

Ethical Considerations for Enrolling Pregnant Individuals in Clinical Studies

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THE UNIVERSITY
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at CHAPEL HILL

PHASES
PREGNANCY + HIV/AIDS
SEEKING EQUITABLE STUDY



Toward the Responsible Inclusion of
Pregnant Women in Medical Research

THE SECOND WAVE INITIATIVE

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PREGNANCY + HIV/AIDS
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Pregnancy Research Ethics
for Vaccines, Epidemics,
and New Technologies

PREVENT



History of exclusion

- **First wave:**

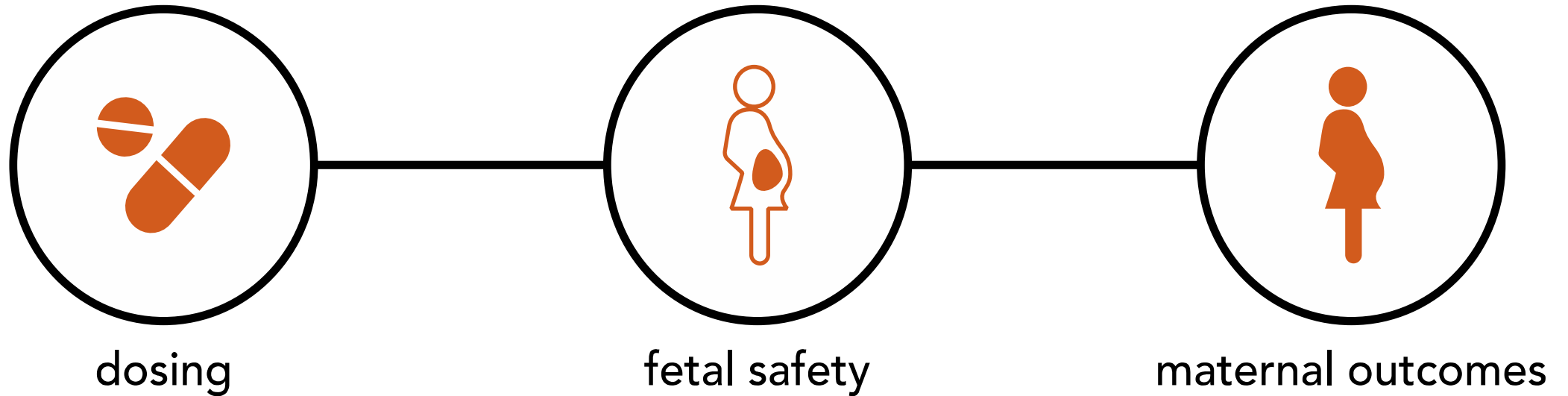
- Early 1990s, women and their health interests under-represented in research
- 1993 NIH Revitalization Act
- Women now a majority of research participants; gaps remain

- **Second wave:**

- Pregnant people and their health interests still under-represented in research
- Result is a dearth of information to guide care
- Second Wave Initiative: ethics requires inclusion

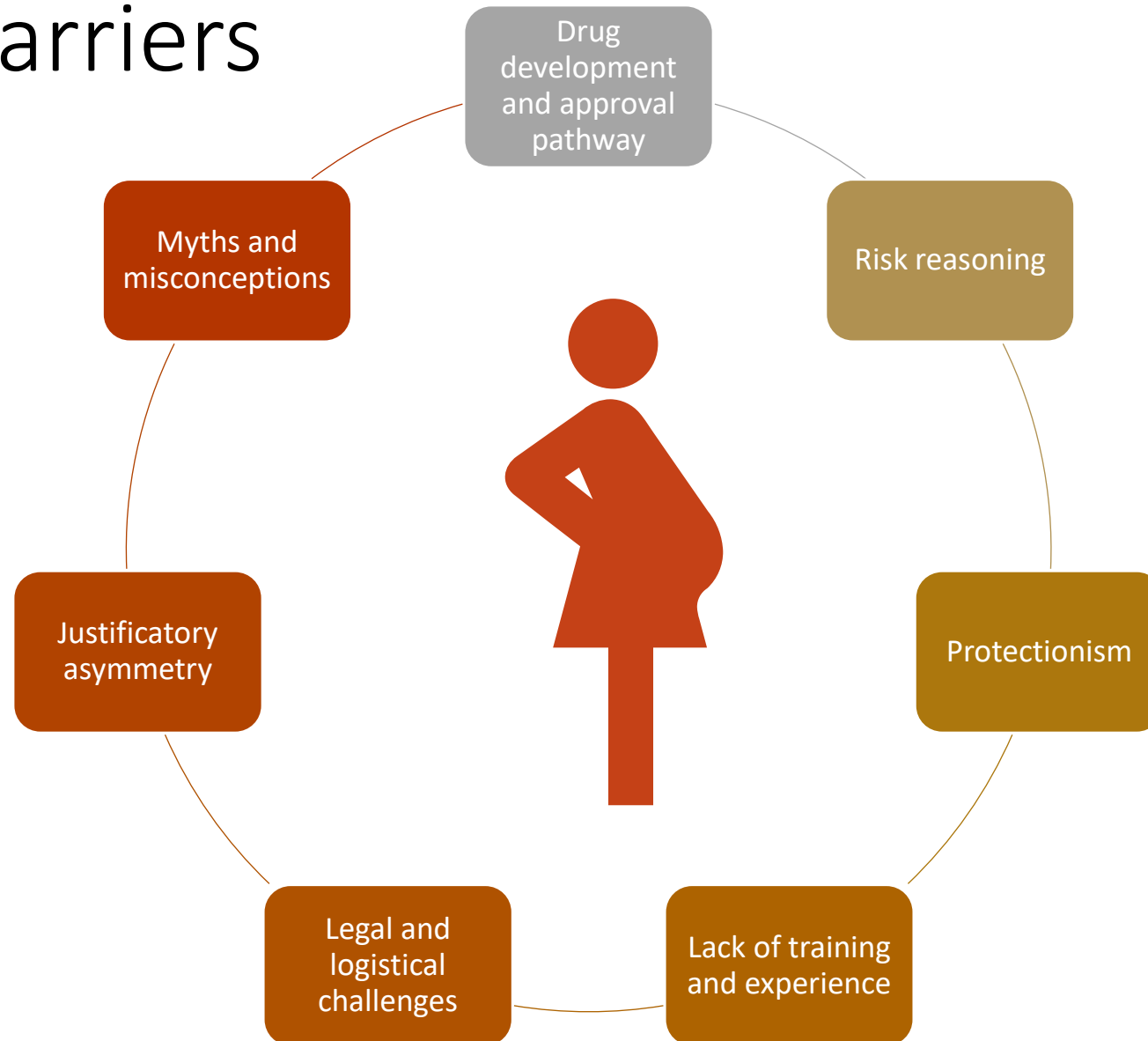


Critical evidence gaps and their costs



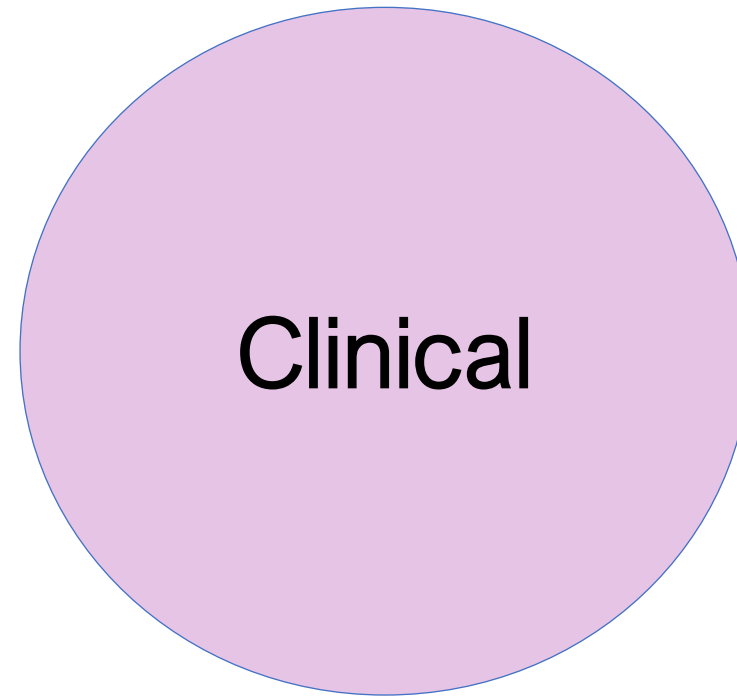
- may be given drugs at the **wrong dose**.
- may be given drugs that carry **unacceptable risk**.
- may be **denied access** to critically needed drugs.

Barriers



“quixotic quest”
to eliminate fetal risk

Risk shifting



Three Conceptual Shifts

Vulnerable population



Complex population

Protection *from* research



Protection *through* research

Presumptive exclusion



Fair inclusion

Ethical Foundations



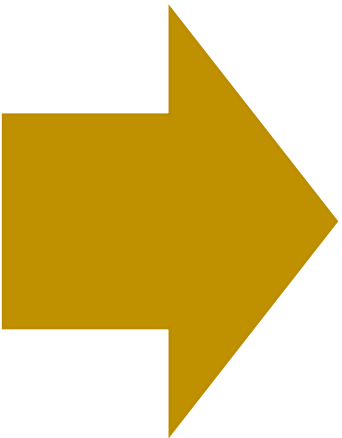
protection



access



respect



Reproductive Justice

- The right to have children
- The right not to have children
- The right to nurture children in a safe and healthy environment

<https://www.sistersong.net/reproductive-justice>

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PHASES Guidance (July 2020)

PHASES
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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

hivpregnancyethics.org

Pregnancy and HIV/AIDS: Seeking Equitable Study

Lyerly AD et al. *Journal of the International AIDS Society* 2021, **24**:e25846
<http://onlinelibrary.wiley.com/doi/10.1002/jia2.25846> | <https://doi.org/10.1002/jia2.25846>

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COMMENTARY

Ending the evidence gap for pregnancy, HIV and co-infections: ethics guidance from the PHASES project

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Abstract
Introduction: While pregnant people have been an important focus for HIV research, critical evidence gaps remain regarding prevention, co-infection, and safety and efficacy of new antiretroviral therapies in pregnancy. Such gaps can result in harm: without safety data, drugs used may carry unacceptable risks to the foetus or pregnant person; without pregnancy-specific dosing data, pregnant people face risks of both toxicity and undertreatment; and delays in gathering evidence can limit access to beneficial next-generation drugs. Despite recognition of the need, numerous barriers and ethical complexities have limited progress. We describe the process, ethical foundations, recommendations and applications of guidance for advancing responsible inclusion of pregnant people in HIV/co-infections research.
Discussion: The 26-member international and interdisciplinary Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) Working Group was convened to develop ethics-centred guidance for advancing timely, responsible HIV/co-infections research with pregnant people. Deliberations over 3 years drew on extensive qualitative research, stakeholder engagement, expert consultation and a series of workshops. The guidance, initially issued in July 2020, highlights conceptual shifts needed in framing research with pregnant people, and articulates three ethical foundations to ground recommendations: equitable protection from drug-related risks, timely access to biomedical advances and equitable respect for pregnant people's health interests. The guidance advances 12 specific recommendations, actionable within the current regulatory environment, addressing multiple stakeholders across drug development and post-approval research, and organized around four themes: building capacity, supporting inclusion, achieving priority research and ensuring respect. The recommendations describe strategies towards ethically redressing the evidence gap for pregnant people around HIV and co-infections. The guidance has informed key efforts of leading organizations working to advance needed research, and identifies further opportunities for impact by a range of stakeholder groups.
Conclusions: There are clear pathways towards ethical inclusion of pregnant people in the biomedical research agenda, and strong agreement across the HIV research community about the need for – and the promise of – advancing them. Those who fund, conduct, oversee and advocate for research can use the PHASES guidance to facilitate more, better and earlier evidence to optimize the health and wellbeing of pregnant people and their children.

Keywords: co-infections; ethics; HIV; pregnancy; prevention; research

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1 | INTRODUCTION

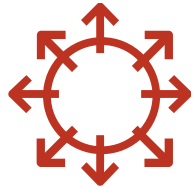
Since the early 1990s, the management of pregnancy has been an important focus for HIV research. The urgent need to identify interventions to prevent perinatal transmission led to remarkable progress towards its elimination: with effective antiretroviral treatment and other interventions, the global rate of perinatal transmission can be reduced to 5% or lower [1].

Yet, critical evidence gaps remain. Pregnant people [2,3] have been excluded from large trials of pre-exposure prophylaxis [4–6] – even as pregnancy increases the risk of HIV

1

- ← 26-member international, interdisciplinary Working Group
- ← Qualitative research, workshops, consultations

Recommendations (12)



Building Capacity (3)



Supporting Inclusion (3)



Achieving Priority Research (3)



Ensuring Respect (3)

Figure 1: Recommendations of the PHASES Guidance*

<p>Building Capacity</p> 	<ol style="list-style-type: none"> Affirm the need for research with pregnant people: Organizations with influence over the development, research, regulatory approval, guidance development, and use of HIV/co-infections drugs should affirm the imperative for responsible research with pregnant people to achieve a timely and equitable evidence base. Formulate a global network for advocacy and resources: The global HIV/co-infections research and advocacy communities, supported by funders, should formalize a network dedicated to advancing needed research with pregnant people. This network should facilitate research with pregnant people by creating a portfolio of shared resources to empower researchers to pursue, and enable oversight committees to effectively evaluate, studies that meet the needs of people who are pregnant. Enhance training: Those involved in the conduct, monitoring, oversight, and community consultation of research in the HIV/co-infections space should be provided training in the ethical and legal issues relevant to research with pregnant people.
<p>Supporting inclusion</p> 	<ol style="list-style-type: none"> Design for inclusion: Researchers designing trials in HIV/co-infections should commit to a goal of integrating pregnant people wherever possible and optimizing opportunities to gather pregnancy-specific data. Review for and facilitate inclusion: Regulatory review sections, research ethics committees, and funders of HIV/co-infections research should require proposed clinical trials protocols to provide justification whenever pregnancy is indicated as a criterion for exclusion or removal from a trial, and should proactively support and incentivize inclusive designs. Ensure equitable research on pregnant persons' own health: Agenda setters in HIV/co-infections research should commit to equitably promoting the study of pregnant persons' own health needs as a key pillar of effort and funding. Research into fetal safety outcomes should be matched by relevant maternal outcomes assessments to ensure that decisions about whether and which options to pursue during pregnancy are made with equitable consideration of the pregnant person's health.
<p>Achieving priority research</p> 	<ol style="list-style-type: none"> Integrate pharmacokinetic (PK) studies: Plans for pregnancy-specific PK pharmacokinetic studies should be integrated into new drug development plans and performed as early as possible, ideally before licensure, for all new preventives and treatments anticipated to be used during pregnancy. Enhance post-approval safety evaluations: The HIV/co-infections research community should commit to a more robust and regularized structure of post-approval safety evaluations to ensure both adequate pharmacovigilance and pregnant people's timely access to important drugs. This includes expanding prospective registries, conducting timely prospective observational studies for drugs in widespread use during pregnancy, and conducting prospective cohort studies of unintended exposures to probe safety signals that stand in the way of pregnant people accessing important drugs. Address legacy evidence gaps: Currently approved HIV/co-infections preventives and treatments should be reviewed for critical pregnancy-related evidence gaps that interfere with safe, evidence-based use in pregnancy, and research should be conducted to address those gaps.
<p>Ensuring respect</p> 	<ol style="list-style-type: none"> Ensure access to life-saving experimental drugs: Pregnant people should be guaranteed fair access to participate in trials and special access programs for experimental interventions that offer potential life-saving benefit in contexts where no or poor alternatives exist. Respect and support decisional authority: When a pregnant person of legal standing is eligible to participate in research, their voluntary and informed consent should be sufficient to authorize participation. Accommodations should be made to facilitate a pregnant person's ability to engage the father, family, or other personal supports, and to promote understanding of the benefits and risks of research participation. Contextualize risk findings: Those conducting HIV/co-infections research with pregnant people should anticipate possible adverse events and proactively develop communication strategies for adequately contextualizing them against baseline rates of such events. Communication of overall findings should take care to contextualize potential risks of an intervention against its potential benefits and the risk/benefit profiles of alternatives, and should include benefits to the pregnant person and those that would accrue secondarily to the child should the pregnant person's health be benefited.

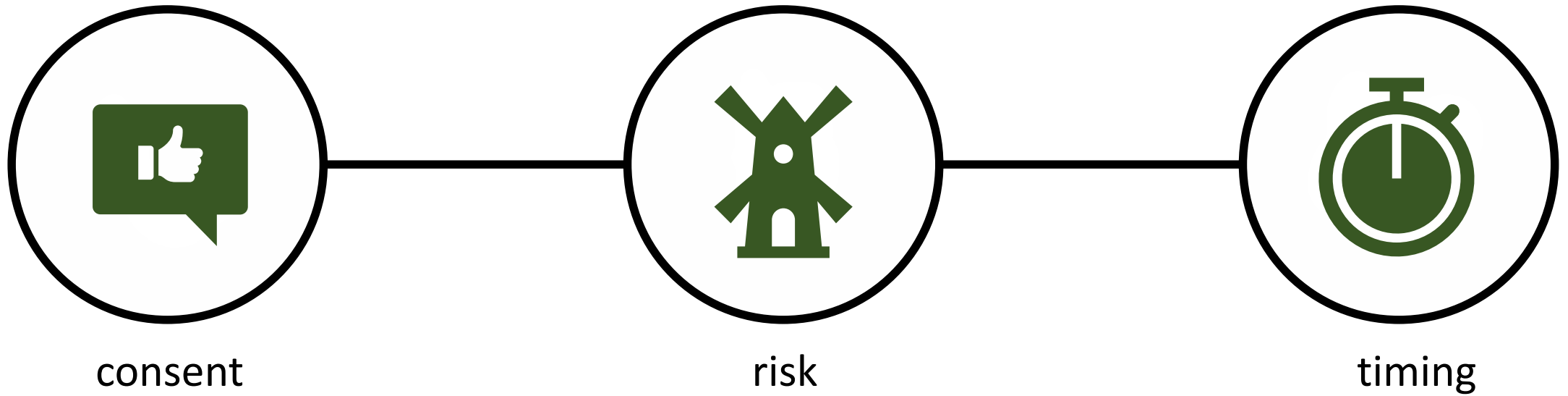
*Updated toward gender-inclusive language.

7. Integrate pharmacokinetic (PK) studies

Plans for pregnancy-specific pharmacokinetic (PK) studies should be integrated into new drug development plans and performed as early as possible, ideally before licensure, for all new preventives and treatments anticipated to be used during pregnancy.

- Drug industry – commit to pursuing PK studies
- Regulators – encourage and require up to authority
- Funders – support post-approval when not achieved by industry

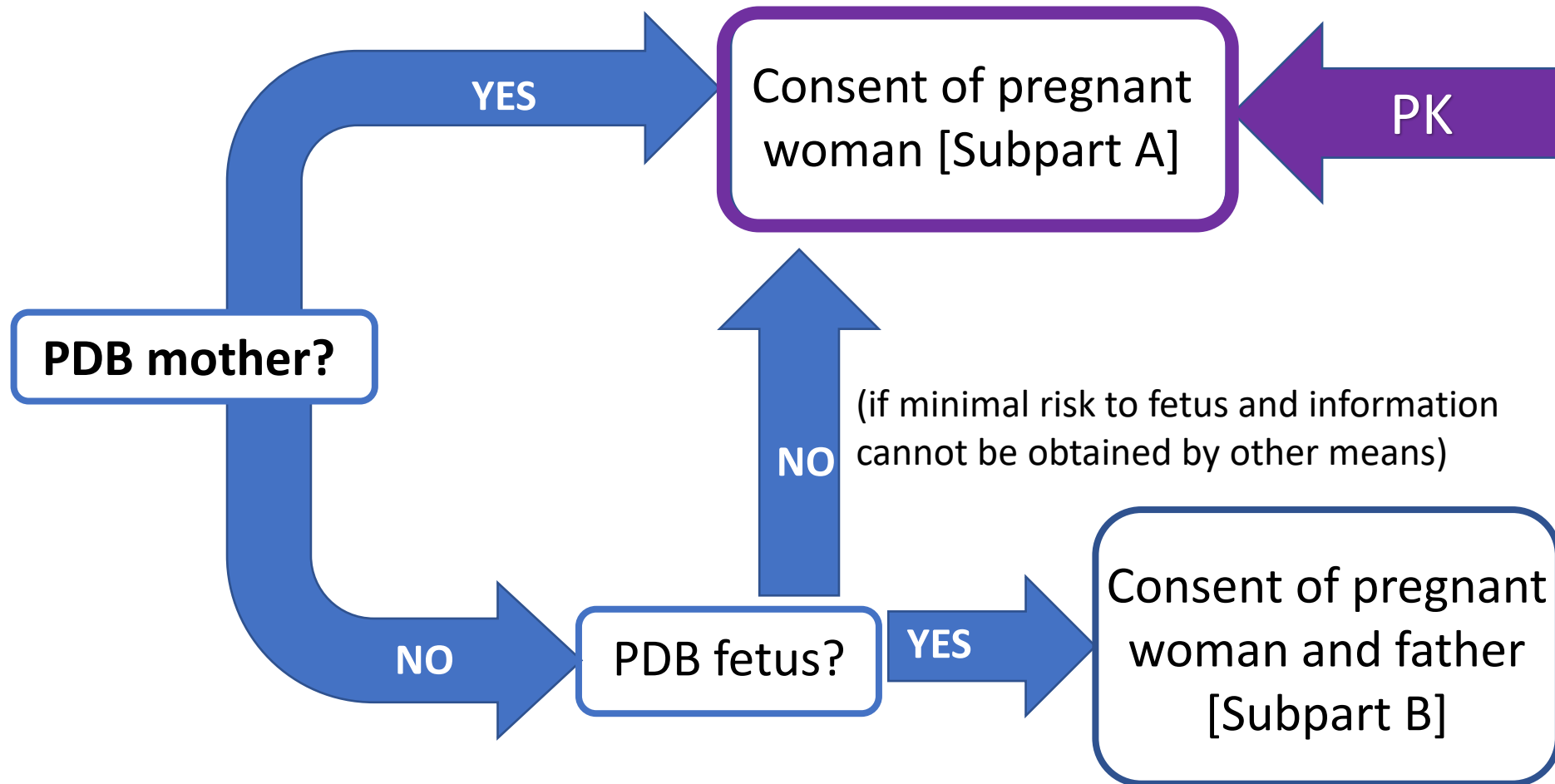
Ethical complexities





Consent

HHS requirements – paternal consent





Risk (and benefit)

Either
woman or fetus (or both)

Reasonable ratio of
risk to benefit

e.g. Phase III

PDB?
(Prospect of
Direct Benefit)

PK

Neither
woman nor fetus

Fetal RRR capped
at minimal risk

e.g. Phase I/II, PK

- Contrasts pediatrics, which allows “minor increase over minimal risk”
- Opportunistic studies offer a potential workaround, but at a cost...



Timing

- Human pregnancy data usually gathered post-approval, if at all
 - Avoids risk conundrum (e.g., PK studies)
 - Avoids exposure to investigational drug or vaccine
 - Addresses (some) liability concerns
 - Financially advantageous
- Delays are extensive, and consequential
 - Average delay for PK data for ARTs (HIV) = 6 years
 - In the meantime, pregnant persons may receive ineffective treatment
 - Risks to woman and fetus (Cobicistat)
 - Compromise trial results (Glyburide)
- Earlier, clinically actionable PK data are an ethical priority

Conclusions

- Broad recognition that research in pregnancy is an ***ethical imperative and a matter of reproductive justice***
 - Pregnant people deserve protection, access, and respect
- PK studies are a crucial element of this imperative
- Immediate opportunities for progress, though complexities remain
 - Consent in accordance with Subpart A
 - Many studies can be conducted without RRR (“low hanging fruit”)
 - Minimal risk standard is limiting, more stringent than pediatrics
 - Timing and incentives require attention

Thank you!

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hivpregnancyethics.org

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