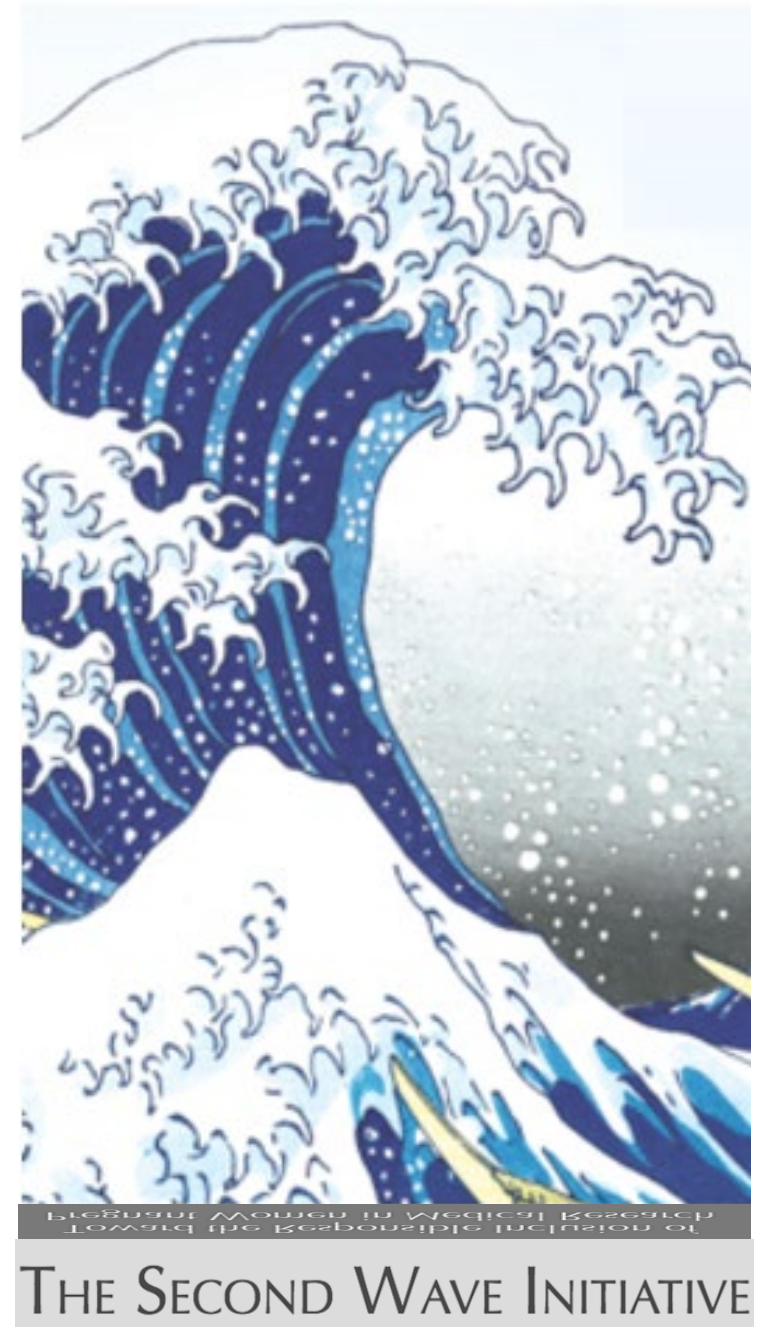
# The first wave:

## Women as research subjects

- Early 1990s women noted to be underrepresented in research
  - Excluded from studies
  - Health concerns not investigated
- Alleged justifications
  - Women's physiologies complicate
  - Protection of women and fetuses
  - Recruitment difficulties
- 1993 NIH Revitalization Act
  - New requirements for inclusion of women and minorities in research
  - Justify exclusion on basis other than cost
- Women now majority of research participants (gaps remain)
- **Pregnant people – left behind**

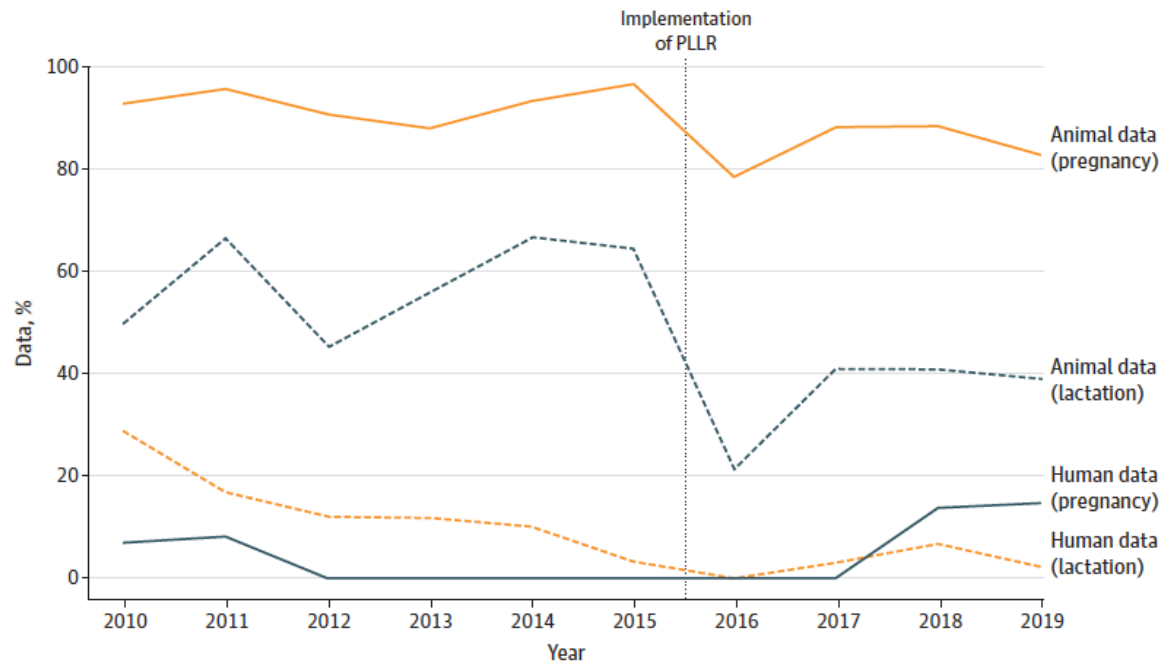
# The Second Wave: Pregnant people as research subjects

- As a matter of justice, all people deserve to safe and effective treatment throughout the lifespan – ***including during pregnancy*** – and deserve an evidence base adequate to that fact.
- Ethics requires **protecting pregnant people not *from* research, but *through* research.**



# Pregnancy specific data: lacking

Figure 2. Pregnancy and Lactation Data Derived From Human and Animal Studies Before and After Implementation Date



Pregnancy-specific data in drugs approved since 2010:

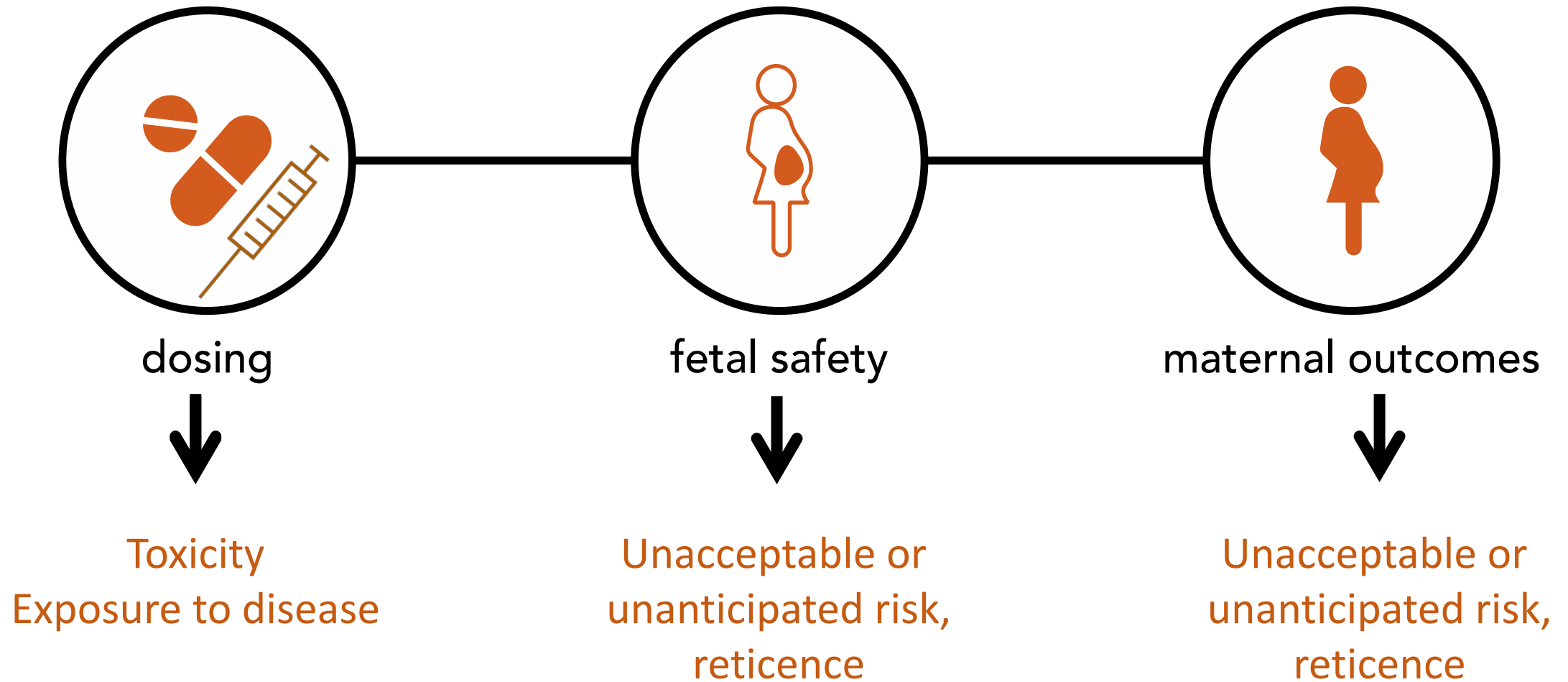
90% - Animal data

10% - Human data

Byrne et al, JAMA 2020

- Limited or no data at time of approval
- Post approval delays in pregnancy-specific data - extensive

# Pregnancy-specific evidence: a critical need



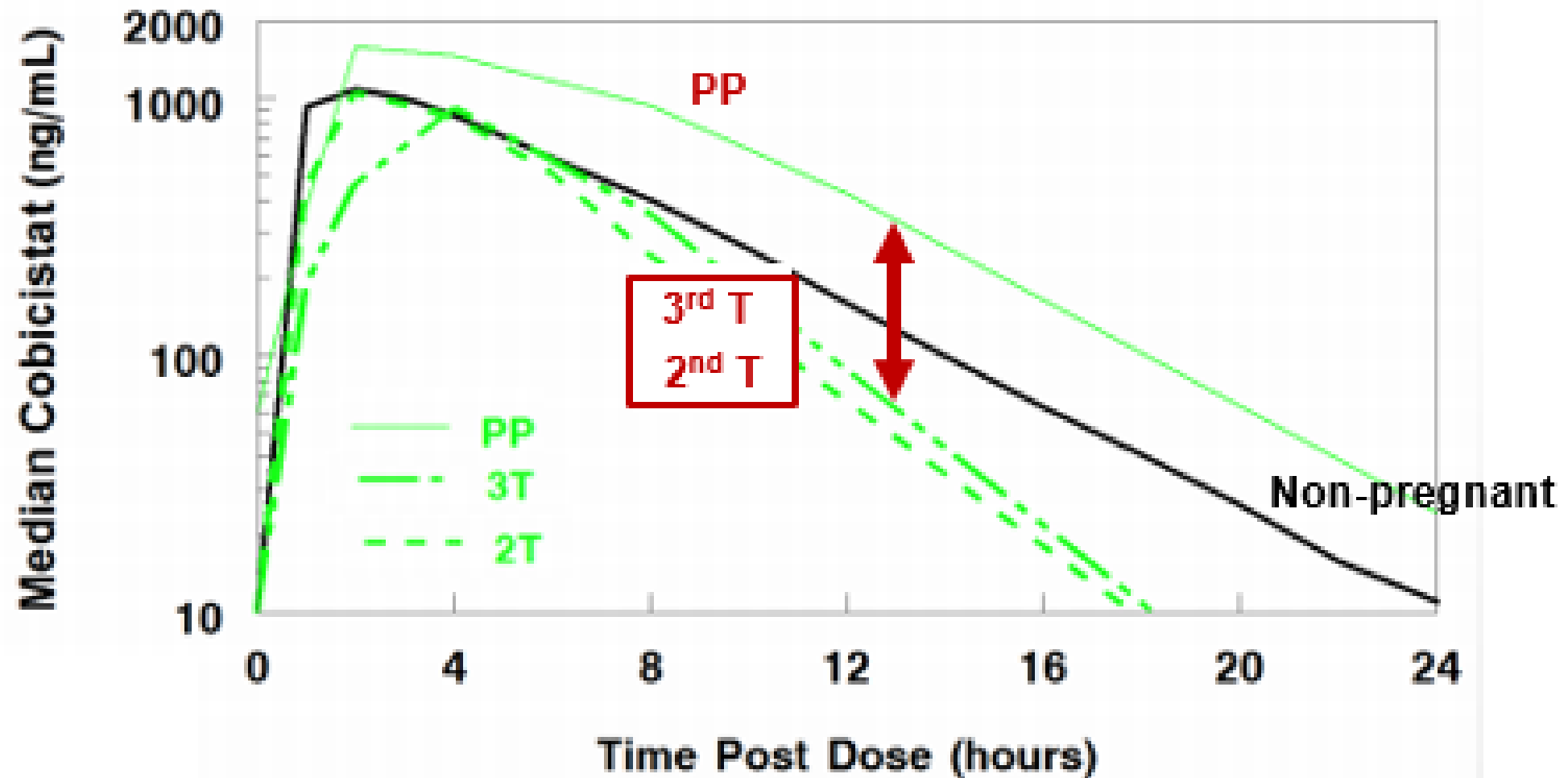
# Dosing

- Pregnancy changes drug metabolism, dosing
  - Pharmacokinetics (PK)
- Dearth of PK data for treatment, prevention, co-I
- Average delay for approved ARVs = 6 years
  
- Harms: underdosing (exposure to disease); overdosing (toxicity)
- Example: cobicistat



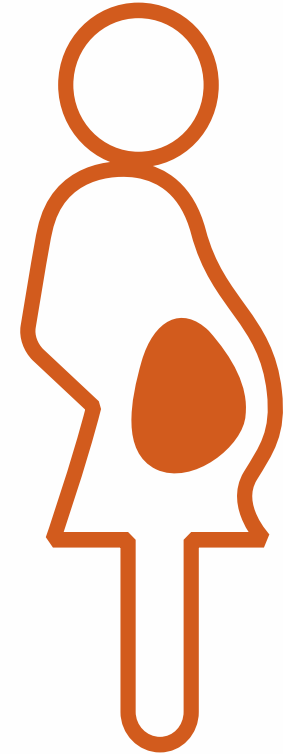


# Cobicistat - PK



# Fetal Safety

- Safety of drugs for fetus is prominent concern
- Most drugs come to market with animal data only
- Post approval data delayed, limited
  
- Harms:
  - Potential for inappropriate risk
  - Barriers to access
- Examples: malaria, TB treatments

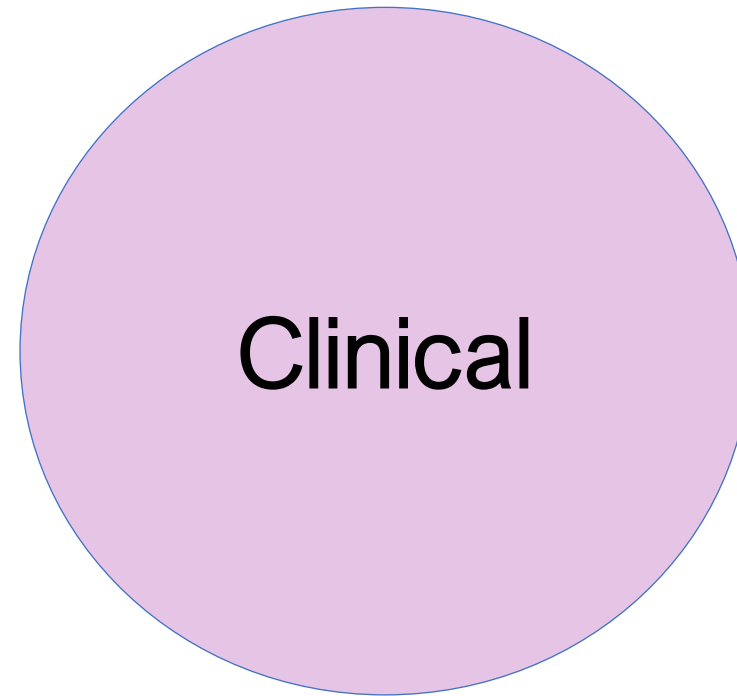


# Maternal outcomes

- Drugs may carry risks specific to pregnancy (preeclampsia, hemorrhage, liver toxicity), especially where drugs are used in combination
- Tendency to focus on/prioritize fetal/neonatal outcomes
- Harms: increased risk of maternal morbidity/death
- Example: ARTs and liver toxicities

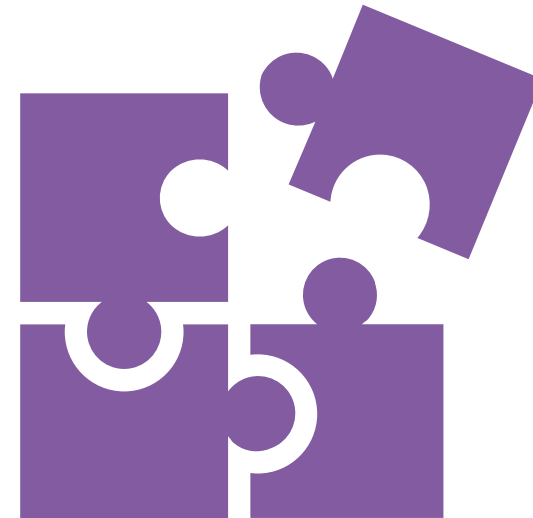


# Risk shifting



# Causes of evidence gaps

- Drug approval and development pathway
  - Lack of requirements, incentives
- Pregnant women and research
  - Myths and misconceptions
  - History of “protectionism”
  - Lack of training
  - Legal and logistical challenges
  - Justificatory asymmetry
- Pregnant women and risk
  - Vessels and vectors
  - Risk distortions



[A] **cultural shift** is necessary to emphasize the importance and public health significance of building a knowledge base to inform medical decision-making for pregnant and lactating women. **Research on therapies for these populations must be facilitated and greatly augmented.”**

PRGLAC, 2018 Report to HHS

# FDA: Draft Guidance

“Filling the knowledge gaps regarding safe and effective use of drugs is **a critical public health need**, but one that raises complex issues”

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## **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

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PHASES  
PREGNANCY + HIV/AIDS  
SEEKING EQUITABLE STUDY



PHASES  
PREGNANCY + HIV/AIDS  
SEEKING EQUITABLE STUDY

# Ending the evidence gap for pregnant women around HIV & co-infections:

A CALL TO ACTION

The PHASES Working Group  
Pregnancy and HIV/AIDS: Seeking Equitable Study

*issued July 2020*



# The PHASES Project



**Engagement**  
Consultations  
Empirical Research



**Conceptual-Analytic**  
Research



**Guidance Development**

# The PHASES Project

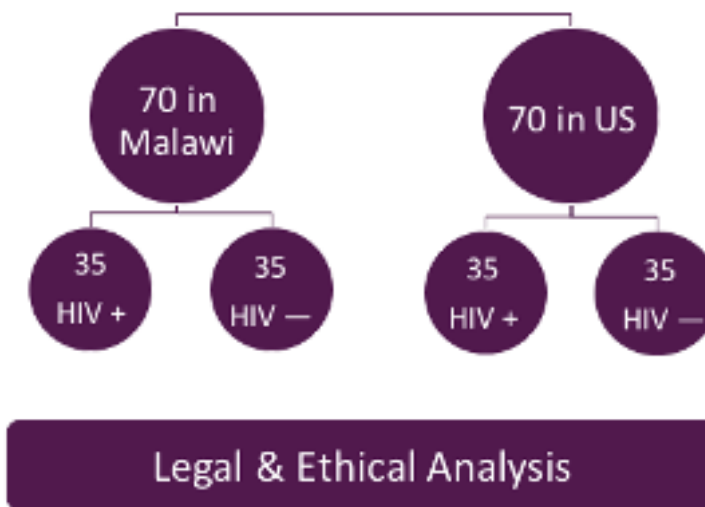


**Engagement**  
Consultations  
Empirical Research

140 Interviews with stakeholders



140 Interviews with pregnant/recently pregnant women



# The PHASES Project



**Engagement**  
Consultations  
Empirical Research



**Conceptual-Analytic**  
Research



**Guidance Development**

## Project Leadership



Anne Lyerly Maggie Little Ruth Faden Kristen Sullivan

## Working Group

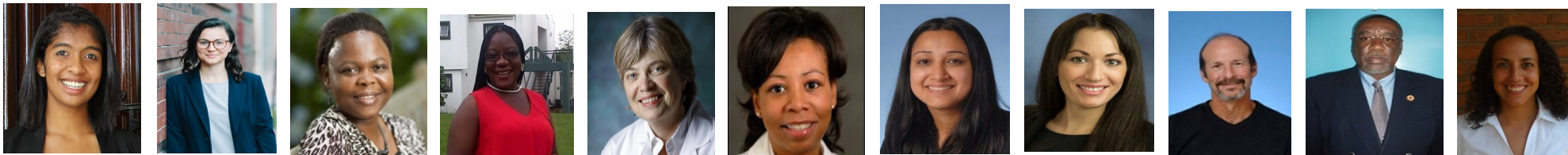


Rich Beigi Linda-Gail Bekker Benjamin Chi Susan Cohn Dazon Dixon Diallo Joseph Eron Angela Kashuba Mary Kasule Carleigh Krubiner Joseph Mfutso-Bengo Lynne Mofenson Victor Mwapasa Lillian Mworeko



Landon Myer Martina Penazzato Annette Rid Roger Shapiro Jerome Singh Marissa Vicari Jacque Wambui Amina White Leslie Wolf

## Research

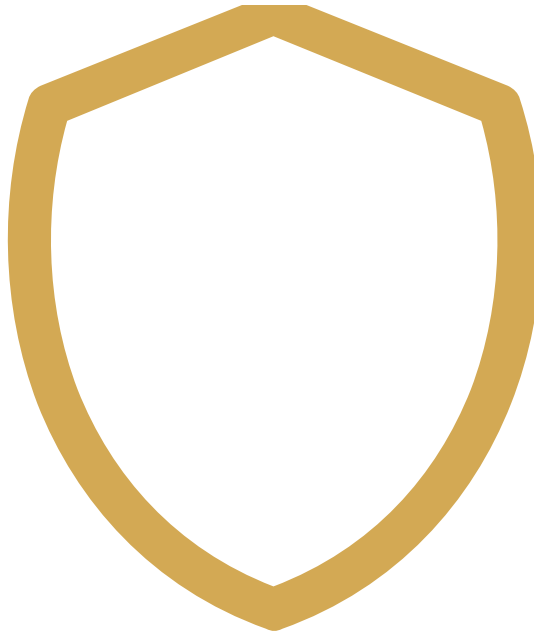


Marisha Wickremsinhe Elana Jaffe Chifundo Zimba Tiwonge Mtande Jean Anderson Jenell Coleman Lisa Rahangdale Marielle Gross Irving Hoffman Francis Martinson Nora Rosenberg

# Ethical Foundations



# Equitable **protection** from drug-related risks



- Mission of research – gather evidence to decrease risks in clinical settings
- Pregnant women and offspring need and deserve such protection
- Exclusion from research doesn't eliminate risks – it exports them to the clinical setting, where they expand

# Equitable **access** to medications and vaccines



- Pregnant people deserve timely access medications and vaccines
- Lack of data leads to reticence to prescribe or take medicines; cautions against use in public health guidance
- Leaves pregnant people and offspring exposed to risks of disease

# Equitable **respect** for pregnant women's health



- Tendency for fetal or child outcomes overshadow attention to maternal outcomes
- Decisions about research (and treatment) should reflect due consideration for the woman's health
- Failure to do so treats her as a “vessel or vector” rather than a person in her own right



# Three Conceptual Shifts

*Vulnerable population*



*Complex population*

Protection *from* research



Protection *through* research

Presumptive exclusion



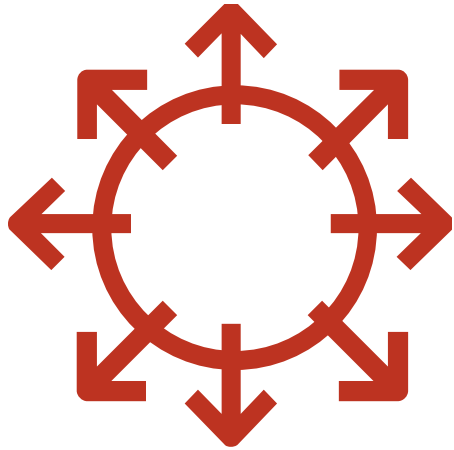
Fair inclusion

# PHASES Guidance

- 12 specific, concrete, and immediately actionable recommendations
- Consistent with current regulatory frameworks
- Directed to multiple stakeholders across the arc of drug development and post-approval research.

# Recommendations

# Building Capacity



1. Affirm the need for research with pregnant women
2. Formalize a global network for advocacy and resources
3. Enhance training

United States Senate

WASHINGTON, DC 20510

March 10, 2020

Dr. Francis S. Collins  
Director  
National Institutes of Health  
9000 Rockville Pike  
Bethesda, MD 20892

Dr. Stephen Hahn  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Dear Dr. Collins and Dr. Hahn:

We write regarding the work the U.S. National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) have done to prioritize the rapid development of treatments and vaccines for the 2019 Novel Coronavirus (COVID-19). As your agencies work to

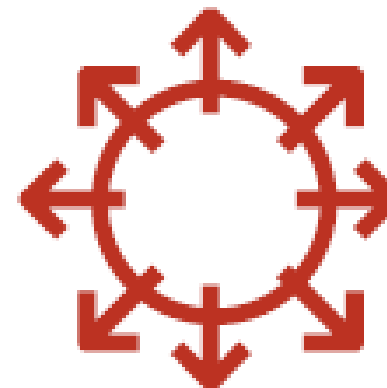
Sincerely,

  
Elizabeth Warren  
United States Senator



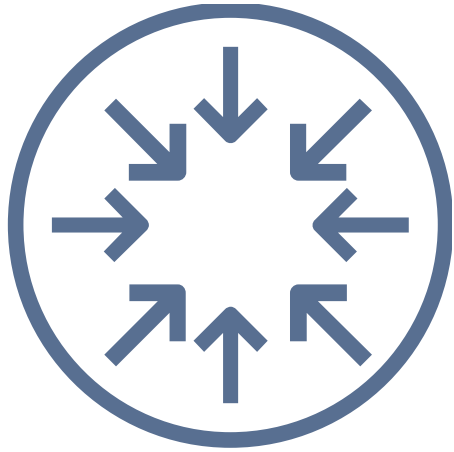
Patty Murray  
United States Senator  
Ranking Member, U.S. Senate Committee on  
Health, Education, Labor, and Pensions

“Pregnant people have historically been left out of research agendas and clinical trials due to the added complexities of ensuring their safety and that of their children”  
“We urge you to account for the unique risks and concerns of populations that have historically been excluded from pandemic research agendas”



➤ **MATERNAL HEALTH  
PANDEMIC RESPONSE ACT**

# Supporting Inclusion



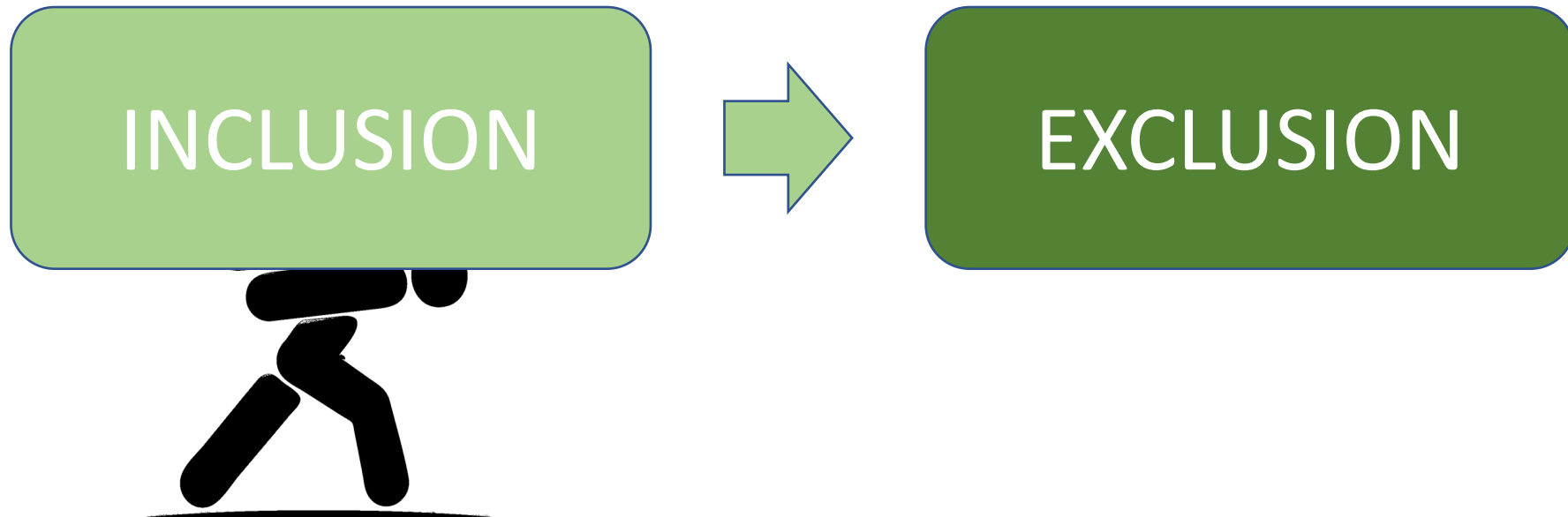
4. Design for inclusion

5. Review for and facilitate inclusion

6. Ensure equitable attention to pregnant women's own health

# Burden of justification

- Shifting burden – require justifying *exclusion*



# Achieving Priority Research



7. Integrate pharmacokinetic (PK) studies

8. Enhance post-approval safety assessments

9. Address legacy evidence gaps



# Ensuring Respect



10. Ensure fair access to life-saving experimental drugs
11. Respect and support women's decisional authority
12. Contextualize risk findings

“It is critical to not just view a pregnant mother, or any woman of childbearing potential, as a vessel for a baby, but as an individual in her own right, who deserves access to the very best, evidence-based treatment available and the right to be adequately informed to make a choice that she feels is best for her.”

**Communique of the Kigali Dolutegravir Stakeholder Meeting  
of African Women Living with HIV, 2018**



NEWS / Pfizer and BioNTech Commence Global Clinical Trial to Evaluate COVID-19 Vaccine in Pregnant Women

## PFIZER AND BIONTECH COMMENCE GLOBAL CLINICAL TRIAL TO EVALUATE COVID-19 VACCINE IN PREGNANT WOMEN

Thursday, February 18, 2021 - 01:30pm EST

**New York, USA and Mainz, Germany, February 18, 2021** — [Pfizer Inc.](#) (NYSE: PFE) and [BioNTech SE](#) (Nasdaq: BNTX) announced today that the first participants have been dosed in a global Phase 2/3 study to further evaluate the safety, tolerability, and immunogenicity of the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) in preventing COVID-19 in healthy pregnant women 18 years of age and older.

# Thank you!

Work from the PHASES Project was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award number R01AI108368. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.



[hivpregnancyethics.org](https://hivpregnancyethics.org)

[@pregnancyethics](https://twitter.com/pregnancyethics)

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