NATIONAL ACADEMIES Sciences Engineering Medicine

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Inclusion of Pregnant and Lactating Persons in Clinical Trials

A Workshop

June 16-17, 2022

Keck Center, Room 100
500 5th Street NW
Washington, DC 20001

NATIONAL ACADEMIES Sciences Engineering Medicine

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Inclusion of Pregnant and Lactating Persons in Clinical Trials

June 16-17, 2022

Briefing Book Table of Contents

NATIONAL ACADEMIES Sciences Engineering Medicine

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Inclusion of Pregnant and Lactating Persons in Clinical Trials

A Workshop

June 16-17, 2022 ▪ Washington, DC

Approximately 4 million persons in the United States give birth annually. Over 60% of them are prescribed a medication during their pregnancy for either a chronic condition or one arising from the pregnancy itself. Yet, due to historical events, such as the widely publicized birth defects resulting from exposure to thalidomide during pregnancy, evaluating the safety and effectiveness of drugs in pregnant and lactating persons has been viewed as risky and has not been prioritized.[1] As a result, pregnant and lactating persons are often taking drugs with limited data to inform safety, dosing, and efficacy. This population, as well as their fetuses and breast-feeding infants, is thus often subjected to treatments with uncharacterized risks and harms due to their exclusion from clinical trials.[2] To address these issues, the Task Force on Research Specific to Pregnant Women and Lactating Women, suggested that the National Academies convene a group of experts to discuss conducting research with pregnant and lactating persons.[3]

This public workshop will provide an opportunity for stakeholders to examine the current state of evidence generation for drug products used by pregnant and lactating persons and discuss barriers and opportunities for including these populations in clinical trials. The workshop will be hosted by the National Academies' Forum on Drug Discovery, Development, and Translation, and is intended to provide a foundation for a forthcoming study on this topic, which was requested by Congress in the Consolidated Appropriations Act, 2022.

The public workshop will feature invited presentations and discussions to:

- Highlight knowledge gaps on drug product use during pregnancy and lactation with consideration for the clinical, ethical, and public health impacts on patient health;
- Discuss the laws and regulations governing drug research and development for these populations;
- Consider the liability risks to private and public stakeholders for conducting drug research and development for medical conditions experienced by pregnant and lactating persons, liability risks associated with the use of drug products in these populations, and other barriers to inclusion of pregnant and lactating persons in clinical trials;
- Discuss practical short- and long-term opportunities and/or actions to improve evidence generation on the risks and benefits of therapeutic interventions for pregnant and lactating persons and increase their inclusion in clinical trials.

The planning committee will organize the workshop, develop the agenda, select and invite speakers and discussants, and moderate or identify moderators for the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

---

[1] Blehar, M. C., C. Spong, C. Grady, S. F. Goldkind, L. Sahin, J. A. Clayton. 2013. Enrolling Pregnant Women: Issues in Clinical Research. *Women's Health Issues*. 23(1).
[2] Mastroianni, A. C., L. M. Henry, D. Robinson, T. Bailey, R. R. Faden, M. O. Little, A. D. Lyerly. 2017. Research with Pregnant Women: New Insights on Legal Decision-Making. Hastings Center Report. 47(3) 38-45.
[3] Task Force on Research Specific to Pregnant Women and Lactating Women. 2020. Report Implementation Plan. https://www.nichd.nih.gov/sites/default/files/inline-files/PRGLAC_Implement_Plan_083120.pdf (accessed August 31, 2021).

Planning Committee

Ruth Faden (co-chair), Johns Hopkins University

Shirley Sylvester (co-chair), Johnson & Johnson

Ebony Boyce Carter, Washington University School of Medicine in St. Louis

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

William Cooper, Vanderbilt University

Darcie Everett, Center for Biologics Evaluation and Research, FDA

Steven Kern, Bill & Melinda Gates Foundation

Leslie Meltzer Henry, University of Maryland

Leyla Sahin, Center for Drug Evaluation and Research, FDA

Kavita Shah Arora, University of North Carolina at Chapel Hill

Diane Spatz, University of Pennsylvania

Brownsyne Tucker Edmonds, Indiana University

Raman Venkataramanan, University of Pittsburgh

Michelle Vichnin, Merck

Carmen Zorrilla, University of Puerto Rico

NATIONAL ACADEMIES Sciences Engineering Medicine

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Inclusion of Pregnant and Lactating Persons in Clinical Trials – A Workshop

CLICK HERE TO JOIN

Meeting ID
943 5323 9836
Passcode
767590

Phone Only
(301) 715-8592

International Numbers

CLICK HERE FOR Q&A

Slido Q&A Code
#4266 618

June 16, 2022, 8:30 am – 5:00 pm (ET)

June 17, 2022, 8:30 am – 12:00 pm (ET)

Keck Center, Room 100
500 5th Street NW, Washington, DC 20001

PURPOSE

This workshop, convened by the National Academies of Sciences, Engineering, and Medicine's Forum on Drug Discovery, Development, and Translation, will provide a venue for stakeholders to examine the current state of evidence generation for drug* products used by pregnant and lactating persons, and discuss challenges and opportunities for including these populations in clinical trials.

The public workshop will feature invited presentations and discussions to:

- Highlight knowledge gaps on drug product use during pregnancy and lactation with consideration for the clinical, ethical, and public health impacts on patient health;
- Discuss the laws and regulations governing drug research and development for these populations;
- Consider the liability concerns of private and public stakeholders for conducting drug research and development that includes pregnant and lactating persons, liability concerns associated with the use of drug products in these populations, and other barriers to inclusion of pregnant and lactating persons in clinical trials;
- Discuss practical short- and long-term opportunities and/or actions to improve evidence generation on the risks and benefits of drug products for pregnant and lactating persons and increase their inclusion in clinical trials.

** A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. For more information, see https://www.fda.gov/industry/regulated-products/human-drugs#drug (accessed March 17, 2022)*

DAY 1: THURSDAY, JUNE 16, 2022

8:30 am WELCOME AND OPENING REMARKS

RUTH R. FADEN, *Workshop Co-chair*
Founder, Johns Hopkins Berman Institute of Bioethics
Philip Franklin Wagley Professor
Johns Hopkins University

SHIRLEY SYLVESTER, *Workshop Co-chair*
Senior Medical Director, Women's Health
Johnson and Johnson

8:50 am SESSION I – MAKING THE CASE: THE NEED FOR EVIDENCE GENERATION TO SUPPORT SAFETY AND EFFICACY OF DRUGS USED DURING PREGNANCY AND LACTATION

Purpose:

- Highlight knowledge gaps on drug product use during pregnancy and lactation;
- Consider the clinical, ethical, public health, and personal implications of excluding pregnant and lactating persons from participation in clinical trials or otherwise failing to collect data on safety and efficacy in pregnancy and lactation; and
- Discuss outputs from the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC).

Discussion Questions:

- How has the exclusion of pregnant and lactating persons from clinical trials and the general lack of evidence for these population groups affected maternal health on an individual and societal level?
- How does the lack of evidence for treating pregnant and lactating persons with drug therapies and vaccines affect decision making for patients, clinicians, and public health authorities?
- What are the potential trade-offs of not taking a prescribed drug during pregnancy and lactation versus taking a prescribed drug during pregnancy and lactation, when there is no or limited evidence for safety and efficacy?
- What information about the relative absence of evidence specific to these populations should be shared with pregnant and lactating persons and their care providers in order to make informed decisions? What information *should* they have?

8:50 am Fireside Chat

MAGGIE LITTLE, *Keynote speaker*
Senior Research Scholar, Professor of Philosophy, and Director of Ethics Lab
Georgetown University Kennedy Institute of Ethics

LEYLA SAHIN, *Moderator*
Acting Deputy Director for Safety
Division of Pediatrics and Maternal Health
FDA

9:20 am Panel Discussion

LEYLA SAHIN, *Moderator*
Acting Deputy Director for Safety
Division of Pediatrics and Maternal Health
FDA

Physiological Differences in Response to Drugs during Pregnancy & Lactation
THOMAS HALE
University Distinguished Professor of Pediatrics and Associate Dean of Research
Texas Tech University

Pregnant & Lactating Person Perspective
SARAH MANCOLL
Mother and Advocate

Gaps in Evidence for Clinical Care of Persons Prescribed Drugs during Pregnancy & Lactation
DAVID HAAS
Robert A. Munsick Professor of Obstetrics and Gynecology
Indiana University

Gaps in Evidence for Public Health Policy Affecting Pregnant & Lactating Persons
AJOKE SOBANJO-TER MEULEN
Vice President, Medical Affairs & Policy, Icosavax
Affiliate Associate Professor in Global Health, University of Washington

9:50 am Q&A/Audience Discussion

10:10 am **COFFEE BREAK (*30 minutes*)**

10:40 am SESSION II – PRACTICAL CHALLENGES AND OPPORTUNITIES FOR INCLUDING PREGNANT AND LACTATING PERSONS IN CLINICAL TRIALS

Purpose:

- Explore the social and cultural contexts for conducting clinical trials that include pregnant and lactating persons;
- Consider the barriers to and opportunities afforded by participation in clinical trials for pregnant and lactating persons; and
- Discuss practical short- and long-term opportunities and/or actions to improve access to clinical trials for pregnant and lactating persons.

Discussion Questions:

- What are the challenges that you or your institution face when considering including pregnant and lactating persons in clinical trials? How should these challenges be addressed to ultimately improve inclusion of these populations in clinical trials?
- What are specific challenges and opportunities to ensuring diversity in research participants and equity in science dissemination in regards to research involving pregnant and lactating persons?
- What should clinicians and researchers know about recruiting pregnant and lactating persons for participation in clinical research?
- What approaches can be used to decrease the burden on clinical trial participants who are pregnant or lactating?

10:40 am **Panel Discussion**

EBONY BOYCE CARTER, *Moderator*
Chief of Clinical Research in Obstetrics and Gynecology
Washington University School of Medicine in St. Louis

Advocating for Pregnant & Lactating Persons in Clinical Trials
ZSAKEBA HENDERSON
Senior Vice President of Maternal Child Health Impact and Interim Chief Medical Officer
March of Dimes

Equity and Diversity Considerations for Including Pregnant & Lactating Persons in Clinical Trials
VERONICA GILLISPIE-BELL
Associate Professor, Senior Site Lead and Section Head of Obstetrics and Gynecology, and Director of Quality for Women's Services, Ochsner Health System
Medical Director, Louisiana Department of Health

Recruitment and Retention of Pregnant & Lactating Persons in Chronic Disease Trials
BRITTANY BETTENDORF
Clinical Assistant Professor
University of Iowa

11:10 am **Q&A/Audience Discussion**

11:45 am **LUNCH BREAK (*1 hour*)**

12:45 pm SESSION III – LEGAL CONSIDERATIONS: REGULATORY PATHWAYS

Purpose:

- Discuss the laws and regulations governing drug research and development for pregnant and lactating persons, including human subject regulation, institutional review boards, and drug approval; and
- Discuss practical short- and long-term opportunities and/or actions to make regulatory pathways more supportive of including pregnant and lactating persons in clinical trials.

Discussion Questions:

- What are the most easily addressable legal and regulatory barriers that have prevented the inclusion of pregnant and lactating persons in clinical trials for both therapeutics and preventatives? How can these barriers be addressed?
- What are the more persistent legal and regulatory barriers to inclusion, and how could government, industry, patients, clinicians, and researchers collaborate to address them? What might that look like?
- How can researchers and institutional review boards address barriers to the inclusion of pregnant and lactating persons in clinical trials?

12:45 pm **Presentation**

Legal Landscape
LESLIE MELTZER HENRY, *Moderator*
Professor of Law
University of Maryland

1:05 pm **Panel Discussion**

Human Subjects Research Regulation Perspective
ANNA MASTROIANNI
Charles I. Stone Professor of Law
University of Washington

FDA Perspective
CATHERINE SEWELL
Acting Deputy Director and Deputy Director for Safety
Division of Urology, Obstetrics, and Gynecology
FDA

Vaccine Regulation Perspective
JEFF ROBERTS
Associate Vice President, Vaccine Clinical Development
Merck Research Laboratories

1:30 pm SESSION IV – ADDRESSING REAL AND PERCEIVED LIABILITY CONCERNS

Purpose:

- Discuss real and perceived liability concerns with including pregnant and lactating persons in drug research and development on the part of private and public sponsors of clinical trials;
- Discuss the real and perceived liability concerns associated with the use of drug products and vaccines in these populations on the part of practicing clinicians, researchers, and other key stakeholders; and
- Discuss practical short- and long-term opportunities and/or actions to address liability concerns.

Discussion Questions:

- What are the most common sources of risks that are more perceived then real (e.g. knowledge deficits, incorrect information presented to stakeholders, augmented risk aversion based on perspective as a clinician, researcher, or industry, other)?
- What are ways that clinicians, researchers, and industry could partner or support each other in

addressing real liability concerns? Are these roles for other stakeholders in also addressing real liability concerns?
- In considering strategies to address liability concerns, is there a logical order in which the solutions should be pursued? Are there any that are low hanging fruit, and which will be the most challenging to address?
- Looking the next 3-5 years, is there a realistic path towards mitigation of actual or perceived liability risks? What is the best-case forecast for where the field could be at the end of 3-5 years?

1:30 pm **Panel Discussion**

WILLIAM COOPER, *Moderator*
Professor of Pediatrics and Health Policy
Vanderbilt University

Clinician Perspective
CARMEN ZORRILLA
Professor of Obstetrics and Gynecology
University of Puerto Rico

Industry Perspective
AVIVA WEIN
Assistant General Counsel
Johnson and Johnson

Research Perspective
JESSICA COHEN
Director, Office of Research Affairs
PATH

2:05 pm **Q&A/Audience Discussion**

2:40 pm **COFFEE BREAK (*30 minutes*)**

3:10 pm SESSION V – BREAKOUT GROUPS

Purpose:
- Discuss opportunities to address liability concerns in the inclusion of pregnant and lactating persons in clinical trials; and
- Consider strategies to advance evidence generation for the clinical care of pregnant and lactating persons.

3:10 pm **Charge to Breakout Groups**

RUTH R. FADEN, *Workshop Co-chair*
Founder, Johns Hopkins Berman Institute of Bioethics
Philip Franklin Wagley Professor
Johns Hopkins University

3:15 pm **Breakout Group Discussions**

Workshop participants can select one of the follow breakout group topics:

Group 1: Opportunities to address liability concerns on the part of clinical investigators

Group 2: Opportunities to address liability concerns on the part of trial sponsors

Group 3: Opportunities to improve evidence generation for persons during pregnancy

Group 4: Opportunities to improve evidence generation for persons during lactation

4:15 pm	**Breakout Group Report-outs**
5:00 pm	**ADJOURN WORKSHOP DAY 1**

DAY 2: FRIDAY, JUNE 17, 2022

8:30 am SESSION VI – FIRESIDE CHAT: PROGRESS TOWARDS INCLUDING PREGNANT AND LACTATING PERSONS IN TRIALS

Purpose:

- Discuss progress towards implementing the PRGLAC recommendations and improving the inclusion of pregnant and lactating persons in clinical trials; and
- Consider next step opportunities to improve the inclusion of pregnant and lactating persons in clinical trials.

Discussion Questions:

- How are the finding and recommendations of PRGLAC advancing the inclusion of pregnant and lactating persons in clinical trials?
- What are the short- and long-term opportunities to execute the PRGLAC recommendations?
- Following the publication of the PRGLAC recommendations, are there any success stories from their implementation that can inform ongoing efforts to improve the inclusion of pregnant lactating persons in clinical trials?
- Are there areas that PRGLAC did not address that still require additional study? What opportunities exist to better understand and begin to resolve these issues?

DIANA BIANCHI, *Keynote speaker*
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH

SHIRLEY SYLVESTER, *Workshop Co-chair, Moderator*
Senior Medical Director, Women's Health
Johnson and Johnson

9:00 am SESSION VII – CASE STUDIES: LESSONS LEARNED IN TRIALS IN MENTAL HEALTH AND COVID-19

Purpose:

- Examine lessons learned from case studies for improving the inclusion of pregnant and lactating persons; and
- Consider opportunities to apply and/or scale-up approaches for including pregnant and lactating persons in clinical trials across therapeutic areas.

Discussion Questions:

- How can the lessons from research with pregnant and lactating persons in the cases of mental health and COVID-19 inform future clinical trials in other therapeutic and public health areas?
- How can stakeholders in this area continue to share lessons learned from clinical trials that include pregnant and lactating persons to build on previous successes?
- What are the opportunities for researchers, trial sponsors, and regulators to expand access to clinical trials to pregnant and lactating persons?
- Are there ways to prioritize clinical research in different therapeutic and public health areas that would provide the greatest benefit to pregnant and lactating persons?

9:00 am **Case Study 1: Lessons Learned from Drug Trials for Mood Disorders**
KATHERINE WISNER
Norman and Helen Asher Professor of Psychiatry and Behavioral Sciences, and Obstetrics and Gynecology
Director, Asher Center for Research and Treatment of Depressive Disorders
Northwestern University Feinberg School of Medicine

9:15 am **Case Study 2: Lessons Learned from COVID-19 Vaccine Trials**
RUTH KARRON
Professor of International Health
Johns Hopkins University Bloomberg School of Public Health

9:30 am **Panel Discussion: Opportunities to Scale-up Evidence Generation across Health Concerns**
KAVITA SHAH ARORA, *Moderator*
Associate Professor and Division Director of General Obstetrics and Gynecology
University of North Carolina at Chapel Hill

Research Perspective
GEETA SWAMY
Associate Vice President for Research and Vice Dean for Scientific Integrity
Professor of Obstetrics and Gynecology
Duke University

Industry Perspective
IONA MUNJAL
Director, Clinical Research and Development, Pfizer Vaccines
Assistant Professor of Pediatrics, Albert Einstein College of Medicine and Montefiore Medical Center

Regulatory Perspective
LYNNE YAO
Director, Division of Pediatric and Maternal Health
FDA

Advocating for Pregnant & Lactating Persons in Clinical Trials
KATHRYN SCHUBERT
President and CEO
Society for Women's Health Research

10:05 am **Q&A/Audience Discussion**

10:30 am **COFFEE BREAK (*30 minutes*)**

11:00 am **SESSION VIII – NEW APPROACHES TO GENERATE EVIDENCE FOR TREATING PREGNANT AND LACTATING PERSONS**

Purpose:
- Consider different approaches to generate evidence on the safety and effectiveness of drug products for pregnant and lactating persons, in addition to randomized control trials; and
- Discuss practical short- and long-term opportunities and/or actions to increase the use of these approaches to evidence generation in both product development and oversight, and clinical and public health practice.

Discussion Questions:

- What methods and approaches are most amenable to generating quality evidence on the short- and long-term safety as well as effectiveness of drugs for use in pregnant and lactating persons?
- What are opportunities for pregnant and lactating persons to be better engaged in designing clinical trials?
- How can evidence generated outside of randomized control trials best inform drug research and development for pregnant and lactating persons?
- For what kinds of questions and for what kinds of drugs can new approaches approximate the quality of evidence generated in RCTs or be an appropriate source of adequate data?
- What are the short- and long-term opportunities to advance the use of new approaches for evidence generation on the safety and effectiveness of drugs for use in pregnant and lactating persons?

11:00 am **Panel Discussion**

STEVEN KERN, *Moderator*
Deputy Director, Quantitative Sciences
Bill and Melinda Gates Foundation

Real World Evidence Perspective
CHRISTINA CHAMBERS
Professor of Pediatrics
University of California, San Diego School of Medicine

Pharmacology Perspective
RAMAN VENKATARAMANAN
Professor of Pharmaceutical Sciences and Pathology
University of Pittsburgh

Novel Approaches to Engage Pregnant & Lactating Persons in Real World Evidence Studies
TOLÚWALÀṢÉ AJAYI
Director of Clinical Research and Diversity Initiatives, Scripps Research Translational Institute
Assistant Professor, Scripps Research

Regulatory Perspective
WEI HUA
Acting Deputy Director, Division of Epidemiology
Office of Surveillance and Epidemiology
FDA

11:30 am **Q&A/Audience Discussion**

11:50 am **WRAP UP DISCUSSION AND CLOSING REMARKS**

RUTH R. FADEN, *Workshop Co-chair*
Founder, Johns Hopkins Berman Institute of Bioethics
Philip Franklin Wagley Professor
Johns Hopkins University

SHIRLEY SYLVESTER, *Workshop Co-chair*
Senior Medical Director, Women's Health
Johnson and Johnson

12:00 pm **ADJOURN DAY 2**

NATIONAL ACADEMIES Sciences Engineering Medicine

COVID-19 Policies for Non-Staff Access to National Academies Facilities

Current Operating Status:

Effective April 8, 2022

All facilities of the National Academies of Sciences, Engineering, and Medicine are **open**.

To prevent infection and spread of the COVID-19 virus, and as an integral measure towards the safety and health of everyone in our buildings, **the National Academies require that all visitors to NASEM facilities be up-to-date on their vaccinations against COVID-19 per CDC guidance. Additionally, do not enter the building if you have flu-like symptoms.**

Visitors must show their official COVID-19 Vaccination Record Card (or a digital photo of the card) before entering any National Academies building. Anyone who fails to present a vaccination card (or its copy) will not be allowed access to our facility; no exemptions or exceptions will be accommodated. For more details regarding access to NASEM facilities and expectations for visitors, please visit our operating status webpage.

If you test positive for COVID-19 recently after attending the workshop in-person, please contact Andrew March (amarch@nas.edu) so that the National Academies can contact other workshop participants who may have been exposed.

All workshop participants are strongly encouraged to wear a mask while indoors at the Keck Center unless eating, drinking, or speaking into a microphone. Please consider using an at-home rapid COVID test the night before or morning of the workshop. The HVAC system in the Keck Center is equipped with MERV 13 filters – the highest grade compatible with their HVAC units, and additional air purifiers will be running in the room. If you would prefer to eat outdoors, you are welcome to take provided meals across the street to the National Building Museum lawn, National Law Enforcement Officers Memorial, or Judiciary Park.

Volunteers and invited guests should not feel obligated to travel to participate in a meeting being held at one of our facilities during this time. We encourage remote attendance to the meeting for anyone who is not comfortable traveling to or participating in an in-person meeting. The National Academies have made investments in new equipment in our meeting rooms to accommodate interactive, hybrid meetings so that the experience for those not in the room will be as engaging as possible. In certain circumstances, such as for meetings involving classified or controlled information or events of significant importance, a request for participants to attend in-person may be extended. Please reach out to the meeting organizer to discuss needed accommodations for hybrid meetings if you are unable to attend in-person.

The National Academies' leadership is closely monitoring the evolving situation related to the COVID-19 pandemic, and is basing their approach to National Academies' business on the current scientific evidence on COVID-19 and the best public health advice. The priority of the National Academies is the safety of our staff and our larger community of volunteers, sponsors, and members. Please be mindful that this may require unanticipated adjustments to events associated with National Academies projects.

- **Nearest drugstore:**
  - CVS: 400 Massachusetts Ave, approx. 7-minute walk from Keck
  - Walgreens: 801 7th St NW, approx. 8-minute walk from Keck
- **Nearest COVID-19 testing site:** CVS at 655 K St NW (appointment required)

NATIONAL ACADEMIES Sciences Engineering Medicine

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Inclusion of Pregnant and Lactating Persons in Clinical Trials – A Workshop Planning Committee Biosketches

Co-chairs

Dr. Ruth Faden, Ph.D., M.P.H. is the founder of the Johns Hopkins Berman Institute of Bioethics, and its director from 1995 until 2016. She is also the Philip Franklin Wagley Professor of Biomedical Ethics. Her research focuses on structural injustice theory and public policy including national and global challenges in public health, food, agriculture and climate, women's health, health systems design and priority setting, and advances in science and technology. Currently Dr. Faden is working at the intersection of structural justice and the COVID-19 response, primarily in vaccine allocation and prioritization, pregnancy, and K-12 education. Her latest book, with Madison Powers, is Structural Injustice: Power, Advantage, and Human Rights (September, 2019; Oxford University Press).

Dr. Shirley Sylvester, M.D., M.P.H. is a Senior Medical Director for Women's Health with the Office of the Chief Medical Officer (OCMO) at Johnson & Johnson. She works with a team to drive change toward reducing maternal mortality in the United States and globally. As a leader of the Women's Health team, she is responsible for providing strategic and scientific expertise in the development and implementation of programs that support the overall aims of Women's Health at Johnson & Johnson and partnering with external stakeholders to develop a policy agenda which supports women's health. Dr. Sylvester also works across the J&J Enterprise and externally to identify and act on opportunities that leverage J&J's collective assets to positively impact women's health through ethically-based, science- and data-driven approaches; and acts as a subject matter expert in health matters related to women, providing guidance to stakeholders on topics related to women's health.

Dr. Sylvester joined Johnson & Johnson in 2013 where she most recently led the creation of the global medical affairs strategy behind the development of Hepatitis B compounds for the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen). She established external collaborations with key stakeholders, including scientific societies, patient advocacy groups and academic institutions to advance the scientific agenda and to deepen Janssen's commitment to "Make Hepatitis History." She also co-led the clinical development of investigational compounds in partnership with Janssen Research & Development.

In previous roles at Johnson & Johnson, Dr. Sylvester served as Medical Director for compounds in Hepatitis C and Multi-Drug resistant TB in the United States. In these roles, Dr. Sylvester provided brand oversight on all medically related aspects of the compounds, including the design and execution of phase IIIb and IV studies in support of the medical affairs strategy.

Prior to joining Johnson & Johnson, Dr. Sylvester had a long history of working in the public sector, having partnered with NGOs, USAID, Bill and Melinda Gates Foundation, WHO, PAHO, ministries of health and other global constituents. Through these collaborations, she helped to design and implement several public health programs around the world focused on Post-Partum Hemorrhage (PPH) Prevention and other maternal health issues, Immunizations, HIV/TB control, Chagas disease and management of complications from obstetric fistula among others.

Dr. Sylvester holds a MD degree from Universidad de Cartagena with focus on Family Medicine and a Master of Public Health with a specialty in Global Health and Infectious Diseases from the Harvard T.H. Chan School of Public Health.

Members

Dr. Ebony Boyce Carter, M.D., M.P.H. is a tenured Associate Professor and Chief of the Division of Clinical Research in the Department of Obstetrics and Gynecology at Washington University School of Medicine. She practices Maternal Fetal Medicine and serves as Associate Editor for Equity at Obstetrics & Gynecology (the Green Journal). Her research focuses on group prenatal care, as a tool to promote health equity, and is funded by the Robert Wood Johnson Foundation, National Institutes of Health, and the American Diabetes Association.

Dr. Carter earned her undergraduate degree in human biology with honors from Stanford University, Master of Public Health in health policy from the University of Michigan, and medical degree from Duke University. She completed residency in Obstetrics and Gynecology at the Harvard integrated program at Brigham and Women's/Massachusetts General Hospitals and fellowship training in Maternal Fetal Medicine at Washington University School of Medicine.

Dr. Nahida Chakhtoura, M.D. is an Obstetrician/Gynecologist who joined the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) in October of 2014 as a medical officer in the Maternal and Pediatric Infectious Disease Branch. As a medical officer, she overseas various mother to child transmission (PMTCT) research including congenital CMV, Zika, as well as HIV/AIDS related clinical trials involving women, adolescents, and infants within the International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) network and overseas grants and clinical trials related to prevention of HIV transmission and Multipurpose Prevention Technologies (MPTs). Her grant portfolio includes PMTCT of HIV, TB, CMV, Hepatitis, as well HIV and contraception.

Dr. William O. Cooper, M.D., M.P.H. is a practicing physician, researcher, teacher, and administrator. He has led School of Medicine programs, including the Center for Patient and Professional Advocacy, the Master of Public Health Program and the Pediatrics Office for Faculty Development. He is an internationally recognized expert in medication safety in children and has published over 140 scholarly articles to date. In his role as Associate Dean for Faculty Affairs for Vanderbilt University School of Medicine and Vice President for Patient and Professional Advocacy, Vanderbilt University Medical Center, Dr. Cooper oversees the Medical Center's professional programs and provides leadership and direction for the Center for Patient and Professional Advocacy.

Dr. Brownsyne Tucker Edmonds, M.D., M.P.H., M.S. is the inaugural Vice President and Chief Health Equity Officer for Indiana University Health and the Associate Dean for Health Equity Research for Indiana University School of Medicine, where she holds an endowed chair for Health Equity Research. She is an Associate Professor of Obstetrics Gynecology (OB/GYN) at Indiana University School of Medicine (IUSM) with training in general OB/GYN, health services research, public health, and clinical ethics. Her research interests are in patient-provider communication and shared decision-making in reproductive health care. She is interested in understanding the impact of race, class, and culture on patient preferences and risk perceptions; physician decision-making and counseling; and ultimately, variations in treatment provision and service delivery. Dr. Tucker Edmonds' work currently focuses on communication and decision-making in the management of periviable deliveries. She utilizes qualitative and quantitative methodologies to develop decision support interventions for parents facing this, and other, preference sensitive decisions in high-risk

obstetrical settings. Dr. Tucker Edmonds previously served as her department's Vice Chair for Faculty Development and Diversity, and also served as an Assistant Dean for Diversity Affairs for the IU School of Medicine. Dr Tucker Edmonds previously served on the Ethics Committee for the American College of Obstetrics and Gynecology (ACOG) and was the Legislative Affairs Chair for Indiana ACOG. She now serves on ACOG's Committee on Government Affairs and is the Chair of the Indiana Section. Dr. Tucker Edmonds was an Anniversary Fellow for the National Academy of Medicine (NAM) from 2015-2017, during which time she served on the committee that authored, *"The health effects of cannabis and cannabinoids: The current state of the evidence and recommendations for research."* Most recently, she served on the committee that authored the report, *"Birth Settings in America: Outcomes, Quality, Access, and Choice."*

Dr. Darcie Everett, M.D., M.P.H. is a Medical Officer for the FDA's Division of Vaccines and Related Product Applications (DVRPA) in the Office of Vaccine Research and Review, Center for Biologics Evaluation and Research. As a clinical reviewer for DVRPA since 2014, she evaluates a variety of investigational vaccines and other biologics in all phases of clinical development. Her professional interests include maternal immunization. Dr. Everett is board-certified in Internal Medicine, Pediatrics and Preventive Medicine. She received her medical degree and a Master of Public Health in International Health and Development from Tulane University in New Orleans. She completed residencies at The Mount Sinai School of Medicine in New York (combined Internal Medicine and Pediatrics), where she also worked as a hospitalist, and at Emory University in Atlanta (Preventive Medicine), where she focused on maternal and infant health.

Dr. Steven E. Kern, Ph.D. is Deputy Director of Quantitative Sciences at the Bill and Melinda Gates Foundation. The Quantitative Sciences group is focused on quantitative analysis to support program strategies for therapeutic projects that the foundation funds across multiple disease domains. Prior to this, he was Global Head of Pharmacology Modeling at Novartis Pharma AG based in Basel Switzerland where he lead a team focused on providing model based drug development support to therapeutics in many disease conditions across all stages of drug development. He joined Novartis in 2010 from the University of Utah in Salt Lake City, Utah where he was Associate Professor of Pharmaceutics, Anesthesiology, and Bioengineering, and served as co-investigator for their NIH funded Pediatric Pharmacology Research Unit. He has designed, conducted, and served as a principal investigator for clinical pharmacology studies in adults and children that spanned the population from preterm infants to elderly adults. He has a bachelor's degree in Mechanical Engineering from Cornell University, a Master's degree in Bioengineering from Penn State University, and a doctoral degree in Bioengineering from the University of Utah. Dr. Kern has published over 70 papers in areas of pharmacokinetic and pharmacodynamic modeling, applying principles of control systems engineering to drug delivery, and clinical pharmacology.

Dr. Leslie Meltzer Henry, Ph.D., J.D., M.Sc. is a lawyer and bioethicist with expertise in assessing, navigating, and advising on a range of ethical and legal issues that arise at the intersection of medicine, public health, and public policy. She is a Professor of Law at the University of Maryland Carey School of Law, and a faculty member at the Johns Hopkins Berman Institute of Bioethics. Her scholarly work primarily focuses on aspects of biomedical research regulation and practice that have implications for, and are implicated by, social justice and public health. Her recent scholarship has addressed barriers as well as potential facilitators to including pregnant people in research, compensation schemes for research-related injuries, challenges associated with including adolescents in research, and the complexities of conducting research during pandemics. She has been an investigator on both NIH and internationally funded grants aimed at developing ethically and legally acceptable strategies for conducting research during pregnancy. Professor Henry's research has been published in the nation's leading law reviews and medical journals. She has served in an advisory capacity to a variety of federal and local agencies and commissions—including the U.S. Department of Defense, Trans-NIH Bioethics Advisory Committee, NIAID, NICHD, NIMH, NIH Office of Research on

Women's Health, and FDA—to identify limits, as well as areas of flexibility, in regulations related to the inclusion of special populations in research. Professor Henry received her J.D. from Yale Law School, Ph.D. from the University of Virginia, and M.Sc. from the University of Oxford, where she was a Wellcome Trust Fellow in the History of Medicine. She completed post-doctoral work at Johns Hopkins University as a Greenwall Fellow in Bioethics and Health Policy.

Dr. Leyla Sahin, M.D. is an obstetrician-gynecologist who is the Acting Deputy Director for Safety in the Division of Pediatrics and Maternal Health in the Office of New Drugs, Center for Drug Evaluation and Research. She has led various maternal health related scientific and regulatory/policy initiatives, including publication of FDA guidances. She was a working group member on the HHS Task Force for Research Specific to Pregnant Women and Lactating Women (PRGLAC). The focus of her work involves advancing FDA's scientific and regulatory policies related to pregnancy and lactation, through all phases of drug development. Her principal area of interest is promoting the public health of pregnant and breastfeeding individuals through improved data collection.

Dr. Kavita Shah Arora, M.D., M.B.E., M.S. is the Division Director for general obstetrics and gynecology and an Associate Professor at the University of North Carolina-Chapel Hill. She is the current Greenwall Fellow in Bioethics at the NAM. She serves as the Chair of the national ethics committee of the American College of Obstetricians and Gynecologists and serves on the Governing Council for the Young Physicians Section of the American Medical Association. She has served on the national ethics committee of the American Medical Association and on the Board of Directors of the American Society for Bioethics and the Humanities. Her clinical, research, and education interests center around reproductive justice and ensuring evidence-based and equitable reproductive health policy, with a focus on sterilization disparities. She completed her BS from the Pennsylvania State University, medical school at Jefferson Medical College, a Master's in Bioethics at the University of Pennsylvania, a Master's of Science in clinical research at Case Western Reserve University, and her obstetrics & gynecology residency at Northwestern Memorial Hospital.

Dr. Diane Spatz, Ph.D., R.N. is a Professor of Perinatal Nursing & the Helen M. Shearer Professor of Nutrition at the University of Pennsylvania School of Nursing sharing a joint appointment as a nurse scientist in lactation the Children's Hospital of Philadelphia (CHOP) in the Center for Pediatric Nursing Research and Evidence Based Practice. Dr. Spatz is the Founder of the CHOP Lactation Program & Mothers' Milk Bank.

Dr. Spatz is an active researcher, clinician, and educator who is internationally recognized for her work surrounding the use of human milk and breastfeeding particularly in vulnerable populations. Dr. Spatz has been PI or co-investigator on over 60 research grants, included several from the NIH. She has authored and co-authored over 210 peer-reviewed publications and written numerous book chapters related to human milk and breastfeeding. Dr. Spatz has authored or co-authored position statements for the International Lactation Consultant Association, the Association of Women's Health Obstetric & Neonatal Nursing (AWHONN), the Society of Pediatric Nurses (SPN) and the National Association of Neonatal Nurses. She has also written the clinical practice guidelines on human milk and breastfeeding for AHWONN and SPN as well as a technical brief for the USAID on human milk and breastfeeding in developing countries.

In 2004, Dr. Spatz develop her 10-step model for human milk and breastfeeding in vulnerable infants. This model has been implemented in NICUs throughout the United States and other countries worldwide (Thailand, India, China, Mexico, Japan, Chile). Dr. Spatz has been named a prestigious "Edge Runner" for the American Academy of Nursing related to the outcomes of her model. Her nurse driven models of care are critical in improving human milk & breastfeeding outcomes and thus the health of women and children globally. Dr. Spatz is the only PhD prepared nurse appointed to the Congressional Task Force on Research Specific to

Pregnant Women and Lactating Women. Dr. Spatz has also been appointed to a World Health Organization Task Force on human milk and milk banking globally. Dr. Spatz was elected to the Executive Committee of International Society of Research in Human Milk and Lactation in April 2020.

Dr. Spatz is also the recipient of numerous awards including: the Lifetime Achievement Award from the National Association of Neonatal Nurses, the Research Utilization Award from Sigma Theta Tau International and from the University of Pennsylvania: the Dean's Award for Exemplary Professional Practice, the Expert Alumni Award and the Family and Community Department's Academic Practice Award She is also the recipient of the Lindback Award for Distinguished Teaching. Dr. Spatz received the Distinguished Lang Award for her impact on scholarship, policy & practice. In 2019, Dr. Spatz received AWHONN's Distinguished Researcher Award and was named Nurse of the Year by the Philadelphia Inquirer.

In the university portion of her job, she teaches an *entire semester* course on breastfeeding and human lactation to undergraduate nursing students and in the hospital portion of her job, she developed the Breastfeeding Resource Nurse program. Dr. Spatz is Past Chair of the American Academy of Nursing's Expert Panel on Breastfeeding and their representative to the United States Breastfeeding Committee.

Dr. Raman Venkatarmanan, Ph.D. is currently a Professor of Pharmaceutical sciences and Pathology in the University of Pittsburgh. He is the director of Clinical Pharmacokinetics Laboratory and the Therapeutic Drug Monitoring program at the University of Pittsburgh. Venkataramanan received his B.Pharm degree from the University of Madras, India; Master of Pharmacy degree from the Birla Institute of Technology and Science, India; and doctorate in Pharmaceutical Sciences from the University of British Columbia, Canada. After a postdoctoral fellowship at the University of Washington, he joined the University of Pittsburgh in July 1980. He has been appointed as a Food and Drug Administration special government employee by Center for Drug Evaluation and Research. Venkataramanan serves as a scientific reviewer for several journals. He is an editorial board member for Therapeutic Drug Monitoring, and four online journals. He is the editor for the American Journal of Analytical Chemistry. He is the recipient of the Distinguished Service Award from AAPS (2021), HiREC Endowed visiting chair at the University of Puerto Rico (Oct 2021), Distinguished Scientists award from American Association of Indian Pharmaceutical Scientists (AAiPS) in 2016, Graduate faculty of the year award from the School of Pharmacy in 2015, 2021, Tyler Prize for Stimulation of Research from the American Pharmacists Association (APhA), in 2011, the Bristol-Meyers Squibb Mentorship in Clinical Pharmacology from the American College of Clinical Pharmacy [ACCP], in 2009; the Provost's Award for Excellence in Graduate Education from the University of Pittsburgh, in 2009; the Innovations in Teaching award the Rho Chi Society at the University of Pittsburgh, in 2009; the Scholarly Contributions award from the Rho Chi Society at the University of Pittsburgh, in 2007, Ranbaxy Research Award in Pharmaceutical Sciences in 1998, and the Distinguished Research scientists award from KDRI in Ahmadabad, India in 1996. The research in his laboratory revolves around "LIFE". One half addresses the first chance in life – Optimizing the use of medications in pregnant women based on pharmacokinetics and pharmacodynamics data; the second half addresses optimization of the use of medications in organ transplant patients—a second chance in life. His current research is funded by NICHD (OPRC-Co-PI), NCI and United Therapeutics. He has presented more than 200 lectures / seminars at national/international meetings and published over 450 scientific articles. He has been an active member in various professional organizations such as American Association of Pharmaceutical Scientists, American Association of Indian Pharmaceutical Scientists, American College of Clinical Pharmacology, American Association of Colleges of Pharmacy, and American Society of Transplantation.

Dr. Michelle Vichnin, M.D. is the Executive Director and Global Lead, Patient Advocacy and Strategic Alliances at Merck, where she and her team are strengthening the company's patient engagement and advocacy

presence around the world. She works on several initiatives to address healthcare disparities, increase health literacy, and explore innovative ways to meet the needs of patients during and beyond the COVID-19 pandemic.

Michelle joined as a US Medical Director for adolescent vaccines in 2007, and became a Global Medical Director in 2009. With her experience in cervical cancer prevention, she served as the medical lead for Merck's public health initiatives to bring vaccines to low income countries. She then served as the Executive Director for Oncology in the Office of the Chief Medical Officer and worked to bring patient perspectives into the company. She is an expert advisor for Merck for Mothers, the company's global initiative to help create a world where no woman has to die while giving life. She also is a member of the Diversity and Inclusion in Clinical Trials team, and recently published a paper in JCO Oncology Practice on strategies for increased inclusion of racial and ethnic minorities in clinical trials.

A board-certified obstetrician/gynecologist, she is a graduate of the Pennsylvania State University/Jefferson Medical College accelerated six-year medical program and performed her residency in Obstetrics and Gynecology at the New York-Presbyterian Weill Cornell Medical Center. Prior to joining Merck, Michelle was an Assistant Clinical Professor in the department of Obstetrics and Gynecology at the University of Pennsylvania School of Medicine. She practiced at Penn Health for Women, a nationally recognized program for excellence in women's health, and was the Director of the Colposcopy Clinic at the Hospital of the University of Pennsylvania, where she received awards for her research. For several years she served on ACOG's Committee on Adolescent Health. She supports numerous nonprofit organizations, has volunteered as an attending physician at a clinic in the Andes Mountains in Peru, and most recently volunteered at a COVID-19 vaccine clinic.

Dr. Carmen Zorrilla, M.D. is a Professor of Obstetrics and Gynecology at the UPR School of Medicine, certified by the American Board of Obstetrics and Gynecology and the American Academy of HIV Medicine. Dr. Zorrilla has experience in Obstetrics and Gynecology and HIV related research that includes behavioral interventions and clinical trials with HIV infected and at-risk populations, as well as with pregnant and non-pregnant women. She was part of the group of examiners for the American Oral Board of Ob-Gyn (ABOG) for 22 years and Past Residency Program Director for the UPR Ob-Gyn program. She established an infrastructure for the care of pregnant and nonpregnant women living with HIV. The transmission rate of HIV infection among the more than 500 infants born to pregnant women living with HIV during the past 20 years at her clinic has been zero. And Dr. Zorrilla worked with the PR health Department in the elimination of HIV transmission for which she published the experience and stating that PR was in fact the first country to eliminate transmission. For almost 2 decades, she has been the PI of the Integrated UPR Clinical Trials Unit (IUPR-CTU), including the Pediatric AIDS Clinical Trials Unit (IMPAACT), the Adult Clinical Trials Unit (ACTG) until last year when funding was modified to protocol-specific. She has been a consultant for diverse national and international organizations including the National Institutes of Health (NIH), the Maternal and Child Health Bureau (MCHB), the Centers for Disease Control (CDC), the Agency for Health Research Quality (AHRQ) and others, and a former member of the Office of Women's Health Advisory Committee and the CDC/HRSA AIDS and STD Advisory Committee (CHAC). Dr. Zorrilla is a member of the National Institute of Health Disparities and Minority Health Advisory Council (NACMHD).

Dr. Zorrilla established the first group prenatal care program in PR (Centering Pregnancy) with funds from the Innovation Center of the Centers for Medicare & Medicaid Services (CMS). This is the first Spanish Centering Program outside of the Mainland US. One of the outcomes of the program has been the reduction in preterm births and low birth weight among infants born of women enrolled in group prenatal care at the University Hospital. Expanding the program to impact and improve the health of mothers and infants is also one of her professional goals. She is part of the group of leaders who spearheaded the research response to the emerging

Zika epidemic among pregnant women in PR. She also established a multidisciplinary clinic for pregnant women with Zika. Dr. Zorrilla is the site PI for the Zika in Infants and Pregnancy (ZIP Study) in San Juan. She is a member of the Scientific Coalition named by PR Governor Hon. Pedro Pierluisi to advise on issues related to the COVID pandemic response and to further incorporate the input of Science into public policy. During the COVID-19 pandemic she spearheaded the development of a Molecular testing program at the RCM, a COVID vaccine center and a Phase III vaccine trial at the UPR-MSC. Her team was responsible for the immunization of 97% of the faculty, students, and staff at the UPR Medical Sciences Campus early in 2021.

NATIONAL ACADEMIES Sciences Engineering Medicine

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Inclusion of Pregnant and Lactating Persons in Clinical Trials – A Workshop

Speaker Biographies

Dr. Tolúwalàṣé (Laṣé) Ajayi, M.D. is a board certified pediatrician and fellowship-trained palliative care physician. She serves as the director of clinical research and diversity initiatives at Scripps Research Translational Institute as well as an Assistant Professor of Pediatrics at UC San Diego and Rady Children's Hospital San Diego where she works as a hospitalist and pediatric palliative medicine physician; she is also the medical director of adult palliative medicine at Scripps Mercy Hospital San Diego.

Dr. Ajayi's research focuses on health disparities and opportunities at the intersection of novel digital medicine technologies and unmet needs in maternal fetal health as well as pain and palliative medicine. She hopes to increase participation of pregnant people and their newborns in clinical research and further investigate how mobile health can provide real time, patient reported outcomes that can be rapidly integrated into individualized clinical plans to reduce health disparity gaps and improve health related quality of life. With these efforts, she hopes to diversify the standard of care provided to pregnant people and augment how we manage the symptoms prevalent in serious illness, with the goal of decreasing distress and associated hospital and emergency room utilization.

Dr. Brittany Bettendorf, M.D. is a clinical assistant professor at the University of Iowa where she started a Pregnancy and Rheumatology clinic in 2017. In this clinic, she sees patients with rheumatologic disease who are pregnant or are hoping to conceive and seeking pre-conception counseling. She received her MD from Medical College of Wisconsin where she also completed her residency in Internal Medicine and Pediatrics as well as her fellowship in rheumatology. She holds an MFA degree in Nonfiction Writing from University of Iowa. Dr. Bettendorf served as a member of the literature review committee and co-author for the 2020 American College of Rheumatology (ACR) Reproductive Health Guideline. She was also part of the ACR working group to develop educational training content for clinical providers on Systemic Lupus Erythematosus and Reproductive Health (SLE-RESPECT). She enjoys the opportunity to network with others who are passionate about taking care of pregnant patients with rheumatic and musculoskeletal disease. Dr. Bettendorf teaches a class to first year medical and physician assistant students on social justice and she also teaches an advanced elective to medical students on Opinion Editorial Writing to help students improve the public's understanding of health and healthcare. She is a faculty member in the Program in Bioethics and Humanities at Carver College of Medicine.

Dr. Diana Bianchi, M.D. is the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and a Senior Investigator in the Center for Precision Health Research at the National Human Genome Research Institute (NHGRI); both are at the National Institutes of Health (NIH). She is responsible for leading a $1.6B research portfolio that focuses on children, reproductive biology and pregnancy, and physical and intellectual disabilities. She received her M.D. from Stanford University and her postgraduate training in Pediatrics, Medical Genetics and Neonatal-Perinatal Medicine at Harvard. Dr. Bianchi's research focuses on noninvasive prenatal screening and development of novel fetal therapies for

genetic disorders. She has published over 350 peer-reviewed articles and is one of four authors of Fetology: Diagnosis and Management of the Fetal Patient, which won the Association of American Publishers award for best textbook in clinical medicine in 2000. She has held multiple leadership positions, including Presidencies of the International Society for Prenatal Diagnosis (ISPD) and the Perinatal Research Society, council memberships in the Society for Pediatric Research (SPR) and the American Pediatric Society, as a member of the board of directors in the American Society for Human Genetics. She served as the Editor-in-Chief of the journal Prenatal Diagnosis from 2007-2020. Dr. Bianchi has received the Neonatal Landmark Award from the American Academy of Pediatrics, the Maureen Andrew Award for Mentorship from the Society for Pediatric Research, the Colonel Harland Sanders Award for lifetime achievement in Medical Genetics from the American College of Medical Genetics, the Pioneer Award from ISPD, and the Health Public Service Visionary Award from the Society for Women's Health Research. In 2013 she was elected to the National Academy of Medicine. She received a Ph.D. *honoris causa* from the University of Amsterdam in 2020.

Dr. Christina Chambers, Ph.D., M.P.H. is a Professor in the School of Medicine at UC San Diego. She is Co-Director of the Center for Better Beginnings, Program Director of MotherToBaby, a service providing evidence-based information on exposures during pregnancy and lactation, and is Program Director of Mommy's Milk, a human milk biorepository for research.

Dr. Chambers leads a number of national and international complex longitudinal cohort studies and clinical trials of prenatal exposures and child health and development. Her research has been instrumental in identifying previously unrecognized human teratogens, as well as ruling out substantial risk for medications and vaccines.

Jessica Cohen, M.H.S. is the Director of PATH's Office of Research Affairs. In this capacity, she manages systems and policies to ensure PATH research is scientifically and ethically sound, directs research training, and provides guidance on best practices for research at PATH. Ms. Cohen serves as the senior co-chair of PATH's research ethics committee, a role she has held since 2006.

Ms. Cohen has also worked as a researcher and project manager at PATH, conducting research to develop, adapt and improve reproductive health and HIV prevention technologies for use in low-resource settings. She has also held advocacy roles to increase support for women-controlled HIV and pregnancy prevention methods, helping to launch the Initiative for Multipurpose Prevention Technologies.

Ms. Cohen has a strong interest in global health bioethics and has most recently worked on issues pertaining to equitable access to human milk for vulnerable infants and disaggregation of sex-based data to support equitable access to antimalaria drugs. She has served as guest faculty for the Fogarty International Center's Training Program on Research Ethics in Argentina and has served on multiple advisory boards, panels and symposia on topics of global health research ethics, microbicide delivery and HIV prevention methods for women.

Ms. Cohen received her MHS in international health from Johns Hopkins University, School of Hygiene and Public Health and her BA in cultural anthropology from the University of California at Santa Cruz. She has been a certified institutional review board (IRB) professional since 2011.

Dr. Veronica Gillispie-Bell, M.D., M.A.S. is a Board-Certified Obstetrician & Gynecologist and Associate Professor for Ochsner Health in New Orleans, Louisiana. She serves as the Senior Site Lead and Section Head of Obstetrics and Gynecology at Ochsner Kenner. Additionally, she serves as the Director of Quality for Women's Services for the Ochsner Health System and is the Medical Director of the Minimally Invasive Center for the Treatment of Uterine Fibroids. She earned her medical degree from Meharry Medical College and completed her residency training at Ochsner Health System. She has a Master of Applied Science in Patient

Safety and Healthcare Quality from the Johns Hopkins Bloomberg School of Public Health. Additionally, she has received certification in Diversity and Inclusion from Cornell University. Clinically, in addition to providing obstetric care, Dr. Gillispie-Bell performs advanced laparoscopic and robotic assisted laparoscopic procedures and is known nationally for her expertise in management of heavy menstrual bleeding associated with fibroids.

Dr. Gillispie-Bell is also the Medical Director of the Louisiana Perinatal Quality Collaborative and Pregnancy Associated Mortality Review for the Louisiana Department of Health. In this role, she leads initiatives in the state of Louisiana to improve birth outcomes for all birthing persons in Louisiana and eliminate the Black-white disparity gap. Dr. Gillispie-Bell has testified before Congress and led Congressional briefings to inform on the drivers of maternal mortality and legislative policy to improve maternal mortality and eliminate the Black-white disparity gap. Additionally, she serves in several leadership roles promoting efforts to achieve health equity. She has served in several local and national leadership roles and received many accolades for her clinical, academic, and community services contributions.

Dr. Thomas Hale, Ph.D., R.Ph. is the University Distinguished Professor of Pediatrics and Assistant Dean of Research at Texas Tech University School of Medicine. He is the founder and director of the InfantRisk Center, a national call center for pregnant and breastfeeding mothers. He holds degrees in Pharmacy and a Ph.D. in Pharmacology and Toxicology and is widely experienced in Pediatric and Breastfeeding Clinical Pharmacology. He is a well-known international lecturer in the pharmacology of lactation and is the author of five books including: Medications and Mothers' Milk, the top-selling drug reference manual in the world. He has authored numerous papers, case reports, and abstracts, and more than 30 books chapters.

Dr. David Haas, M.D., M.S. is a board certified OB/GYN physician. He is the Co-Director and Editor of the US Satellite of the Cochrane Collaboration Pregnancy and Childbirth Group and has served on World Health Organization Guideline Development Groups. He has recently been appointed the Medical Director for Statewide Research for the Indiana Clinical and Translational Sciences Institute. As a practicing OB-GYN physician-scientist, his research interests revolve around prevention and treatment of medical and obstetric complications. He has a particular focus on medications and pregnancy and on long term health outcomes stemming from pregnancy complications for both the pregnant individuals and their babies. He runs a research team with expertise in recruitment to obstetric cohorts, biobanking, and clinical trials. He also directs the research mentorship program for OB/GYN residents. He collaborates on several multicenter trials and has a passion for team interdisciplinary science.

Dr. Zsakeba Henderson, M.D. is currently the Senior Vice President of MCH Impact and Interim Chief Medical Officer at March of Dimes, providing strategic direction and clinical expertise across the organization to help end the maternal and infant health crisis, including the direction of March of Dimes Mission programs and services, professional and patient education, and government affairs and advocacy. She is a board-certified obstetrician-gynecologist, and previously led the program in support of state-based perinatal quality collaboratives at the Centers for Disease Control and Prevention Division of Reproductive Health, including leading the establishment of the National Network of Perinatal Quality Collaboratives (NNPQC). Dr. Henderson currently serves as an Executive Committee Member and the Obstetric Co-Chair for the NNPQC. She received her BS degree in Biochemistry from Oakwood University in Huntsville, Alabama, and her medical degree from Harvard Medical School in Boston, Massachusetts. She also completed her internship and residency at Harvard, at the Brigham and Women's Hospital/Massachusetts General Hospital Integrated Residency Program in Obstetrics and Gynecology. She subsequently entered the Epidemic Intelligence Service at the Centers for Disease Control and Prevention, in the Division of STD Prevention. Her work and experience includes program development and research in the areas of perinatal quality improvement to reduce maternal

and infant morbidity and mortality, prevention of preterm birth, and the development of robust partnerships and networks to improve population-level outcomes for mothers and infants.

Dr. Wei Hua, M.D., Ph.D. is currently Acting Deputy Director of Division of Epidemiology-I in the Office of Surveillance and Epidemiology, CDER, FDA. She received her medical degree from China and PhD from the Johns Hopkins University School of Public Health. Her areas of expertise include infectious disease epidemiology and pharmacoepidemiology with experience in both experimental and observational studies using primary and secondary data in the U.S. and through multi-site international collaborations. Over the past ten years, Dr. Hua has held multiple roles in the FDA centers for biologics and drugs leading and overseeing epidemiological research and review, including pregnancy safety, in the regulatory setting.

Dr. Ruth Karron, M.D. is a Professor of International Health in the Bloomberg School of Public Health with a joint appointment in the Department of Pediatrics in the School of Medicine, Johns Hopkins University. Dr. Karron is a pediatric infectious diseases physician, virologist, and vaccinologist, and is Director of the Johns Hopkins Vaccine Initiative. Dr. Karron has substantial experience in the evaluation of respiratory virus vaccines in adult and pediatric populations. Dr. Karron's research interests also include the development of immune responses to respiratory viral infections in early life, the epidemiology of RSV and other respiratory viral diseases in low resource settings, and public policy and ethical issues related to vaccine development and distribution. She co-led the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group, which released "Pregnant Woman & Vaccines Against Emerging Epidemic Threats: Ethics Guidance for Preparedness, Research and Response", a guidance document with specific actionable recommendations to ensure that pregnant women are no longer excluded from receiving vaccines against emerging infectious diseases, and was co-developer of the COVID-19 Maternal Immunization Tracker (www.comitglobal.org). Dr. Karron has been a member of a number of national and international vaccine advisory committees and panels, including the CDC Advisory Committee on Immunization Practices (ACIP), the Gavi Vaccine Innovation Prioritisation Steering Committee (VIPS), and the COVAX ACT-acclerator COVID vaccine Maternal Immunization Working Group, and has chaired the FDA Vaccine and Related Biological Products Advisory Committee (VRBPAC) and the Vaccines Advisory Panel for the Wellcome Trust. She is currently deputy chair of the WHO Product Development for Vaccines Advisory Committee (PDVAC). In 2016, Dr. Karron received the Robert M. Chanock award for outstanding contributions to RSV research.

Dr. Maggie Little, BPhil, Ph.D. is Senior Research Scholar at the Kennedy Institute of Ethics, and Professor of Philosophy at Georgetown. Her research interests include issues in reproduction, clinical research ethics, data ethics, and the structure of moral theory. A Rhodes Scholar and fellow of the Hastings Center, she has twice served as Visiting Scholar in residence at the National Institutes of Health Department of Bioethics, and was appointed to the Ethics Committee of the American College of Obstetrics and Gynecology. She is co-founder of The Second Wave Initiative, which works to promote responsible research into the health needs of pregnant women.

In her previous role as Director of the Kennedy Institute, Dr. Little oversaw a time of transformative development, including the launch of the world's first Introduction to Bioethics MOOC in April 2014; the inauguration of Conversations in Bioethics, an annual campus-wide event focused on a critical issue in bioethics; the deployment of a series of experimental undergraduate courses utilizing project-based learning and design studio methods. Dr. Little is founder and Director of EthicsLab, a unique team of Philosophers and Designers at Georgetown University that develops new methods to help people build ethical frameworks to better address real-world problems. Ethics Lab works to help surface the moral values at stake in emerging, complex issues, including data ethics and AI, to help build responsible progress. She is a founding co-chair of the Tech and Society Initiative at Georgetown.

Sarah Mancoll, M.S. is a mother and advocate. Without clinical data to help guide her decision-making in consultation with her doctors, Sarah made the difficult choice to stop receiving treatment for her chronic autoimmune disorder, alopecia areata, during the years that she was pregnant and lactating. Her autoimmune condition worsened, and since then, she has become an advocate for research that includes pregnant and lactating persons. Outside of her personal advocacy work, Sarah is the policy director of a scientific association. Sarah received her bachelor's degree in human development from Cornell University and her master's degree in social policy and planning from the London School of Economics and Political Science.

Anna Mastroianni, JD, M.P.H. is a Charles I. Stone Professor of Law at the University of Washington School of Law and Associate Director of the university's Institute for Public Health Genetics. She holds additional faculty appointments in the UW's School of Public Health and School of Medicine. Before joining the UW faculty, she worked as a practicing health care attorney and served in a number of legal and governmental policy positions in Washington, D.C. Her scholarly work examines the intersection of law, bioethics, public health, and health policy, with special emphasis on the legal and ethical challenges arising in research with pregnant women, the use of genetic technologies in public health, reproductive rights, and family building through assisted reproductive technologies.

Professor Mastroianni is an elected Fellow of the American Association for the Advancement of Science, recognized for her contributions to health policy, law, and bioethics. She serves on consensus, advisory, and oversight committees, both nationally and internationally. For the National Academies of Sciences, Engineering and Medicine, that work has included examining: ethics and policy for oversight of social sciences research, policies for the National Immunization Program's research procedures and data sharing, ethical and policy issues in the introduction of mitochondria replacement techniques, and ethics of health standards for long-duration space flight. She has served as a member of the National Institutes of Health Recombinant DNA Advisory Committee and as Trustee of the Population Council. She is a current member of the Standing Committee on Aerospace Medicine and the Medicine of Extreme Environments, and since 2014 has chaired the Wellcome Trust (UK) Medical Humanities & Social Science Selection Panel.

Dr. Iona Munjal, M.D. is a Director in Pfizer Vaccine Clinical Research and Development service as a medical monitor on vaccine trials. A board certified pediatric infectious diseases physician and assistant professor of pediatrics at the Albert Einstein College of Medicine, she is a graduate of Georgetown University and Rutgers Medical School. She did her residency and chief residency in pediatrics at Mount Sinai Hospital. She followed that with a fellowship in infectious diseases at The Children's Hospital at Montefiore where she was awarded the best scientific research abstract by the New York Infectious Diseases Society. Dr. Munjal worked in hospital administration in epidemiology and emerging infectious diseases, including the health system's response to Ebola and Zika viruses. She founded and oversaw the hospital's pediatric antimicrobial stewardship program which seeks to promote sensible use to improve patient outcomes, decrease adverse events, and prevent the emergence of resistant pathogens. She served as a principal investigator in multiple anti-infective and vaccine clinical trials during her tenure in academia. Since she joined Pfizer Vaccine Clinical Research and Development in 2016, she has contributed to provide expertise and oversight to the Staphylococcus aureus vaccine program and the COVID-19 pediatric vaccine trials. She is currently the global clinical lead for Pfizer's maternal RSV vaccine programs.

Dr. Jeff Roberts, M.D. joined Merck Research Laboratories (MRL) in November 2021 as Associate Vice President, Vaccine Clinical Development. In this role, he is responsible for clinical development of candidate and licensed vaccines for a variety of disease targets, such as HPV, CoV, HSV, ebola, and chikungunya. Prior to joining MRL, Jeff was Associate Director for Scientific Affairs in the Office of Vaccines Research and Review at the U.S. FDA. His focus included emerging disease threats/medical countermeasures and use of

digital health tools, alternative clinical trial designs, and real world evidence to support product development/licensure. He also led discussions/coordination on vaccine development with other regulatory authorities. Prior to that, and for most of his 14 years at the FDA, Jeff served as Clinical Branch Chief in the Division of Vaccines and Related Product Applications (DVRPA), where he managed the clinical review activities for development programs and licensure applications for multiple products, including vaccines, allergenic products, phage therapy, and live biotherapeutics. Jeff received his MD degree from the University of Alabama School of Medicine. He spent several years at the National Cancer Institute at NIH doing basic research and animal modeling with HPV prior to moving to the FDA.

Kathryn G. Schubert, M.P.P. joined the Society for Women's Health Research (SWHR) as President and CEO in April 2020. Under Katie's leadership SWHR developed a strategic plan focused on fulfilling the organization's mission of promoting research on biological sex differences in disease and improving women's health through science, policy, and education. She previously worked for the Society for Maternal-Fetal Medicine (SMFM), where she served as the organization's chief advocacy officer, growing SMFM's role nationally and building its reputation in women's health.

Katie is a trusted leader and consensus builder among women's health stakeholders, particularly in the policy arena. She has served in multiple Board roles for nonprofit organizations in the Washington, DC-area, including as Chair of the Board of the Maternal Mental Health Leadership Alliance and as advisor to the John E. Lewy Fund for Children's Health. She is a past president of Women in Government Relations.

Prior to SMFM, Katie served as senior vice president at CRD Associates, where she advised clients — including nonprofit patient advocacy groups, medical professional organizations, and private companies — on government relations and public policy related to health and biomedical research issues, among others. She has also spent time working in key legislative roles on Capitol Hill. She received her BA from Mary Washington College and her Masters of Public Policy from George Washington University. Katie lives in Virginia with her husband, three children, and dog George.

Dr. Catherine Sewell, M.D., M.P.H. is currently the Acting Deputy Director and is the Deputy Director for Safety in the Division of Urology, Obstetrics and Gynecology as well as co-chair of the Drug Safety Team for Pediatrics, Rare Diseases, Obstetrics, Gynecology, Urology and Maternal Health at the US FDA. In these roles she provides leadership and technical direction to pre-market scientific review staff engaged in the evaluation of Investigational New Drug Applications (INDs) and NDA/BLA applications; provides scientific, clinical, and technical authority on all medical and scientific decisions and judgment in connection with the review and evaluation of drugs. She also advances OND's policies, research agenda, training, and collaboration across other divisions, offices and stakeholders, creation of Division level plans to meet these goals.

She further coordinates processes that span the Division's post-marketing safety activities including overseeing the development, tracking, and follow up of safety studies and clinical trials, safety labeling changes and Risk Evaluation and Mitigation Strategies (REMS) for approved drugs. Dr. Sewell is part of the process modernization effort at the FDA, aiming to improve the mechanisms for monitoring and evaluating premarket and postmarket safety signals. Additionally, she liaises with other FDA offices and other regulatory agencies, industry, professional organizations, academia, and the public. In prior roles at FDA she was a clinical reviewer and acting clinical team leader.

Dr. Sewell is a board-certified obstetrician/gynecologist. She graduated from Swarthmore College with Honors, the University of Pennsylvania Perelman School of Medicine and the Johns Hopkins Bloomberg School of Public Health with Honors. She completed her Gynecology and Obstetrics residency at Johns Hopkins. She was

a member of academic faculty, as Director of the Hopkins Fibroid Center in the Department of Gynecology and Obstetrics at Johns Hopkins and as Medical Director of the Jefferson Obstetrics and Gynecology Associates in the Department of Obstetrics and Gynecology at Thomas Jefferson University. She was also the Chief of the Department of Obstetrics and Gynecology at the University of Maryland St. Joseph Medical Center, providing full-scope direct gynecologic patient care and surgery, overseeing the department's clinical care and patient safety initiatives, and mentoring and teaching medical students and DNP students. Dr. Sewell has been a co-investigator for several research studies, has co-authored numerous publications and crafted documents for JHPIEGO, a non-profit health organization affiliated with Johns Hopkins.

Ajoke Sobanjo-ter Meulen, M.D., M.Sc. is the Vice President, Medical Affairs & Policy at Icosavax. In her role she leads the medical affairs strategy for Icosavax's vaccine programs. Prior to joining Icosavax, Ajoke led the global maternal immunization initiative with a focus on Group B streptococcus and pertussis maternal vaccine development at the Bill & Melinda Gates Foundation. Previously, Ajoke led the Group B streptococcus maternal immunization clinical development program at Novartis Vaccines. In response to the COVID-19 pandemic Ajoke co-chaired the COVAX Maternal Immunization Working Group to enable access to COVID-19 vaccine for pregnant women worldwide. Ajoke is board-certified in pediatric and adolescent medicine from the Julius-Maximilian University in Wuerzburg, Germany, completed a pediatric infectious diseases fellowship at Mount Sinai School of Medicine New York, and holds a MSc in Infectious Disease Epidemiology from the London School of Tropical Medicine and Hygiene, UK. Ajoke serves as an affiliate associate professor in Global Health at the University of Washington.

Dr. Geeta Swamy, M.D. is Professor of Obstetrics and Gynecology in the Division of Maternal-Fetal Medicine, having served as the director of the Duke Perinatal Research Center and Vice Chair for Research and Faculty Development in the Department of ObGyn. She has achieved international acclaim as a clinician researcher and expert in the field of maternal immunization and perinatal infection. As a consultant to the World Health Organization, Dr. Swamy contributes her knowledge to advance international work to evaluate the immunogenicity, safety, and efficacy of vaccines in pregnant women. The American College of ObGyn has grown to be the "collective voice" for women's health, and Dr. Swamy has been a leader within that organization for the last two decades. She currently serves as the Co-Principal Investigator for the NIH-NIAID Vaccine Treatment and Evaluation (VTEU) and CDC Clinical Immunization Safety Assessment. In addition, she has been a leader at Duke and nationally in promoting a culture of scientific integrity and transparency in research. She has been instrumental in developing and leading the School of Medicine's research initiatives in administration, regulatory oversight, and compliance. In 2018, she became Vice Dean for Scientific Integrity in the School of Medicine and Associate Vice President for Research for Duke University. In these roles she oversees the Duke Office of Scientific Integrity (DOSI) which houses the Advancing Scientific Integrity, Services, & Training (ASIST) initiative, conflict of interest, clinical quality management, incident response in research, and research misconduct. She also oversees the Duke Office of Research Initiatives, the Duke Health IRB, Office of Research Administration (ORA), and Office of Research Contracts (ORC).

Aviva Wein, J.D. is an Assistant General Counsel at Johnson & Johnson where she is the Group Leader of the Litigation Policy and Risk Management Group within the Litigation Group. Aviva is responsible for the development and implementation of proactive policy initiatives to protect and further the Company's interests. In her role, Aviva is tasked with developing processes aimed toward anticipating and mitigating litigation risks that may arise during the lifecycle of the Company's products. Aviva is also responsible for products liability litigation for several of the company's medical device and pharmaceutical products worldwide.

Aviva joined Johnson and Johnson in 2012. Prior to joining Johnson & Johnson, Aviva worked for an international law firm in New York City, as well as a law firm in Princeton, New Jersey where she focused on

securities litigation, consumer fraud and products liability litigation matters. Aviva received her bachelor's degree with honors in political science from Brooklyn College – The City University of New York and her law degree from Fordham University School of Law. Aviva clerked for the Honorable K. Michael Moore in the United States District Court for the Southern District of Florida.

Dr. Katherine Wisner, M.D., M.S. obtained her M.S. in Nutrition and an M.D. from Case Western Reserve University, followed by a categorical pediatric internship and general and child psychiatry residency at Children's Hospital of Pittsburgh and Western Psychiatric Institute and Clinic. She completed a post-doctoral fellowship in Epidemiology at the University of Pittsburgh Graduate School Of Public Health, fellowships in Professional Ethics at Case Western Reserve University and in biomedical ethics at Northwestern University, and the Physician Leadership and Management Program at the Katz Graduate School of Business at the University of Pittsburgh. Dr. Wisner is board-certified in general and child and adolescent psychiatry.

Dr. Wisner is a pioneer in perinatal psychiatry. Her research has advanced our understanding of the natural history of mood disorders across childbearing, benefit-harm decision-making for pharmacotherapy during pregnancy and lactation, and the pharmacokinetics of medications across pregnancy and lactation. She is internationally recognized as an expert in the treatment of mood disorders during pregnancy and the postpartum period. Dr. Wisner has received over $21 million from NIH across her career, and has 250 peer-reviewed publications (h-index=60) and 21 book chapters. Her work has far-reaching influence, and has been cited by authors in more than 90 countries.

She received the Woman in Science Award from the American Medical Women's Association in 2011 and the Alexandra Symonds Award from the American Psychiatric Association in 2012. She was awarded the annual APA Award for Research at the meeting in 2017. Dr. Wisner was honored with the Distinguished Mentor Award from the Institute for Clinical Research Education, University of Pittsburgh School of Medicine in 2012. She received the Marcè International Society for Perinatal Mental Health's Medal for lifetime contributions to the field of Perinatal Psychiatry. Dr. Wisner has served on the Editorial Board of the American Journal of Psychiatry and currently serves on the Editorial Boards of JAMA Psychiatry and the Journal of Clinical Psychiatry. She is a Fellow of the American College of Neuropsychopharmacology and a Distinguished Life Fellow of the American Psychiatric Association. With her experience as a past president of the Marcé International Society for Perinatal Mental Health, she developed the business startup plan for the North American Society for Perinatal Mental Health (now Marcé of North America- MONA), and served as its inaugural president.

Dr. Lynne Yao, M.D. is the Director, Division of Pediatric and Maternal Health in the Office of New Drugs, Center for Drug Evaluation and Research. Dr. Yao received a B.S. degree in Biology from Yale University, and an M.D. degree from the George Washington University School of Medicine. She is board certified in both Pediatrics and Pediatric Nephrology. Prior to joining FDA, Dr. Yao was the Director of Dialysis and Associate Pediatric Residency Program Director at the Inova Fairfax Hospital for Children in Fairfax, VA. She has been with the FDA since 2008. The Division of Pediatric and Maternal Health oversees quality initiatives which promote and necessitate the study of drug and biological products in the pediatric population; and improve collection of data to support the safe use of drugs and biological products in pregnant and lactating individuals. She collaborates with numerous stakeholders both inside and outside of FDA to advance development of safe and effective therapies for children, and pregnant and lactating women.

Breakout Group Worksheet (Virtual)

Breakout group discussions will be held **3:10 – 5:00 pm (ET) on Thursday, June 16.** The breakout groups will offer workshop participants the opportunity to identify barriers to the inclusion of pregnant and lactating persons in clinical trials and to the generation of adequate evidence for the use of drugs in this population. Breakout groups will then prioritize these barriers and collectively brainstorm solutions that would provide opportunities to overcome these barriers.

Zoom participants will have the ability to self-select which breakout group they would like to join. To ensure you are able to select the breakout group of your choice, **please update your Zoom application prior to the workshop.**

Instructions:

- Click on the 'Breakout Rooms' icon in the Zoom controls. A pop-up window will appear with four room options, each corresponding to the numbered groups below. Once you have identified the group you would like to join based on your affiliation and/or interest, find the corresponding room number in the list on the pop-up window and click 'Join.'
    - Group 1: Opportunities to address liability concerns on the part of clinical investigators
    - Group 2: Opportunities to address liability concerns on the part of trial sponsors
    - Group 3: Opportunities to improve evidence generation for persons during pregnancy
    - Group 4: Opportunities to improve evidence generation for persons during lactation

- Breakout groups will have approximately 45 minutes to answer the discussion questions below. A designated facilitator in each breakout group will help guide this discussion and report out key points.

Discussion Questions:

1. Based on your assigned group topic, what are the barriers or concerns that prevent the inclusion of pregnant and lactating persons in clinical trials (Groups 1 & 2) OR the barriers or concerns that prevent the adequate generation of evidence to inform clinical care of pregnant and lactating persons (Groups 3 & 4)? Prioritize the top 2-3 barriers that are the most easily addressed and have the greatest impact. (Suggested Duration: 10 minutes)

2. How can the barriers prioritized in question 1 be effectively addressed? For example, are there educational/outreach approaches for engaging particular audiences, research design/methodologies that could be implemented, and/or incentives or regulatory/policy changes to spur a change in behavior on the part of particular stakeholders? (Suggested Duration: 35 minutes)

ABOUT THE FORUM

The Forum on Drug Discovery, Development, and Translation of the National Academies of Sciences, Engineering, and Medicine was created in 2005 by the Board on Health Sciences Policy to provide a unique platform for dialogue and collaboration among thought leaders and stakeholders in government, academia, industry, foundations, and patient advocacy with an interest in improving the system of drug discovery, development, and translation. The Forum brings together leaders from private sector sponsors of biomedical and clinical research, federal agencies sponsoring and regulating biomedical and clinical research, the academic community, and patients, and in doing so serves to educate the policy community about issues where science and policy intersect. The Forum convenes several times each year to identify, discuss, and act on key problems and strategies in the discovery, development, and translation of drugs. To supplement the perspectives and expertise of its members, the Forum also holds public workshops to engage a wide range of experts, members of the public, and the policy community. The Forum also fosters collaborations among its members and constituencies. The activities of the Forum are determined by its members, focusing on the major themes outlined below.

INNOVATION AND THE DRUG DEVELOPMENT ENTERPRISE

Despite exciting scientific advances, the pathway from basic science to new therapeutics faces challenges on many fronts. New paradigms for discovering and developing drugs are being sought to bridge the ever-widening gap between scientific discoveries and translation of those discoveries into life-changing medications. There is also increasing recognition of the need for new models and methods for drug development and translational science, and "precompetitive collaborations" and other partnerships, including public–private partnerships, are proliferating. The Forum offers a venue to discuss effective collaboration in the drug discovery and development enterprise and also hosts discussions that could help chart a course through the turbulent forces of disruptive innovation in the drug discovery and development "ecosystem."

Key gaps remain in our knowledge about science, technology, and methods needed to support drug discovery and development. Recent rapid advances in innovative drug development science present opportunity for revolution- ary developments of new scientific techniques, therapeu- tic products, and applications. The Forum provides a venue to focus ongoing attention and visibility to these important drug development needs and facilitates exploration of new approaches across the drug development lifecycle. The Forum has held workshops that have contributed to the defining and establishment of regulatory science and have helped inform aspects of drug regulatory evaluation.

CLINICAL TRIALS AND CLINICAL PRODUCT DEVELOPMENT

Clinical research is the critical link between bench and bedside in developing new therapeutics. Significant infrastructural, cultural, and regulatory impediments challenge efforts to integrate clinical trials into the health care delivery system. Collaborative, cross-sector approaches can help articulate and address these key challenges and foster systemic responses. The Forum has convened a multiyear initiative to examine the state of clinical trials in the United States, identify areas of strength and weakness in our current clinical trial enterprise, and consider transformative strategies for enhancing the ways in which clinical trials are organized and conducted. In addition to sponsoring multiple symposia and workshops, under this initiative, the Forum is fostering innovative, collaborative efforts to facilitate needed change in areas such as improvement of clinical trial site performance.

INFRASTRUCTURE AND WORKFORCE FOR DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

Considerable opportunities remain for enhancement and improvement of the infrastructure that supports the drug development enterprise. That infrastructure, which includes the organizational structure, framework, systems, and resources that facilitate the conduct of biomedical science for drug development, faces significant challenges. The science of drug discovery and development, and its translation into clinical practice, is cross-cutting and multidisciplinary. Career paths can be opaque or lack incentives such as recognition, career advancement, or financial security. The Forum has considered workforce needs as foundational to the advancement of drug discovery, development, and translation. It has convened workshops examining these issues, including consideration of strategies for developing a discipline of innovative regulatory science through the development of a robust workforce. The Forum will also host an initiative that will address needs for a workforce across the translational science lifecycle.

Forum on Drug Discovery, Development, and Translation

Gregory Simon (Co-Chair)
Kaiser Permanente Washington Health Research Institute

Ann Taylor (Co-Chair)
Retired

Christopher Austin
Flagship Pioneering

Linda Brady
National Institute of Mental Health, NIH

John Buse
University of North Carolina School of Medicine

Luther Clark
Merck & Co., Inc.

Barry Coller
The Rockefeller University

Thomas Curran
Children's Mercy, Kansas City

Richard Davey
National Institute of Allergy and Infectious Diseases, NIH

Katherine Dawson
Biogen

James Doroshow
National Cancer Institute, NIH

Jeffrey Drazen
New England Journal of Medicine

Steven Galson
Retired

Carlos Garner
Eli Lilly and Company

Deborah Hung
Harvard Medical School

Lyric Jorgenson
National Institutes of Health

Esther Krofah
FasterCures, Milken Institute

Lisa LaVange
University of North Carolina Gillings School of Global Public Health

Aran Maree
Johnson & Johnson

Cristian Massacesi
AstraZeneca

Ross McKinney, Jr.
Association of American Medical Colleges

Joseph Menetski
Foundation for the NIH

Anaeze Offodile
University of Texas MD Anderson Cancer Center

Sally Okun
Clinical Trials Transformation Initiative

Arti Rai
Duke University School of Law

Mark Rogge
University of Florida

Klaus Romero
Critical Path Institute

Joni Rutter
National Center for Advancing Translational Sciences, NIH

Susan Schaeffer
The Patients' Academy for Research Advocacy

Joseph Scheeren
Retired

Anantha Shekhar
University of Pittsburgh School of Medicine

Jay Siegel
Retired

Ellen Sigal
Friends of Cancer Research

Mark Taisey
Amgen

Amir Tamiz
National Institute of Neurological Disorders and Stroke, NIH

Pamela Tenaerts
Medable, Inc.

Majid Vakilynejad
Takeda Pharmaceuticals

Jonathan Watanabe
University of California Irvine Samueli College of Health Sciences

Alastair Wood
Vanderbilt University

Cris Woolston
Sanofi

Project Staff

Carolyn Shore, Ph.D.
Forum Director

Andrew March, M.P.H.
Associate Program Officer

Deanna Marie Giraldi, M.P.H.
Associate Program Officer

Melvin Joppy
Senior Program Assistant

For more information, please visit:

NATIONALACADEMIES.ORG/DRUGFORUM

Health and Medicine Division
Board on Health Sciences Policy
The National Academies of
SCIENCES • ENGINEERING • MEDICINE

List of Recommendations from the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

This information comes from the PRGLAC Report to the HHS Secretary and Congress, September 2018 (PDF 7 MB).

The Task Force submits the following recommendations to the Secretary of HHS regarding research and the development of safe and effective therapies specific to pregnant women and lactating women based on information gleaned during four meetings and a public comment period. The Task Force developed these recommendations in open, public sessions and voted on each recommendation at the May 2018 meeting.

The central theme of all recommendations is the need to alter cultural assumptions that have significantly limited scientific knowledge of therapeutic safety, effectiveness, and dosing for pregnant and lactating women. It is critical to facilitate and augment research on therapies for these populations.

1. **Include and integrate pregnant women and lactating women in the clinical research agenda**
    - Remove pregnant women as an example of a vulnerable population in the Common Rule
    - The Food and Drug Administration (FDA) should harmonize with the Common Rule and remove pregnant women as a vulnerable population
    - The Department of Health and Human Services (HHS) should develop guidance to facilitate the conduct of research in pregnant women and lactating women
2. **Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women**
    - Provide additional resources and funding for research to obtain clinically meaningful and relevant data for specific and co-existing conditions in pregnant women and lactating women, including but not limited to:
        - Develop preclinical models
        - Expand basic science research to inform drug development
        - Develop new tools and methods to assay therapeutic products, such as those that utilize small volumes and are sensitive to detect minute quantities in human milk
        - Develop new tools to assess pharmacodynamic response in pregnant women, lactating women, and children
        - Fund clinically relevant research and studies to inform therapeutic product use in pregnant women and lactating women
        - Design trials to capture long-term maternal, obstetric, and child outcomes

- Utilize longer award periods by government funders (beyond the typical 5-year award), when needed, for study design and data collection

3. **Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics**
    - Develop and support training and career development opportunities in obstetric and lactation pharmacology and therapeutics for both clinical and basic science
    - Develop mentors in obstetric and lactation pharmacology and therapeutics for both clinical and basic science
    - Increase the knowledge and engagement of health care providers regarding obstetric and lactation pharmacology and therapeutics
4. **Remove regulatory barriers to research in pregnant women**
    - Modify subpart B of the Common Rule
        - Change 46.204(e) in subpart B to maternal consent alone
            - Given the recognized autonomy of a pregnant woman, the evolution of family structure, that for a child only one parental signature is required for research to benefit the child and to align with parental consent for pediatrics
        - Add in the option of "Minor increase over minimal risk" from subpart D to 36.046
5. **Create a public awareness campaign to engage the public and health care providers in research on pregnant women and lactating women**
    - Highlight the importance of research on therapeutic products in pregnant women and lactating women, including the impact of not taking the medication during pregnancy and lactation as well as the impact of not breastfeeding on mother and child
    - Engage stakeholders such as Department of Health and Human Services (HHS), professional societies, industry, advocacy groups, and public and global partners
6. **Develop and implement evidence-based communication strategies with health care providers on information relevant to research on pregnant women and lactating women**
    - Increase the knowledge of health care providers regarding obstetric and lactation therapeutics and research needs
    - Increase the engagement of health care providers to disseminate information from research findings to their patients
    - Increase the engagement of health care providers to discuss participation in clinical trials, research, and registries
    - Develop appropriate strategies for sharing and interpreting research findings and risk
7. **Reduce liability to facilitate an evidence base for new therapeutic products that may be used by women who are, or may become, pregnant and by lactating women**
    - Implement a liability-mitigation strategy for conducting research and evaluating new therapeutic products in pregnant women and lactating women

    - Using the Vaccine Injury Compensation Program (VICP) as a model, however include mitigation whether or not the therapeutic product achieves marketing approval
  - If liability mitigation is insufficient, consider implementing a targeted incentive program and/or strengthening FDA authority to require clinically relevant data (such as pharmacologic and clinical data) on pregnant women and lactating women to inform dosing and safety
8. **Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the NIH BPCA as a model**
   - Provide specific funding
   - Develop separate prioritization processes for therapies and/or conditions in pregnant women and lactating women
9. **Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women**
   - Create separate prioritization processes for pregnant women and lactating women
     - Unmet need examples in lactation: low milk supply, mastitis
     - Unmet need examples in pregnancy: preterm labor, hyperemesis
   - Consider a Biomedical Advanced Research and Development Authority (BARDA)-like model and the NIH vaccine model that takes clinical development up to phase II
10. **Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research**
    - Investigators/sponsors must specifically justify exclusion in study design
    - Ensure studies are designed to capture the time dependency of physiologic changes in pregnancy and lactation
    - Develop a systematic plan on how data for pregnant women and lactating women will be obtained in a timely fashion to include pharmacokinetics/pharmacodynamics and safety
    - Develop guidance for institutional review boards and investigators about the inclusion of pregnant women and lactating women in research
    - Develop a systematic plan for if a woman becomes pregnant in a study to include whether product should continue, if un-blinding is necessary, how to capture opportunistic information on pharmacology, clinical data, and pregnancy outcome information
11. **Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women**
    - Provide financial support and incentives to established and develop new multicenter infrastructures that capitalize on standard of care procedures (opportunistic studies), innovative designs, and methodologies.
    - Broaden focus of ongoing research networks to include research on therapeutic products in pregnant women and lactating women
    - Encourage networks/collaborations to engage in public-private partnerships to facilitate research

12. **Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant women and lactating women**
    - Design health record systems to link mother and infant records
    - Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries
    - Use novel data resources
    - Use innovative methods of data analytics
    - Require common data elements to facilitate collaboration and use
13. **Optimize registries for pregnancy and lactation**
    - Create a user-friendly website for registry listing
    - Develop registry standards and common data elements that facilitate input of pertinent data with easy, transparent access to obtain information in real time
        - Include maternal, obstetric, and child outcomes, along with birth defects
    - Facilitate access to data and transparency of information in registries
        - Use the ART registry as a model
    - Develop disease/condition-focused registries
        - Move toward a single registry for all therapeutic products with input from stakeholders
14. **The Department of Health and Human Services Secretary should consider exercising the authority provided in law to extend the PRGLAC Task Force when its charter expires in March 2019 (Extended March 13, 2019 – March 13, 2021)**
15. **Establish an Advisory Committee to monitor and report on implementation of recommendations, updating regulations, and guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical research (*Deferred*)**

Content Owner Office of the Director**Last Reviewed Date**6/7/2019

TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN

Report Implementation Plan

To the Secretary, Health and Human Services

August 2020

Overview: Themes and Issues

Introduction

As the 2018 Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) Report to the Department of Health and Human Services (HHS) Secretary documents[1], longstanding obstacles to inclusion of pregnant women and lactating women in clinical research studies have limited the collection of data to support the safety and appropriate dosing of medications and other therapeutics used during pregnancy and lactation. Following submission of the 2018 PRGLAC Report, the Secretary extended PRGLAC's charter, asking for further guidance on implementation of the 15 Recommendations included in the Report. While some steps have been taken to address obstacles to this research, such as the recent change to the federal regulations protecting human subjects who participate in research[2] (the "Common Rule"), the culture of protecting pregnant women and lactating women from research has proven resistant to change. The presumption that ceasing use of medications throughout pregnancy and lactation is "healthier" for a woman and her offspring is inaccurate in many cases and may actually endanger their health. This danger applies not only to treatments for conditions arising directly from pregnancy, but even more so for treatment of conditions that occur in reproductive-aged women, whether pregnant, lactating, or neither. In the vast majority of cases, the scientific evidence does not support either continued use or cessation of using the therapeutics, primarily because that evidence does not exist or is insufficient. Inclusion of pregnant women and lactating women in vaccine and treatment trials during the current SARS-CoV-2 pandemic illustrates this point.

PRGLAC Implementation Plan: Common Themes

Just as the recommendations made by the PRGLAC in its 2018 report comprised an interrelated response to congressional concerns about inclusion of pregnant and lactating women in clinical research studies, the implementation steps developed for each of the recommendations are also integrated throughout the plan. In framing these potential steps, several common themes emerged, providing a useful overview of the major steps needed to move ahead.

Leveraging or expanding existing federal programs or networks

Most of the working groups discussed which existing federal programs, or components of those programs, could serve as potential models for efforts to maximize inclusion of pregnant women and lactating women in clinical research studies. The groups also recognized that existing research networks supported by the federal government could be expanded to further research on therapeutics used during pregnancy and lactation (Recommendations 1, 2, 3, 7, 8, 9, 11, and 12).

[1] https://www.nichd.nih.gov/about/advisory/PRGLAC

[2] https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html

Developing a systematic plan to collect data in pregnant women and lactating women

A systematic plan for the timely collection of data (e.g., safety, pharmacokinetic [PK], pharmacodynamic [PD]) during pregnancy and lactation must be established (Recommendations 1, 2, 10, and 13).

Developing research tools and strategies

Addressing practical considerations that have posed difficulties for researchers or would expand the power of their studies by allowing comparisons or linkages of study cohorts, could facilitate more research on therapeutics used during pregnancy and lactation. Use of a central Institutional Review Board (IRB) for multisite studies, agreement on common data elements across studies, and the development of preclinical models offer some examples (Recommendations 1, 2, 7, 10, 12, and 13).

Considering trial design

For ethical and other reasons, the gold standard randomized clinical trial design to test therapeutics used during pregnancy and lactation may not be feasible. Several of the implementation steps suggest exploring alternative trial designs that would more easily accommodate inclusion of a diverse group of pregnant women and lactating women in study populations (Recommendations 2, 6, and 10).

Utilizing registries and usable data sources

Datasets that can be linked (e.g., pregnant women, infants) would help researchers compare results across studies. Encouraging women to participate in existing clinical, industry, or research registries would facilitate the creation of research hypotheses and clinical trial recruitment (Recommendations 2, 6, 7, 8, 11, 12, and 13).

Establishing a prioritization process for studying therapeutics used during pregnancy and lactation

Over 90 percent of women use at least one medication during pregnancy, and about 70 percent use at least one prescription medication.[3] According to one recent source, 90 to 99% of women receive at least one medication during the first week after delivery.[4] Many women who become pregnant or are lactating already have chronic conditions needing treatment, in addition to conditions that may arise as a result of pregnancy. Consequently, because so few studies have been conducted, some prioritization is necessary to determine which therapeutics should be studied first, possibly based on current processes established for other areas of research (Recommendations 2, 8, and 9).

Addressing ethical considerations, liability concerns, and potential incentives

[3] https://www.cdc.gov/pregnancy/features/pregnancy-meds-keyfindings.html

[4] Wambach, K., and Spencer, B. (eds.), 2021, *Breastfeeding and Human Lactation, 6th Edition*, Jones and Bartlett Learning, Burlington, MA, p. 127.

Although revisions to the federal regulations for protection of human subjects (the "Common Rule") participating in research removed pregnant women as an example of a "vulnerable population," ethical concerns and the potential for liability remain for research conducted during pregnancy and lactation. While no single solution to these concerns may be apparent, a mix of incentives and continued protections (informed consent) may partly address these issues (Recommendations 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10).

Fostering education and awareness

Building awareness of the changes to the federal regulations and encouraging diverse groups of women to participate in research will require making pregnant and lactating women, and the healthcare providers who care for them, aware of the options for participating in clinical research (Recommendations 3, 5, 6, and 10).

Creating partnerships

Creating a culture change that allows for research on therapeutics used during pregnancy and lactation could be greatly bolstered through collaborations and partnerships among the many stakeholders on this issue, including partnering on the design of research, sharing of data and/or biospecimens, clinical trial recruitment, and funding. Some existing collaborations have great potential for expansion (Recommendations 2, 5, 6, 11, 12, and 13).

Conclusion

Many issues related to the inclusion of pregnant women and lactating women in clinical research studies have defied resolution for decades, despite efforts over the years to address them. Among these, concerns about liability faced by researchers and clinicians working within the U.S. healthcare and legal systems are more pervasive than the issue of including pregnant women and lactating women in research alone. While the wide range of perspectives and experience among PRGLAC and ad hoc working group members provided the grounding in reality necessary to develop implementation steps for each of the Task Force's original recommendations, the working group deliberations made it clear that some issues warrant further and more in-depth discussions.

To avoid becoming mired in issues that are out of the Task Force's power to solve on its own, the committee took a pragmatic approach to the Secretary's request to provide guidance on implementation of the PRGLAC recommendations. The Task Force offers feasible and actionable steps that could make realistic progress toward ensuring that pregnant women and lactating women are more comprehensively and appropriately included in research in the near future. To achieve this important goal, each of the stakeholder groups represented on the Task Force—government, industry, clinicians, and women—has a critical role in carrying out these implementation steps.

For the full Report Implementation Plan, visit https://www.nichd.nih.gov/sites/default/files/inline-files/PRGLAC_Implement_Plan_083120.pdf

IMPROVING REPRESENTATION

in Clinical Trials and Research

Building Research Equity For Women and Underrepresented Groups

REPORT CONCLUSIONS

The United States has long made substantial investments in clinical research with the goal of improving the health and wellbeing of our nation. There is no doubt that these investments have contributed significantly to treating and preventing disease and extending human life. **Nevertheless, large swaths of the U.S. population, and those that often face the greatest health challenges, are less able to benefit from these discoveries because they are not adequately represented in clinical research studies.**

In 2020, the National Academies of Sciences, Engineering, and Medicine was tasked by Congress to undertake a study *"examining and quantifying the long-term medical and economic impacts of the inclusion of women and racial and ethnic minority population subgroups in biomedical research and subsequent translational work"*.

Five overarching conclusions, based on a comprehensive analysis of the research, were identified by the report committee.

01

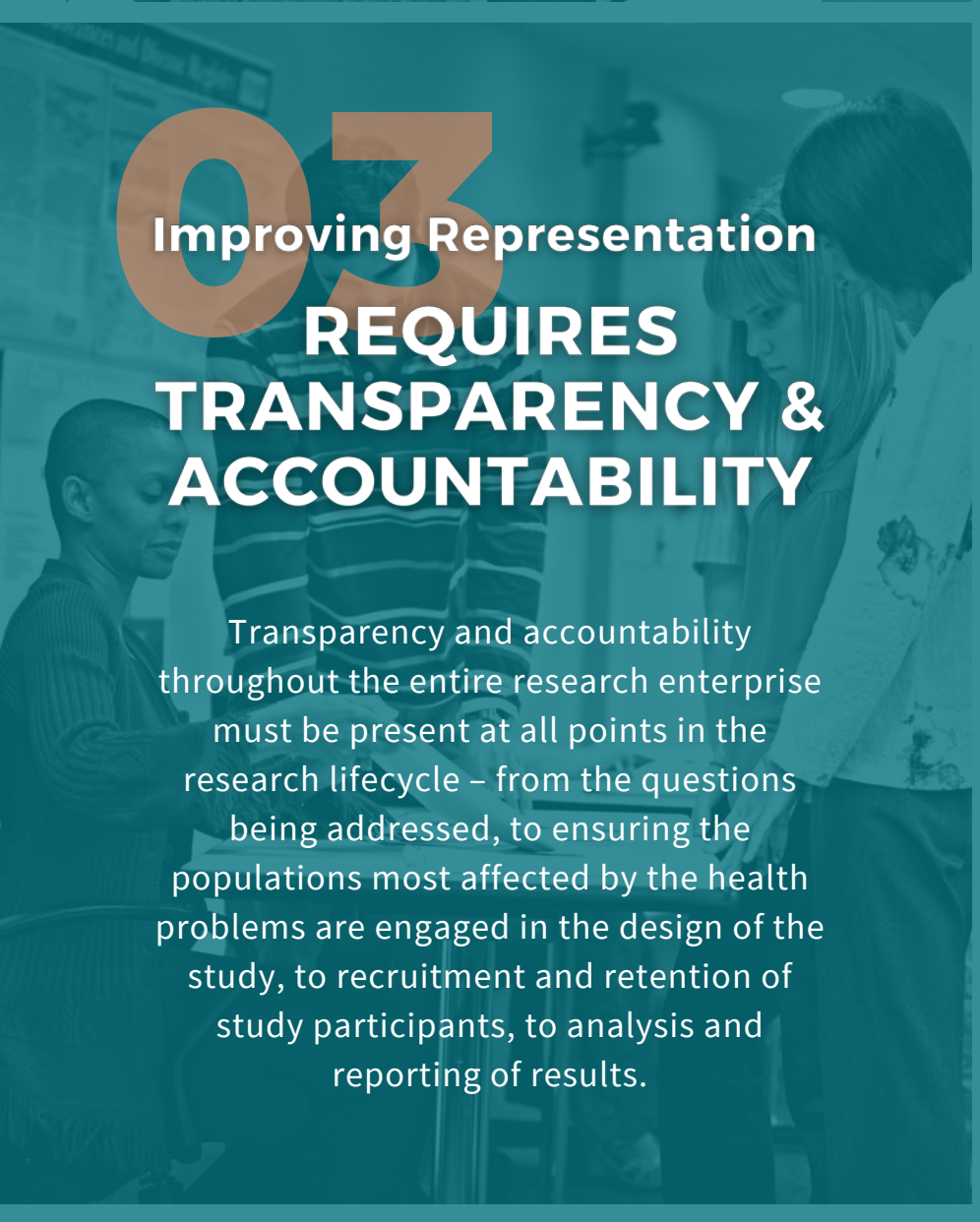
Improving Representation IS URGENT

Despite greater diversity in the United States today, deep disparities in health are persistent, pervasive, and costly. Failing to reach these growing communities will only prove more costly over time and prevent meaningful reductions in disparities in chronic diseases.

02

Improving Representation REQUIRES INVESTMENT

In order to better address health disparities, our workforce should look more like our nation. Building trust with local communities cannot be episodic or transactional and pursued only to meet the goals of specific studies; it requires sustained presence, commitment, and investment.



03

Improving Representation REQUIRES TRANSPARENCY & ACCOUNTABILITY

Transparency and accountability throughout the entire research enterprise must be present at all points in the research lifecycle – from the questions being addressed, to ensuring the populations most affected by the health problems are engaged in the design of the study, to recruitment and retention of study participants, to analysis and reporting of results.

04

Improving Representation IS THE RESPONSIBILITY OF EVERYONE INVOLVED

The clinical research landscape involves multiple stakeholders— participants, communities, investigators, IRBs, industry sponsors, institutions, funders, regulators, journals, and policy-makers. The responsibility (and cost) will be borne to some extent by all stakeholders in the larger research ecosystem, acting in consort to improve representation.

05

CREATING A MORE EQUITABLE FUTURE ENTAILS A PARADIGM SHIFT

The clinical research field must embrace a paradigm shift that moves the balance of power from institutions and puts at the center the priorities, interests, and voices of the community.

An ideal clinical trial and research enterprise pursues justice in the science of inclusion through scalable frameworks, expects transparency and accountability, invests more in people, institutions and communities to drive equity, and invests in the science of community engagement and empowerment.

READ THE FULL REPORT

www.nationalacademies.org/improve-representation

SOURCE: National Academies of Sciences, Engineering, and Medicine. 2022. *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups.* Washington, DC: The National Academies Press.

The National Academies of

SCIENCES ENGINEERING MEDICINE

Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups (2022)

DETAILS

440 pages | 6 x 9 | PAPERBACK

ISBN 978-0-309-27820-1 | DOI 10.17226/26479

CONTRIBUTORS

Kirsten Bibbins-Domingo and Alex Helman, Editors; Committee on Improving the Representation of Women and Underrepresented Minorities in Clinical Trials and Research; Committee on Women in Science, Engineering, and Medicine; Policy and Global Affairs; National Academies of Sciences, Engineering, and Medicine

SUGGESTED CITATION

National Academies of Sciences, Engineering, and Medicine 2022. *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups.* Washington, DC: The National Academies Press. https://doi.org/10.17226/26479.

IMPROVING REPRESENTATION IN CLINICAL TRIALS AND RESEARCH

Building Research Equity for Women and Underrepresented Groups

Kirsten Bibbins-Domingo and Alex Helman, *Editors*

Committee on Improving the Representation of Women and Underrepresented Minorities in Clinical Trials and Research

Committee on Women in Science, Engineering, and Medicine

Policy and Global Affairs

A Consensus Study Report of

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

Summary

The United States has long made substantial investments in clinical research with the goal of improving the health and well-being of our nation. There is no doubt that these investments have contributed significantly to treating and preventing disease and extending human life. Nevertheless, clinical research faces a critical shortcoming. Currently, large swaths of the U.S. population, and those that often face the greatest health challenges, are less able to benefit from these discoveries because they are not adequately represented in clinical research studies.

In the past three decades, diversity in clinical trials has become an important policy priority, advanced by federal agency offices such as the National Institutes of Health (NIH) Office of Research on Women's Health, the Food and Drug Administration (FDA) Office of Women's Health, the Society for Women's Health Research, and the FDA Office of Minority Health. While progress has been made on some fronts, particularly with representation of white women in clinical trials and clinical research, progress has largely stalled on participation of racial and ethnic minority population groups. Additionally, older adults, pregnant and lactating individuals, LGBTQIA+ populations, and persons with disabilities remain underrepresented and even excluded from clinical trials and clinical research.[1] An equitable clinical research enterprise would include trials and studies that match the demographics of the disease burden under study. However, we remain far from achieving this goal.

By failing to achieve a more diverse clinical trial and clinical research enterprise, the nation suffers serious costs and consequences, including the following:

[1] Throughout this report, LGBTQIA+ is used as an inclusive term for the various gender identities and sexual orientations, including lesbian, gay, bisexual, transgender, questioning, queer, intersex, asexual, and pansexual.

1. **Lack of representation compromises generalizability of clinical research findings to the whole US population.** Women, pregnant people, children, older adults, and racial and ethnic minority population groups can have distinct disease presentations or health circumstances that affect how they will respond to an investigational drug or therapy. These variable therapeutic responses can result in the delivery of health care that is not always evidence based.
2. **Lack of representation costs hundreds of billions of dollars.** An economic analysis carried out by the committee, using the Future Elderly Model, demonstrates high financial and social costs, measured by life expectancy, disability-free life, and years in the labor force, in the hundreds of billions of dollars range (see Box 2-1). Given the assumption that better representation in clinical trials would reduce health disparities by even a modest amount, the analysis found that achieving diverse representation in research would be worth billions of dollars in savings to the United States.
3. **Lack of representation may hinder innovation and new discoveries.** Diversity in study participants allows for greater exploration of variation in the overall effectiveness of a particular intervention. Exploring "heterogeneity of treatment effects" may be necessary not only to understand variation that affects safety and effectiveness of an intervention in underrepresented and excluded populations but also to identify new biological processes that may, in turn, lead to new discoveries important for all populations.
4. **Lack of representation may compound low accrual that causes many trials to fail.** According to an analysis by GlobalData, low accrual was the cause for stopping 55 percent of all Phase I–IV clinical trials that were terminated, suspended, or discontinued during 2008–2017. Thus, increasing enrollment of underrepresented and excluded populations would help solve the leading cause of clinical trial failure.
5. **Lack of representation may lead to lack of access to effective medical interventions.** Approval and indications for new therapeutics are often restricted to the demographics of the populations included in the clinical studies. Lack of representation may therefore impede access to a specific therapeutic

agent. Guideline-making bodies must synthesize various lines of evidence when making recommendations. The generalizability of these recommendations to all populations may be limited when the evidence base for a specific population does not exist. When these recommendations are tied to insurance coverage, these gaps may affect reimbursement of, and therefore access to, health care.

6. **Lack of representation may undermine trust of the clinical research enterprise and the medical establishment.** For example, the lack of inclusion of pregnant people in the clinical trials of the SARS-CoV-2 vaccines led to lack of clarity on the use of these vaccines in pregnant people and may have contributed to vaccine hesitancy, even as subsequent observational data emerged showing the safety of vaccine use in pregnant individuals, as well as data on the importance of preventing COVID-19 infection during pregnancy. Efforts to create more representative and inclusive research environments may work to increase trust in science and medicine.
7. **Lack of representation compounds health disparities in the populations currently underrepresented and excluded in clinical trials and clinical research.** While achieving health equity and reducing health disparities requires far more than just equitable representation in clinical research, failure to achieve equity on this dimension leaves health disparities unaddressed and reinforces inequities.

STATUS OF CLINICAL TRIAL PARTICIPATION

Gaining a fully accurate status of the current participation of underrepresented populations in clinical trials and clinical research, and trends in participation over time, is very challenging due to insufficient data-reporting practices at a national level. Although reporting to ClinicalTrials.gov is required for ongoing studies, the committee found major inconsistencies in how data was reported in this national database. Further, NIH does not currently have longitudinal data available for clinical trial enrollment by disease type.

Working within these constraints, the committee commissioned an analysis to examine available data from the FDA and NIH, which found that women now represent over 50 percent of clinical trial participants in the United States, particularly for white women. However, pregnant and lactating individuals, sexual- and gender-minority populations, and racial and ethnic subgroups of women remain underrepresented in clinical trials. The analysis also revealed that the racial and ethnic diversity of clinical trials is largely stagnant, with little changes in diversity over time.

UNDERREPRESENTED AND EXCLUDED POPULATIONS ARE WILLING TO PARTICIPATE IN CLINICAL RESEARCH, IF ASKED

Due to well-documented historical and contemporary abuses against certain excluded and underrepresented populations in medical research, members of the research community often assume that a lack of willingness to participate in research is the major driver of poor representation of some populations in research. However, the evidence on this issue is clear: Asian, Black, Latinx Americans, and American Indian/Alaska Native individuals are no less likely, and in some cases are more likely, to participate in research if they are asked. Distrust and mistrust are commonly assumed to be the reason underlying a lack of participation in clinical trials. While there is no doubt that the legacy of abuses in medical research is an important factor driving the lack of engagement of underrepresented and excluded populations with both health care and research, several studies have found that distrust and mistrust are not necessarily associated with a lack of willingness to participate in medical research. The evidence suggests that concerns of researchers about the willingness of underrepresented and excluded populations to participate in research due to distrust or mistrust in the medical establishment may misrepresent barriers to participation in research or are surmountable with effort from research teams, funders, and policy makers.

BARRIERS TO REPRESENTATION OF UNDERREPRESENTED AND EXCLUDED POPULATIONIS IN CLINICAL RESEARCH

The committee found that the existing research system has served to reduce participation by a diverse population in clinical trials and clinical research through a range of factors, operating at multiple levels. Individual research studies, the institutions that conduct research, funders of studies, institutional review boards (IRBs), medical journals, and the broader landscape of national policies and practices that govern research can all contribute to barriers to inclusion of underrepresented and excluded populations in clinical research.

1. **Individual research studies.** At the level of an individual research study, the factors and problems that lead to the underrepresentation and exclusion of certain populations in clinical trials and research begin with and follow the life cycle of a project. Understanding and resolving underrepresentation and exclusion of these populations in research requires careful examination of almost every stage in the research process itself, including
   - the development of research questions;
   - the composition, training, and attitudes of the research team;
   - research site selection;
   - participant selection, including sampling and recruitment methods and inclusion and exclusion criteria;
   - study protocols, including informed consent processes and remuneration; and
   - development and inclusion of multilingual recruitment and consent documents.

   Institutional structures. Medical institutions of different types face a range of structural barriers to inclusion in clinical trials. For example, although academic medical centers conduct 55 percent of the extramural medical research

supported by the National Institutes of Health, and operate 98 percent of the nation's 41 comprehensive cancer centers as of 2019, sustainably and meaningfully engaging underrepresented and underrepresented and excluded populations often does not align with the traditional incentive structures for researchers at these institutions. Recruiting diverse population groups and properly engaging with community members, which is time-consuming and requires investments to build and sustain trust, are only minimally considered in promotion and tenure decisions at academic medical centers. And while community health centers serve a much more diverse community than academic medical centers, these institutions also face barriers to clinical trials and research recruitment, which, which include limited provider knowledge about available research opportunities and challenges with electronic health record (EHR) infrastructure that can limit providers' ability to query the EHR using study inclusion and exclusion criteria.

2. **Institutional review boards.** IRBs can also present barriers to diverse participation in clinical trials by limiting the types and amount of compensation given to research participants to avoid the impression of coercion or undue influence. However, limiting incentives may ultimately compromise beneficence and justice, two of the ethical principles for research with human subjects detailed in the *Belmont Report*.
3. **Research funders.** Research funders also have several roles and responsibilities that can influence the diversity of clinical trials**.** These include setting funding priorities, deciding which projects ultimately get funded, providing adequate funding to recruit and retain participants, requiring transparent reporting, and evaluating research outputs.
4. **Industry funders.** Most clinical trials are funded by industry, and these trials present barriers, including out-of-pocket costs for participants, which are often not discussed in the informed consent process, industry pressures to gather data quickly, and the selection of easy-to-recruit samples being incentivized. It should be noted that some of these barriers are not solely unique to industry-sponsored trials.

5. **Medical journals.** Peer-reviewed Medical journals serve as the gatekeepers to scientific advancements in clinical practice and health. Their editors yield great power for what is, and is not, published in their pages. Lack of representation on editorial boards and other journal leadership positions may contribute to biases in publication.

FACILITATORS TO SUCCESSFUL INCLUSION IN RESEARCH

There is substantial quantitative data demonstrating the size and scope of the problem of underrepresentation and exclusion of populations in research; however, there is a dearth of critical qualitative data about facilitators of successful inclusion in clinical research. This committee supplemented existing literature with commissioned research with 20 researchers who worked on trials that met criteria for diverse trial enrollment. From this research, eight major themes emerged, which provide insights into key facilitators to inclusion:

1. **Starting with intention and agency to achieve representativeness.** From goal setting to community partnering strategies, intentionality and planning are critical themes for overcoming the systemic barriers previously outlined to the inclusion of underrepresented and excluded populations in research. This intentionality applies to building relationships with community members, designing studies that seek to recruit these groups, considering barriers to access and the lived-realities of participants in the research design, and external factors, such as requirements from funding agencies.
2. **Establishing a foundation of trust with participants and the community at large.** Building and maintaining trust with both study participants and their larger communities is foundational to achieving equity in research. The

development of trust requires a long-term commitment by principal investigators, study teams, and local institutions involved in the research. Building trust over time takes consistent engagement in the community beyond the confines of the study itself, developing meaningful relationships with study participants, and giving to the community without the expectation of anything in return.

3. **Anticipating and removing barriers to study participation.** Building rapport with study participants and attending to their needs is critical for making sure studies have broad accessibility. In addition, recognizing heterogeneity within cultural groups is key; a one-size-fits-all approach to developing protocols will not work.
4. **Adopting a flexible approach to recruitment and data collection.** Flexibility in recruitment techniques, data collection, and visit windows to adapt to study needs is critical to having diverse study enrollment and retention. These changes are more helpful when made with input from community representatives and other relevant stakeholders.
5. **Building a robust network by identifying all relevant stakeholders.** Research suggests that engaging in mapping to identify all the relevant stakeholders in a community can help study teams develop more equitable study designs and identify individuals and organizations that can help drive the recruitment and retention of diverse study participants. These stakeholders include caregivers, family members, friends, clinical providers and administrators, community advocates, peers, religious leaders, and political figures.
6. **Navigating scientific, professional peer, and societal expectations.** Efforts to promote representativeness, and decisions made to support these efforts, are not always embraced or supported by colleagues and organizations responsible for making funding and/or budget decisions. It is helpful if funding agencies, as well as those responsible for approving proposals and distributing budgets, understand the challenges and costs associated with nontraditional research approaches to enhance inclusion.

7. **Optimizing the study team to ensure alignment with research goals.** Diverse study teams, including study leadership, are helpful to recruitment and to enhance congruence between research teams and potential participants. It also helps to retain staff over time for recruitment and retention success.
8. **Attaining resources and support to achieve representativeness.** The investment of time and money are necessary to successfully engage in the long-term strategies and relationship building needed to drive inclusion in studies. This includes expanded budgets for teams recruiting and retaining diverse participants, support to expand infrastructure for community organizations, and investments in community-based partnerships to reduce power differentials between researchers and participants.

CONCLUSIONS

The committee identified five overarching conclusions, based on a comprehensive analysis of the research, presented throughout the report, which serve to frame the consensus recommendations.

1. **Improving representation in clinical research is urgent.**

   The scientific necessity to improve research equity is urgent. The 2020 U.S. Census found that the number of people who identify as white has shrunk for the first time since a census started being taken in 1790, and despite the country becoming more diverse, the nation's health disparities persist. Without major advancements in the inclusion of underrepresented and excluded populations in health research, meaningful reductions in disparities in chronic diseases such as diabetes, cancer, and Alzheimer's remain unlikely. Purposeful and deliberate change is needed. As the United States becomes more diverse every day, failing to reach these growing communities will only prove more costly over time (see Chapter 2).

2. **Improving representation in clinical research requires investment.**

   Improving the representation of underrepresented and excluded populations in clinical trials and clinical research requires a substantial investment of time, money, and effort. Investment of time and resources are needed to build and restore trust with underrepresented and excluded communities. Building trust with local communities cannot be episodic or transactional and pursued only to meet the goals of specific studies; it requires sustained presence, commitment, and investment. Investments are also needed in the systems and technologies that reduce burdens to participation by underrepresented and excluded populations, such as by adequately compensating participants financially for their time when participating in research and by investing resources in making participation more physically accessible, and by providing research materials that are culturally informed and multilingual. Lastly, we need to invest in creating a more diverse workforce that better reflects the diversity of our country. This has implications not just for study site personnel and their direct interactions with participants, but it also influences the types of research questions that get asked, the types of research that get funded, and even the types of research that are published. To better address health disparities and ensure health equity for all, the U.S. workforce should look more like the nation (see Chapter 4).

3. **Improving representation requires transparency and accountability.**

   Transparency and accountability throughout the entire research enterprise will be critical to driving change and must be present at all points in the research life cycle—from the questions being addressed, to ensuring the populations most affected by the health problems are engaged and considered in the design of the study, to recruitment and retention of study participants, to analysis and reporting of results. Individual investigators and research institutions on the front lines bear responsibility for transparency in reporting progress toward the goals of inclusion in research. Transparency and accountability must also be

reinforced by the funding that agencies and industry sponsors have across their portfolios, that regulatory agencies have in their role governing the conduct of research as well as the approval and reimbursement of the drugs and devices that are often the final products of clinical research, and that journal editors and others that disseminate research have in communicating findings (see Chapters 3, 4, and 5).

4. **Improving representation in clinical research is the responsibility of everyone involved in the clinical research enterprise.**

The clinical research landscape is complex and involves multiple stakeholders—participants, communities, investigators, IRBs, industry sponsors, institutions, funders, regulators, journals, and policy makers. Each of these stakeholders has a critical role to play in achieving the goal of improving representation in clinical research, but the complex nature of the research ecosystem and research processes, combined with lack of accountability and historic underinvestment, means that an issue that should be everyone's responsibility can become no one's priority. In this report, the committee emphasizes that the research supports taking a systematic approach to addressing this issue, one in which all stakeholders take responsibility for the important role they can play in ensuring representation in clinical research participation.

The committee was asked, "Who bears the cost of more inclusive science?" The responsibility (and therefore the cost) will be borne to some extent by all stakeholders in the larger research ecosystem, acting in consort to achieve this larger societal and scientific goal. Those that profit from scientific discovery bear particular responsibility in shouldering the cost of inclusivity. The federal government has a notably prominent role and responsibility in achieving the goal of more inclusive research, as a primary funder of the research enterprise with taxpayer dollars, regulator of the processes of scientific research, gatekeeper to approvals for monetizing scientific discovery, and purchaser of new drugs and devices. More coherence of federal policy to align

investment and accountability to achieve the goals of inclusive science is warranted.

In answering the question of who bears the cost of more inclusive science, we must also ask, "Who bears the cost of the current lack of inclusivity?" That cost is large (as evidenced by the analysis in Chapter 2) and is borne disproportionately by underrepresented and historically excluded communities, but saps the health and economic strength of the entire society.

5. **Creating a more equitable future entails a paradigm shift.**

The committee sees the need for both pragmatic approaches and an aspirational vision. To realize a more equitable future, the report epilogue challenges the field to embrace a paradigm shift that moves the balance of power from institutions and puts at the center the priorities, interests, and voices of the community. An ideal clinical trial and clinical research enterprise pursues justice in the science of inclusion through scalable frameworks; expects transparency and accountability; invests more in people, institutions, and communities to drive equity; and invests in the science of community engagement and empowerment. These ideals should be the foundation of the actions that stakeholders take to make sustainable change.

RECOMMENDATIONS

The committee's recommendations focus on tangible actions that must urgently be taken within the context of the existing structures of the clinical research ecosystem in order to achieve the goals of representation and inclusion. Although individual researchers can take many actions to improve health equity in clinical trials and clinical research, as described in Chapter 5, the committee focused on system-level recommendations to drive change on a broader scale. The committee presents 17 recommendations (see Chapter 6) to

improve the representation of underrepresented and excluded populations in clinical trials and clinical research and create lasting change.

The urgency of addressing the equity in research participation and the lack of substantial progress despite stated commitments led the committee to propose bold recommendations with potentially far-reaching implications. The committee is aware that the complexity of the United States health-care system poses significant challenges to transforming the clinical research system, and these systematic challenges will also influence the implementation of the committee's recommendations. While providing a complete policy assessment for each recommendation was outside of the committee's scope and charge, the committee does not deny that there will be costs—both fiscal and political—associated with the implementation of the recommendations. These costs must be carefully weighed against the potential for long-term benefit. Changing our nation's approach to clinical research may require significant upfront costs to more equitably recruit and retain a diverse group of participants and to hold investigators accountable when they do not meet these goals. In addition, it will require incentivizing sponsors of clinical research to change the status quo. However, based on the committee's expert opinion and the available evidence, the committee believes that implementation of its recommendations is necessary to truly drive significant and sustained change to the clinical research system.

Reporting and Accountability

1. **The Department of Health and Human Services (HHS) should establish an intradepartmental task force on research equity charged with coordinating data collection and developing better accrual tracking systems across federal agencies, including the Food and Drug Administration (FDA), National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), Agency for Healthcare Research and**

Quality (AHRQ), Health Resources Services Administration (HRSA), Indian Health Services (IHS), Centers for Medicare and Medicaid Services (CMS), and two departments outside of HHS, the Department of Veterans Affairs and Department of Defense. This task force should be charged with the following:

a. **Producing an annual report to Congress on the status of clinical trial and clinical research enrollment in the United States, including the number of patients recruited into clinical studies by phase and condition; their age, sex, gender, race, ethnicity, and trial location (i.e., where participants are recruited); their representativeness of the conditions under investigation; and the research sponsors.**
b. **Making data more accessible and transparent throughout the year, such as through a data dashboard that is updated in real time.**
c. **Determining what "representativeness" means for protocols and product development plans.**
d. **Developing explicit guidance on equitable compensation to research participants and their caregivers, including differential compensation for those who will bear a financial burden to participate**.

2. **The Food and Drug Administration should require study sponsors to submit a detailed recruitment plan no later than at the time of Investigational New Drug and Investigational Device Exemption application submission that explains how they will ensure that the trial population appropriately reflects the demographics of the disease or condition under study and that provides a justification if these enrollment targets do not match the demographics of the intended patient population in the United States.**

3. **The NIH should standardize the submission of demographic characteristics for trials to ClinicalTrials.gov beyond existing guidelines so that trial characteristics are labeled uniformly across the database and can be easily**

disaggregated, exported, and analyzed by the public. The data reported should include the number of patients; their age, sex, gender, race, ethnicity, and trial location (i.e., where participants are recruited); who sponsors them; and language accessibility.

4. **In grant proposal review, the NIH should formally incorporate considerations of participant representativeness in the score-driving criteria that assess the scientific integrity and overall impact of a grant proposal. These criteria should be part of the assessment of the scientific approach, including whether it is appropriate for generating insights for the populations to whom the results are intended to generalize. The criteria should also be incorporated in the assessment of whether investigative teams and environment have detailed and feasible plans to meet the goals of representative study enrollment. Additionally, the NIH should assess in its annual review of progress reports of funded studies whether a given study has met the proposed enrollment goals of representativeness by race/ethnicity, sex, and gender, and should establish a plan for remediation for the investigator and/or organization that includes criteria for putting funding on hold that has not met predefined recruitment goals.**

5. **Journal editors, publishers, and the International Committee on Medical Journal Editors should require information on the representativeness of trials and studies for submissions to their journals, particularly relative to the affected population; should consider this information in accepting submissions; and should publish this information for accepted manuscripts. The information required should include the following:**
   a. **The disease, problem, or condition under investigation.**
   b. **Special considerations related to sex and gender, age, race or ethnic group, and geography.**

c. **The overall representativeness of the trial, including how well the study population aligns with the target population in which the results are intended to generalize. If the study population does not align with the population affected by the disease, authors should provide scientific justification for why this is the case.**

6. **The Office of Human Research Protections (OHRP) and the FDA should direct local institutional review boards (IRBs) to assess and report the representativeness of clinical trials as one measure of sound research design that it requires for the protection of human subjects. Representativeness should be measured by comparing planned trial enrollment to disease prevalence by sex, age, race, ethnicity and trial location (i.e., where participants are recruited). Protocols in which the planned enrollment diverges substantially from disease prevalence should require justification. The OHRP and FDA should establish a plan for remediation for local IRBs that frequently approve protocols that are not representative.**

7. **The CMS should amend its guidance for coverage with evidence development (CED) to require that study protocols include the following:**
   a. **A plan for recruiting and retaining participants** who **are representative of the affected beneficiary population in age, race, ethnicity, sex, and gender**

   b. **A plan for monitoring achievement of representativeness as described above, and a process for remediation if CED studies are not meeting goals for representativeness**

Federal Incentives

8. **In order to determine how to take action on the most effective accountability and incentive structures, Congress should direct the FDA to enforce existing accountability measures, as well as establish a taskforce to study new incentives for new drug and device for trials that achieve representative enrollment. Incentive programs should be designed to improve representativeness in clinical research, improve clinical outcomes, and ensure they do not reduce access to new therapies. Some ideas include**:
   a. **Tax incentives, such as tax credits for research and development.**
   b. **Fast-Track criteria and exemption from some FDA drug application fees.**
   c. **Extended market exclusivity to sponsors who meet predefined criteria of representativeness.**
   d. **Refusing to file an application that does not appropriately represent the target population under study.**

9. **The CMS should expedite coverage decisions for drugs and devices that have been approved based on clinical development programs that are representative of the populations most affected by the treatable condition.**

10. **The CMS should incentivize community providers to enroll and retain participants in clinical trials by reimbursing for the time and infrastructure that is required. Through the creation of new payment codes, CMS should reimburse activities associated with clinical trial participation, including but not limited to data collection and personnel (e.g., community health workers, patient navigators) to support research education and recruitment.**

11. **The Government Accountability Office (GAO) should assess the impact of reimbursing routine care costs associated with clinical trial participation for both Medicare (enacted in 2000) and Medicaid (enacted in 2020). The assessment should include an analysis of whether there is timely and complete reimbursement, any implications for innovation and care delivery to underrepresented populations, and any challenges to implementation.**

Remuneration

12. **Federal regulatory agencies, including OHRP, NIH, and FDA, should develop explicit guidance to direct local IRBs on equitable compensation to research participants and their caregivers. In recognition that research participation may pose greater hardship or burdens for historically underrepresented groups, the new guidance should encourage and allow for differential compensation to research participants and their caregivers according to the time and financial burdens of their participation. Differential compensation may include additional reimbursement for expenses including but not limited to lost wages for those with lower socioeconomic status (SES), transportation costs, per diem, dependent care, and housing/lodging where applicable.**

13. **All sponsors of clinical trials and clinical research (e.g., federal, foundation, private and/or industry) should ensure that trials provide adequate compensation for research participants. This compensation may include additional reimbursement for expenses including but not limited to lost**

wages for lower SES participants and family caregivers, transportation costs, per diem, dependent care, and housing/lodging where applicable.

Education, Workforce, and Partnerships

14. **All entities involved in the conduct of clinical trials and clinical research (academic centers, health-care systems, sponsors, regulatory agencies, and industry) should ensure a diverse and inclusive workforce, especially in leadership positions.**

15. **Leaders and faculty of academic medical centers and large health systems should recognize research and professional efforts to advance community-engaged scholarship and other research to enhance the representativeness of clinical trials as areas of excellence for promotion or tenure.**

16. **Leaders of academic medical centers and large health systems should provide training in community engagement and in principles of diversity, equity, and inclusion for all study investigators, research grants administration, and IRB staff as a part of the required training for any persons engaging in research involving human subjects. This training should incorporate strategies to enhance diverse recruitment and retention in clinical research, as well as planning of and budgeting for these efforts and timely reimbursement of partnering agencies and organizations.**

17. **HHS should substantially invest in community research infrastructure that will improve representation in clinical trials and clinical research. This funding should go to agencies such as the HRSA, NIH, AHRQ, CDC, and IHS to**

expand the capacity of community health centers and safety-net hospitals to participate in and initiate clinical research focused on conditions that disproportionately affect the patient populations they serve.

WOMEN AND HEALTH RESEARCH

ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES VOLUME I

Anna C. Mastroianni, Ruth Faden, and Daniel Federman, *Editors*

Committee on the Ethical and Legal Issues Relating to the
Inclusion of Women in Clinical Studies
Division of Health Sciences Policy
INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C. 1994

Executive Summary

There is a general perception that biomedical research has not given the same attention to the health problems of women that it has given to those of men, and that women may not have benefited from advances in medical diagnosis and therapy because of their lower rates of participation in clinical studies. These perceived inequities have recently become the focus of public attention and legislative action, as women's health advocates and others challenge the content of the national research agenda. Recent policy responses to these perceptions present very real challenges to Institutional Review Boards (IRBs) and investigators, in no small part because their requirements appear to constrain the independence of the scientific community.

At the request of the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), the Institute of Medicine established a Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies. It is within the context of public doubt about the equitable involvement of women and racial and ethnic groups in clinical research, skepticism about the methods and motives of investigators, and legislation enacted that attempts to address these concerns, that the committee executed its charge.

The committee was asked to examine the ethical and legal implications of policies that seek broader inclusion of women in clinical studies, including pregnant women and women of childbearing potential. In its analysis, the committee was asked to pay particular attention to the participation of

women in drug trials and the legal liabilities resulting from injuries to research subjects. The charge did not include a review of the state of scientific knowledge about gender differences, but the committee found that a basic understanding of the subject was necessary to its deliberations.

WOMEN'S PARTICIPATION IN CLINICAL STUDIES

The current concern about women's participation in clinical studies arises from the conflict of two public policy positions: protectionism and access. Emphasis on the need to protect research subjects burgeoned in the 1950s and 1960s in response to revelations of abuses of the research process. This emphasis was reinforced by the discovery of adverse outcomes in the children of women who had taken certain drugs during pregnancy. In the mid-1970s, legislation was passed that was designed to protect research subjects from unethical treatment. The regulations and guidelines stemming from this legislation also were designed to protect against fetal injury in their restrictions on the inclusion of pregnant women and women of childbearing potential in drug trials.

In recent years, guidelines and regulations put in place to protect research subjects have been challenged by claims that they are overprotective and overly exclusive, and therefore detrimental to the health of the very persons they were intended to protect. This shift in perspective developed in the early and mid-1980s, when women's health groups and Acquired Immune Deficiency Syndrome (AIDS) activists drew attention to inequities in the health research agenda and the exclusion of women and other groups from research studies. Since then, there has been a call for greater access to health care research for women, as well as members of diverse racial and ethnic groups. The shift in emphasis from protectionism to access gained momentum in 1990 with the release of a General Accounting Office (GAO) report that found that NIH had failed to fully implement its 1986 policy of greater inclusion of women in clinical studies, and that women were indeed "underrepresented" in some clinical studies. The report lent credence to the claims that women's health needs were not being adequately addressed and has stimulated legislative efforts to correct the imbalance.

The National Institutes of Health Revitalization Act, passed on June 10, 1993, represents one such effort. The Act includes several provisions relating to clinical studies, one of which has stirred considerable controversy. This much-debated provision requires that each NIH-funded study include representative samples of subpopulations (particularly women and members of diverse racial and ethnic groups) unless their exclusion is justified; notably, cost is not a justifiable criterion for exclusion. The Act is clearly intended to promote justice in clinical research by changing the prevailing assumption of exclusion to one of inclusion, a move strongly supported by many in the research community and by the members of this committee. On

the other hand, many—this committee included—have expressed concern that if the act is too rigidly interpreted, it will make costly and unreasonable demands on the scientific research process and impede the implementation of its noble goal.

Before attempting to delineate how the goal of the NIH Revitalization Act might be more effectively achieved, the committee believed it was important to ascertain the current level of women's participation in clinical studies. Are women "underrepresented" in clinical studies, as many have claimed? Like others who had tried to assess women's participation in the whole of clinical research, the committee was frustrated by the lack of any systematic, centralized collection of data on the gender composition of study populations. Although the ORWH has begun such a collection at NIH, the results are not yet available. As an alternative approach, the committee undertook its own data collection and review of the published literature. The committee found the available data inadequate for determining whether women have participated in the whole of clinical studies to the same extent as men, and whether women have been disadvantaged by policies regarding their participation or a failure to focus on their health interests in the conduct of research. The literature detailing past research on heart disease and AIDS does, however, provide some evidence of gender inequity in these areas of study.

The committee can conclude from its survey that there are many unanswered questions about gender-based differences in response to treatment, and that, in general, investigators have not done one or more of the following: reported the results of gender analyses, performed gender analyses of study results, or recruited adequate numbers of women to support the kind of subgroup analysis that would be needed to resolve these questions.

That the committee was unable to draw conclusions about women's participation in clinical research as a whole from available data underscores the need for systematized collection of information. The NIH Revitalization Act's mandate that ORWH create a registry focused solely on women's health and the collection of women's health data is too narrow—without information on men's health issues and men's levels of participation in such studies, monitoring of the relative levels of participation in the future will be difficult and open to bias.

The committee supports the efforts of NIH to establish a registry of clinical studies and recommends that such a registry include information on the participation of women and men and on the racial and ethnic composition of participants in such studies, as well as the research questions addressed, that such information be reasonably accessible to investigators and the public, and that the scope of the studies included in the registry be comprehensive.

The committee views this registry as a potentially valuable resource in the development of national research agendas, preparation of reports to Congress, preparation of grant requests by investigators, recruitment of study participants, and development of cooperative efforts among institutes and other study sponsors, including multicenter studies. Such a registry would facilitate the development of the NIH research agenda. Another purpose might be to provide data for reporting to Congress on implementation of the legislative mandate to include women and racial and ethnic groups in clinical studies.

A comprehensive scope is vital to achieving the above purposes and avoiding the potential waste of limited research dollars on duplicative research. At a minimum, the registry should include ongoing studies as well as published studies.

The committee recommends that NIH work with other federal agencies and departments that conduct clinical research to ensure reporting of all federally funded clinical studies. The committee further recommends that representatives of NIH initiate discussions with FDA concerning the feasibility of including privately funded studies in such a registry.

The kinds of information to be included and reported to the registry should be uniform. In addition to gender composition of the study population, the registry might include an abstract of the study, the investigator name, and other study population characteristics, such as age and racial and ethnic identification. In implementing such a registry, NIH should consider the costs, reporting pathways, accessibility of information, enforceability of reporting requirements, and quality control. NIH should also consider and take precautions against problems that might be posed by such a registry, particularly with private industry involvement, including considerations of confidentiality, insurance reimbursement implications, endorsement of studies through inclusion in registry, access to non-peer-reviewed studies, administrative burden, and cost considerations.

JUSTICE IN CLINICAL STUDIES: GUIDING PRINCIPLES

Concerns about justice in the conduct of biomedical research involving human subjects received little attention until the publication in 1978 of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research's *Belmont Report.* This report outlined three ethical principles that should govern research: respect for persons, beneficence, and justice. With an understanding that calls to rectify women's alleged "underrepresentation" in clinical studies are based on concerns about un

equal distribution of the benefits of biomedical research, the committee chose to form its analysis around principles of justice. Justice is not served when the nation's research agenda ignores important questions regarding the health of one gender when one gender does not participate in clinical studies, and when one gender is treated with interventions that have not been adequately tested in that gender. Based on these observations, the committee recommends three general principles of justice with regard to questions of gender in the conduct of clinical research:

1. **The scientific community and the institutions that support it must ensure that scientific advances in medicine and public health fairly benefit all people, regardless of gender, race, ethnicity, or age. Therefore, the national research agenda must ensure that medical research promotes the health and well-being of both women and men.**
2. **Where it is established that specific health interests of women, men, or other groups have not received a fair allocation of research attention or resources, justice may require a policy of preferential treatment toward these specific areas in order to remedy a past injustice and to avoid perpetuating that injustice.**
3. **Volunteers for clinical studies should be offered the opportunity to participate without regard to gender, race, ethnicity, or age. Women and men should be enrolled as participants in clinical studies in a manner that ensures that research yields scientifically generalizable results applicable to both genders.**

SCIENTIFIC CONSIDERATIONS

There is a general belief among clinical researchers that, in most situations, women and men will *not* differ significantly in their response to treatment. The evidence to support this belief is not easily assembled, however, and there are countervailing concerns that gender differences have been insufficiently studied. Some of the known gender differences in response to treatments are related to physiological differences between the genders. Important examples include hormonal differences, particularly the variation in drug response by women during different stages of the menstrual cycle, the physiological changes that accompany pregnancy and lactation (conditions that carry the additional concern of the effect of drugs on the fetus and nursing infant), and pharmacokinetic effects such as differential rates of drug absorption and excretion. Hormonal contraceptives and

hormone replacement therapy in menopause may also have their own effects on the natural course of disease as well as on diagnosis and treatment interventions. Other differences are psychosocial in origin or are mediated by tendencies of men and women to act differently with respect to health care.

These true gender differences (and differences associated with gender, e.g., weight) have implications for the design of clinical trials, the subset of clinical studies that provides the most rigorous and reliable test of the effectiveness and safety of new drugs and treatment interventions. For example, greater heterogeneity among research subjects may permit the investigator to spot trends that might otherwise be missed, even if the numbers are too small for statistically reliable subgroup analysis. At the same time, greater homogeneity among research subjects reduces unexplained variance.

The committee has focused particularly on treatment trials in reaching its conclusions. The committee finds that the weight of scientific evidence, as well as practical considerations, supports the inclusion of both gendersand indeed all kinds of demographic subgroups—wherever possible. The most compelling scientific reasons for exclusion are found in investigations of diseases, conditions, or risk factors (including behavior) that are highly concentrated in a single gender. Some would argue that excluding women is justified in a study where there is no anticipated difference in how women and men respond to a treatment but where the disease is less common among women. These arguments rest on a false assumption that women's presence diminishes homogeneity and thereby lessens the ability to observe the main effect of the treatment (i.e., whether the treatment is effective for any subject). Person-years of follow-up are person-years of follow-up whether they are female or male years, *unless* the researchers have plausible hypotheses about gender differences in response. And if they *do* have convincing hypotheses about qualitative gender-specific differences, then this too argues for including both genders, but in sufficient numbers to test for gender-specific results.

This is not to say that there are no significant gender-specific diseases or treatment effects, nor does the committee mean to argue that sufficient attention has been paid to the possibility of gender-specific differences. The committee supports the need to examine these issues systematically where they are based on well-grounded scientific hypotheses, and we support attempts to encourage scientists and clinicians to consider and pursue such gender-related hypotheses. The committee acknowledges, however, that most treatments and most diseases do *not* differ significantly by gender. This observation reinforces rather than reduces the justification for a principle of inclusion: if indeed most treatment effects in the setting of treatment trials do not differ by gender, then it is reasonable for treatment trials to include both genders.

In general, the committee's findings are compatible with the goals of NIH's legislative mandate for greater inclusion of women and racial and ethnic groups in clinical studies, albeit with certain important exceptions. When there are no anticipated treatment effects by gender, however, a policy that requires scientists to include sufficient representation of both genders to permit subgroup analyses would require, at a minimum, that clinical studies significantly increase their size (to detect the main effect in each group) and proportionately increase their expenses. In an era of concern about the nation's resources, and about expenditures on health in particular, it is argued that a study-by-study application of this requirement makes for both questionable policy and questionable science. When no subgroup differences are anticipated, *requiring* scientists to enroll sufficient numbers to ensure the statistical power to detect unsuspected differences would produce little additional information at a greatly increased cost. Instead of this blanket requirement, the committee recommends a continuing review of the evidence on gender-specific effects and greater attentiveness to questions of gender at every level of the research process, from the design of individual studies to the setting of the national research agenda.

The committee recommends that NIH commission a study to identify known gender differences in drug response.

The committee recommends that investigators be attentive to factors associated with possible gender differences in drug response and design their studies accordingly. Further, NIH should commission a study that will assist investigators in their effort to detect such differences.

The committee recommends that in the design of studies investigators avoid exclusions based on demographic characteristics.

The committee recommends that investigators proposing research involving human subjects provide a reasonable review of the evidence and plausibility of gender-specific effects relevant to their research, and that studies be required to be designed with sufficient power to detect subgroup differences only when such a review indicates that such a design is warranted. When there is no information concerning possible gender differences, however, the investigator should, when feasible, include both genders in sufficient number to detect differences.

Strategies other than clinical trials, (e.g., surveillance techniques) are available to help devise hypotheses about the differential response of men and women

to medical interventions. These strategies may be significantly less costly than large-scale clinical trials that include sufficient numbers of men and women to detect gender differences in response.

The committee recommends that NIH assist investigators in this effort by: (1) identifying, developing, and disseminating alternative methods for detecting or formulating hypotheses about gender differences and (2) providing guidance for the use of these methods by investigators, initial review groups, and study sections.

SOCIAL AND ETHICAL CONSIDERATIONS

Clinical research is both shaped and constrained by the social and ethical context in which it takes place. While federal research regulations clearly delineate the ethical boundaries of research involving humans subjects, more subtle social influences—notably, biases—also play a role in determining the diseases and populations that are studied. In a society such as ours, composed of people of different races, ethnicities, and economic backgrounds, both unconscious and conscious biases may render those of lesser status "invisible" (or unimportant) to those of greater power and status. Accordingly, the health interests of persons of lower social status may not receive attention equal to that of the health interests of others. These biases may also operate with respect to gender, where women and their concerns have traditionally been assigned lower status. Two forms of unconscious gender bias have particular relevance for the design and conduct of clinical studies: *male bias* (observer error caused by adopting a male perspective and habit of thought) and the *male norm* (the tendency to use males as the standard and to see females as deviant or problematic, even in studying diseases that affect both sexes). Both have been thought to contribute to a predominant focus on men's health problems and on men as research participants.

Within the scientific community, there is no consensus concerning whether scientific objectivity can be achieved. Some scientists believe that the research process cannot easily be disentangled from the social world within which it is conducted. Societies stratified by gender, race, ethnicity, and socioeconomic status provide different "lenses" through which to see and understand social and scientific reality. These unconscious biases may permeate the entire scientific research process, influencing the research topics selected, the definition and operationalization of concepts examined, the study design, the method of data collection employed, and the research participants chosen for inclusion. Furthermore, such unconscious assumptions contribute to the view that men's physical makeup and experiences are the standard by which to measure and compare women's; to the extent that women's experiences differ from the established male norm, they may be

categorized as deviant. These biases impede the progress of the scientific enterprise and produce findings that are not valid for large segments of the population.

The committee recommends that NIH and IRBs engage in educational efforts that will ensure that investigators are aware of such gender biases and that studies are equitably conceived and designed with respect to gender.

One way to reduce the influence of such gender biases may be to have a greater number of women scientists active in the research enterprise, through, for example, identification and removal of any institutional barriers to their increased participation. The perspectives they bring to bear may differ markedly from those of their male colleagues, thus aiding in the dissolution of unwarranted and inaccurate assumptions about women in the research enterprise.

The committee recommends that NIH continue its efforts to encourage women of all racial and ethnic groups to become scientific researchers and to assume positions of authority within the scientific hierarchy.

Gender is not the only variable that science has been charged with ignoring. There are other important differences among groups—such as race, ethnicity, socioeconomic status—that are capable of affecting health and illness. The lack of attention to or inadequate conceptualization and measurement of these variables in clinical studies has resulted in findings that are inapplicable to particular racial, ethnic, and socioeconomic groups. For example, in order to accurately determine the effects of race on health and treatment outcomes, it is important to clearly distinguish the biological and sociological components of race. Standard methods of data collection may be inappropriate to certain cultural groups and may need to be modified to ensure that the information obtained is valid and for the risk-benefit ratio to be acceptable. Thus, studies must be planned, designed, and executed to produce valid and generalizable results to the populations under investigation. Investigators and IRBs should utilize the expertise of scholars with experience in studying these populations to avoid the weaknesses evidenced in earlier research.

The history of government-sponsored health research and health care efforts in racial, ethnic, and socioeconomic groups has not been unblemished—past unethical treatment has led individuals from these groups to be wary of participation in current studies. Because of the requirements of the NIH Revitalization Act of 1993, researchers now stand to gain or lose support in accordance with their success in recruiting and retaining participants

from these same groups, the federal mandate has the potential effect of exacerbating past problems of exploitation. Knowledge of the history of health research in relevant racial or ethnic groups and an awareness of the cultural and political frames of reference employed by the members of these groups will enable researchers to avoid perpetuating the problems.

Informed consent is the primary mechanism for protecting subjects from unethical treatment. NIH, IRBs, and investigators must work together to tailor the consent process so that it will be effective for every group that participates in clinical studies. This entails, for example, both understanding and avoiding what might constitute excessive inducement (monetary or otherwise) for members of a group. If the benefits of research are to accrue to all groups equally, then proper study design and fully informed consent are critical elements to the achievement of that end. Collaboration among clinical investigators, IRBs, and those with research expertise in these groups (e.g., social scientists) would facilitate the design of clinical studies that are socially, as well as scientifically, valid and ethically acceptable.

The committee recommends that NIH commission a study of attitudinal and institutional barriers to participation in research among women, racial and ethnic groups, and the poor.

The committee recommends that NIH train initial review groups (IRGs), technical evaluation groups (TEGs) and investigators in recruitment and retention issues; part of this training should emphasize methodological and ethical issues in conducting research with women of diverse racial and ethnic groups and poor women.

The committee recommends that investigators tailor study designs and recruitment and retention efforts to the specific populations to be included in the study. Investigators must consider the relevance of race, ethnicity, socioeconomic status, and other subgroup variables to their study and develop appropriate definitions, methods, and measurements, to ensure the validity of their research efforts among these groups.

The committee recommends that in designing recruitment and consent procedures, investigators be cognizant of concerns and needs of communities that have a history of exploitation or abuse in previous clinical studies. Investigators also must ensure that such information be presented and carefully explained, orally and/or in writing, in the potential participant's preferred language.

LEGAL CONSIDERATIONS

Health-related research and development in the United States is supported by the federal government (predominantly through the National Institutes of Health [NIH]), the pharmaceutical industry, and private foundations. This institutional structure can affect the conduct of research because it is the source not only of funding, but also of procedures for reviewing the ethics of scientific research—including whether a proposed plan for selecting research participants is just—and of the legal requirements applicable to research.

Current federal policies—in the form of statutes, regulations, and agency guidelines and memoranda—affect the achievement of equity in clinical studies. These policies govern research funded, conducted, or otherwise regulated by the federal government, its agencies, and departments. The policies vary: some appear to promote inclusion of both genders, others refer to inclusion of women and racial and ethnic groups, and others specify conditions applicable to women of childbearing potential and pregnant women. Application of a particular policy may depend on funding origin, type of research, condition studied, or fertility status of the proposed study participant. Particularly in the area of drug development, clinical studies receiving federal funding or performed at institutions supported by federal funding may be subject to a number of policies prior to a drug's entrance into the market. The many recent changes in relevant federal policies promote inclusion, rather than exclusion. As a result, policies have become more congruent. Consistency and, where possible, congruence among these policies is important to promote compliance and prevent confusion.

The committee recommends that NIH work closely with the FDA and with other Public Health Service (PHS) agencies to make regulations and policies on inclusion of women and racial and ethnic groups consistent with one another and, wherever possible, to make them congruent.

If the policies of federal agencies are harmonized, there will still remain the task of educating the research community concerning what is required, and motivating that community to comply. Enunciation of sound and congruent policies, in conjunction with a comprehensive educational program, will ensure that policies and the rationales for the policies are properly understood by the research community.

The committee recommends that NIH, in cooperation with FDA, should institute a comprehensive education program directed at in

vestigators, institutions, and IRBs on policies concerning the inclusion of women and racial and ethnic groups in clinical studies.

The policies and activities of federal agencies are subject to constitutional challenge and review. It is unclear whether research policies that *constrain* the involvement of women in government-sponsored or government regulated research could be held to violate constitutional standards of liberty and equality. Such challenges could possibly be based in principles of decisional privacy and equal protection derived from the Fourteenth Amendment. For example, the Fourteenth Amendment's protection of "life, liberty, and property" has been interpreted to provide decisional privacy with respect to terminating life-sustaining treatment and obtaining an abortion. It remains to be seen, however, how this protection could be read to imply a right to assume the risk of taking an experimental drug. Similarly, the Fourteenth Amendment guarantees all citizens "equal protection of the laws," which the Supreme Court has interpreted as prohibiting the government from treating similar individuals and groups differently. Research policies that result in the exclusion of women as a class might be found to contradict the equal protection clause unless a court found the justification for such exclusion to be adequate.

Both individuals and organizations involved in the conduct of research must deal with another set of legal considerations—liability. Fear of potential legal liability has been cited as one of the reasons that women of childbearing age and pregnant women have traditionally been excluded from clinical trials of drugs. The focus of liability concerns is on possible injury to potential offspring. Although recent evidence may indicate that exposure of a father to some chemicals may cause harm to a developing fetus, the focus has overwhelmingly been on the potential for harm to offspring resulting from the mother's exposure either before or after conception.

More recently, pharmaceutical companies have begun to recognize that they could also be liable for *not* including women in clinical research. For example, a pharmaceutical company may be liable if a drug that has never been tested in women is nevertheless marketed for use by both genders and prescribed for a woman who then suffers an adverse reaction. Similar approaches to liability could be used as well where men, or subpopulations of women or men, were not included in a study population but suffered an injury. This creates a paradox for clinical trial sponsors whose efforts to exclude women in order to protect themselves from liability may actually risk liability for exclusion.

The committee concluded that it is impossible to quantify the risk of tort liability from the inclusion of women in clinical studies at this time, because: (1) there is no complete compendium of *unreported* cases involving settlements and (2) pregnant women and women of childbearing age

have not been included in some major studies in the past. But, difficulties of prediction are compounded even more because tort law is governed by the individual states, with many variations on issues such as whether a woman's informed consent will serve to bar an independent action by a child injured as a fetus during such research. Analysis of existing legal rules and principles seems to indicate that the likelihood of successful damage actions is limited. Nevertheless, broadening the research population to include those groups previously excluded may also generate additional legal actions that will test existing legal doctrine.

Although there is a general lack of case law on liability for injuries to research participants, there is some precedent for liability for exclusion from research. The case law suggests that if a drug was found to cause injuries to women, and yet women had been excluded from clinical trials of the drug, the sponsor might be held liable for failing to test the drug in women. For some drugs, however, the potential for teratogenic or mutagenic effects is low or the negative effects are manifested after a long latent period. For these drugs, even adequate testing in all relevant populations unfortunately may not reveal their potential to cause harm.

The committee recognizes that, regardless of their basis or justification, fears about liability are real. On balance, however, the committee concludes that liability concerns should not represent an impediment to implementation of public policies that favor the broader inclusion of women in clinical studies.

A special set of concerns in the research area stems from the differing bases for liability according to which party is a defendant. A pharmaceutical company, for example, might be sued on the basis of strict liability, while a researcher ordinarily would be sued only on the basis of negligence in the informed consent process. With regard to the latter, the new federal policies calling for inclusion of women in clinical studies will help establish new standards that will be relevant to legal actions.

Many of the concerns voiced about liability in the context of research including women are the same as those with regard to the tort system in general. For example, expert scientific testimony is necessary to establish that a particular drug caused an injury. There are inherent difficulties in assuring the unbiased nature of such testimony in what are often highly technical cases.

The committee recommends that current and future initiatives toward general tort reform include attention to issues of research-related injury, including issues of proof of causation.

The question of whether there should be a special compensation scheme for injuries sustained by children as a result of a parent's participation in a

clinical study is similar to that raised in the context of research subjects in general. Because of the difficulty in quantifying the risk of liability, the committee does not recommend adoption—at this time—of a special compensation scheme limited to coverage of children injured prenatally or preconceptually. Any new compensation scheme focusing only on such injuries poses especially difficult problems with regard to establishing causation and averting large numbers of questionable recoveries.

The committee recommends that NIH thoroughly review the area of compensation for research injury in general and that consideration of implementation of any compensation scheme include attention to prenatal and preconceptual injuries to children resulting from a parent's participation in a clinical study.

Our current health care reimbursement system does not include coverage for medical care resulting from injuries sustained during research. This could be accomplished through a system of universal access with adequate coverage.

The committee recommends that health care reform efforts include considerations of medical care for research-related injury.

RISKS TO REPRODUCTION AND OFFSPRING

Historically, concern for the risks of new drugs has focused on women of reproductive potential, including pregnant and lactating women, but risks to the male reproductive system also may merit attention. Men and women of reproductive age get sick and take medications, and drugs intended for use by this population should therefore be tested in this population. Some of these drugs, however, have potential risks to reproduction or for the development of offspring. These risks give added importance to informed consent and contraceptive options. Risk assessment for reproductive and developmental toxicity may be complicated by the high background rates of infertility and birth defects, as well as the difficulty of identifying the specific effects of the drug under investigation. Techniques, such as animal studies, in vitro analysis, as well as surveillance for developmental effects, among others, can provide some information on potential hazards to humans. Laboratory animals and humans can differ in toxicokinetics, however, and the use of data from animals to determine health risks in humans must be assessed carefully.

Investigators should take these reproductive and developmental risks into consideration in the design and conduct of clinical trials. If men and women of reproductive potential are included in a trial in which they will be ex

posed to a potential reproductive or developmental toxicant, the potential risks must be characterized as accurately as possible so they can make an informed decision about whether or not to participate. If they decide to participate, they also may wish to consider measures to prevent pregnancy. Information about toxicity risk can help participants determine the likelihood that the baseline incidence of adverse pregnancy outcomes will have been increased by study participation, should a pregnancy occur during the trial. When the study involves lactating women, the exposure and impact of the agent on the nursing infant also should be discussed.

The committee recommends that investigators and IRBs not exclude persons of reproductive age from participation in clinical studies. In the case of women of reproductive age, the potential or prospect of becoming pregnant during the study may not be used as a justification for precluding or limiting participation. Risks to the reproductive system should be considered in the same manner as risks to other organ systems. Risks to possible offspring of both men and women who are not pregnant or lactating should not be considered in the risk-benefit calculation. It is the responsibility of investigators and IRBs to assure that the informed consent process includes an adequate discussion of risks to reproduction and potential offspring, including, where appropriate, an adequate discussion of relevant considerations of birth control.

The committee recommends that the participant be permitted to select voluntarily the contraceptive method of his or her choice where there are no relevant study-dependent, scientific reasons for excluding certain contraceptives (e.g., drug interaction).

The committee recommends that pregnancy termination options be discussed as part of the consent process in clinical studies that pose unknown or foreseeable risks to potential offspring.

The committee recommends that investigators and IRBs not exclude women who are lactating from participation in clinical studies. It is the responsibility of investigators and IRBs to ensure that the informed consent process includes, wherever appropriate, an advisory to potential participants that there may be special risks to their children if nursing mothers participate. No nursing mother should be permitted to agree to participate without first receiving additional information about these special risks.

The inclusion of pregnant women in clinical studies, creates new con

cerns and risks, but the lack of proven safe treatment options for ill pregnant women carries its own set of concerns and risks. The committee believes that it is important to encourage clinical research to advance the medical management of pregnant women who are or may become ill.

The committee recommends that NIH strongly encourage and facilitate clinical research to advance the medical management of preexisting medical conditions in women who become pregnant (e.g., lupus), medical conditions of pregnancy (e.g., gestational diabetes) and, conditions that threaten the successful course of pregnancy (e.g., preterm labor).

Clinical trials (as well as other studies) have limited power to detect some adverse effects due to the relatively small numbers of subjects included in research compared with the number of persons who eventually may use the drug under study. Adverse effects may not become evident until the drug is in widespread use. Therefore, systematic surveillance for developmental effects is essential to any plan to include pregnant women in clinical research. Together, both methods will further our understanding of the medical management of the ill pregnant woman.

The committee recommends that a review be undertaken of existing birth defects monitoring programs to critically define what they are capable of doing and suggest improvements and reasonable expectations for their use.

In the context of encouraging clinical research to advance the medical management of pregnant women who are or may become ill, the committee reviewed the current Department of Health and Human Services (DHHS) regulations concerning the involvement of pregnant women as research subjects. The committee's review of current DHHS regulations was limited to situations in which the pregnant woman is the subject of the research. It did *not* include situations involving fetal research (currently covered by the same regulation) since this topic was outside of the committee's charge.

The DHHS regulations begin with a presumption of exclusion—that is, "no pregnant woman may be a research subject" except under certain conditions; the regulations also classify pregnant women as a "vulnerable population" deserving of special protection. In this context, "vulnerable" suggests that pregnant women are less autonomous or more easily exploited, by virtue of their pregnancy, than other persons—an inference that the committee has found no evidence to support. Removal of pregnant women from the regulatory category of "vulnerable" potential subjects would avoid any such inference.

The committee was unanimous in the view that pregnant women should be presumed to be eligible for participation in clinical studies. The committee also unanimously endorsed the importance of recognizing in public policy as well as in the deliberations of IRBs and investigators, that pregnant women should be treated as competent adults capable of making their own decisions about participation in research.

The committee recommends that pregnant women be presumed to be eligible for participation in clinical studies. It is the responsibility of investigators and IRBs to ensure that pregnant women are provided with adequate information about the risks and benefits to themselves, their pregnancies and their potential offspring. Even when evidence concerning risks is unknown or ambiguous, the decision about acceptability of risk to the pregnancy or to offspring should be made by the woman as part of the informed consent process.

It is critical to note that the committee *is not* advocating active recruitment of pregnant women into each and every clinical study. Rather, it is urging that the prevailing presumption regarding the participation of pregnant women in clinical trials and other intervention studies be shifted from one of *exclusion* to one of *inclusion.* The committee believes that a strengthened informed consent process can address specific concerns regarding the inclusion of pregnant women in clinical studies. This process should include a special disclosure statement detailing in lay language what is known about the risks and benefits of participation. The statement should be reviewed carefully with the pregnant woman and she should be encouraged to consult with her obstetrical care provider as well as with the potential baby's father. Only after the woman demonstrates an adequate understanding of the risks and benefits of participation should consent be solicited. It should be noted that the committee rejects any requirement that the consent of the potential baby's father be a condition of the participation of a pregnant woman in research.

The committee recognizes that, as in all clinical studies, there may be scientifically and medically valid reasons for excluding pregnant women from a particular study. A pregnant woman would be excluded if the medical condition of pregnancy disqualifies her as a subject in the same sense that anyone else, pregnant or nonpregnant, would be disqualified based on medical conditions that would interfere scientifically with the study. For example, a pregnant woman would be excluded from a study of hormone replacement or contraception.

Recording by the IRB in writing of both its reasons for permitting any exception to the general presumption of inclusion of pregnant women and

frequency with which it grants such exceptions would help the IRBs to implement properly any exceptions to the presumption. There was considerable discussion within the committee about whether there are any exceptional instances in which IRBs can be given the discretion to exclude pregnant women from participation for other than scientific reasons. *Most* committee members ultimately endorsed the following recommendation:

Investigators and IRBs may exclude pregnant women from participation only when the IRB finds, and records its finding in writing, that the following standard has been met: (1) there is no prospect of medical benefit to the pregnant woman, and (2) a risk of significant harm to potential offspring is known or can be plausibly inferred.

A finding that a risk of significant harm to potential offspring is "known or can be plausibly inferred" may be based on evidence from animal studies, in vitro studies, structure-activity relationship data, or previous clinical experience. Under the above standard, IRBs may exclude pregnant women from the earliest phases of many drug trials, but most clinical studies would remain open to pregnant women.

A few members of the committee, however, were not able to endorse the above standard. They wished to reserve for the IRB the discretion to exclude pregnant women from participation not only when there is no prospect of medical benefit to the women but also when there is the potential for benefit to them that could be characterized as minimal or insignificant.

The committee also struggled with how to accommodate within its support for the shift of the presumption to *inclusion* of pregnant women (from that of exclusion) a role for conscience and an individual investigator's moral commitments. It was agreed that, at a minimum, such a mechanism would require that the investigator provide the IRB with a written explanation of his or her concerns of conscience and that the IRB review any such requests in light of a presumption that favors the inclusion of pregnant women in clinical studies. It is because of the potential for abuse of a "conscience" exemption that the committee could not resolve whether or under what conditions such an exemption should be constructed.

At least a technical amendment to Subpart A, sec. 46.111(a)(3), eliminating the reference to pregnant women as a "vulnerable population" will be required by the recommended revision to Subpart B.

The committee recommends that OPRR revise and reissue subpart B of the DHHS regulations for the Protection of Human Subjects, titled "Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human

In vitro Fertilization [45 C.F.R. 46, subpart B] in accordance with the committee's recommendation.

IMPLEMENTATION

Policies requiring the inclusion of women and racial and ethnic groups in clinical studies are already in place. The present emphasis placed by NIH on the recruitment of diverse population groups into clinical research is a strong initial step in the pursuit of equity in clinical studies. Where earlier versions of the current NIH policy on inclusion of women in clinical studies simply encouraged investigators to include women in study populations, more recent policy statements require that "clear and compelling" rationales be given for the exclusion of women from proposed research. The challenge for those involved in clinical research is to achieve full implementation of these guidelines in a way that enhances the overall enterprise *and* deals with the various problems identified by this report. The committee believes that every level of the research structure must actively participate in the efforts to increase subgroup participation in clinical studies. However, the committee does not believe that the interests of justice in advancing the health of all people are best served by an exceptionless requirement that *every* clinical study be large enough to conduct valid analyses of every relevant subgroup comparison. As reflected in the committee's guiding principles 1 and 2 (see Chapter 3), the final burden for achieving justice falls on the national research agenda as a whole and cannot be implemented by a mechanical approach to the selection of subjects on a study-by-study basis.

The ultimate criteria for judging the success of a public policy to achieve justice and promote inclusion will be changes in research policy and clinical practice, and ultimately improvements in health status indicators, particularly in areas where unjustifiable disparities currently exist. Specific objectives include the following:

- Establish accountability for implementation at every level of the research enterprise, including levels well above that of the individual investigator;
- Provide the necessary database to shape adherence and identify gaps in knowledge;
- Establish a system for monitoring compliance with specific inclusion-based requirements and evaluating the extent to which fairness is being achieved;
- Use the preceding processes and data bases to educate, inform, and promote discussion among policy makers, bureaucrats, investigators, IRBs, IRGs, TEGs, and the general public.

The committee has attempted to frame its recommendations as actions that can be taken by all of the actors in the research process, some immediately and some in the longer term, to ensure the broad participation of women and other groups in clinical studies and to advance fairly the health of all persons. The committee strongly believes that tracking both the study populations' composition and topics of funded studies, and providing this information on a regular basis to all those involved in the research process, will in and of itself raise the level of awareness and activity concerning the issues of both study composition and attention to women's health concerns.

The Investigator

Immediate Actions

NIH already requires investigators to report the composition of study populations, which keeps investigators aware of the need to involve diverse populations. It is important that individual investigators be aware of both the state of the science and the state of clinical practice with respect to gender and other subgroup differences in their areas of research. **In designing studies, investigators should conduct literature reviews to determine (1) the extent to which an evidentiary base exists for suspecting gender-specific and subgroup effect, and (2) the extent to which women and other groups have served as participants in relevantly similar research.**

If there is a plausible basis for suspecting gender differences, investigators should make every effort to recruit sufficient participants of both genders to conduct analyses to detect these differences. In the absence of such an evidentiary base, investigators should recruit participants of both genders. Where sample size is large enough, investigators also should conduct analysis of gender differences in these studies. Investigators should strive to collect sufficient data on gender-related variables to permit a refined interpretation of any observed gender differences (e.g., potential confounders or mechanistic variables such as hormonal status of women, weight, and adiposity) and to reveal trends or suggest hypotheses.

As Soon as Feasible

Investigators should draw on the expertise available in the social science community to improve the ways in which the variables of gender, race, and ethnicity are conceptualized, operationalized and measured in their studies. Such collegial exchanges will enable investigators to tailor their study designs, recruitment and retention efforts, and informed

consent procedures to the study population selected, to avoid unwarranted exclusions of potential participants, and to be prepared to collect sufficient data on gender-related and subgroup variables to analyze for confounding effects.

Investigators clearly need broad-based support from the other actors within the research process in order to carry out their part of a comprehensive agenda. **The committee recommends that IRBs, IRGs, TEGs, scientific advisory councils, and NIH management become more directly involved with investigators in activities that promote development of more inclusive study designs.** Measures recommended by the committee, such as IRB review of protocols for study population composition and NIH provision of opportunities for investigator training and access to needed databases, facilitate investigator efforts to realize the goal of greater inclusion.

The IRB

Immediate Actions

As part of the IRBs' responsibility for ensuring the just selection of persons to be participants in research, IRBs should require investigators to provide the proposed gender, racial, and ethnic composition for each study, as well as information about the distribution of the condition under study in the population at large and the composition of subjects in previous relevant research. It is the IRBs' responsibility to make a determination that the composition of the proposed study is equitable.

As Soon as Feasible

IRBs, in concert with NIH, should engage in educational efforts that will ensure awareness among investigators of gender and racial and ethnic biases. Research organizations could draw upon the expertise of social scientists experienced in the conceptualization, operationalization, measurement, and analysis of variables relevant to these issues to assist investigators.

The committee believes that providing feedback to IRBs concerning the characteristics of the study populations and research topics it has approved will serve to raise the level of awareness of IRBs to issues of justice and inclusion. **The NIH Office of Protection from Research Risks (OPRR) should require IRBs to collect data on study population composition and research topics of all studies subject to IRB review.** OPRR could monitor study population composition through, for example, a representative sample of general assurance IRBs.

IRGs and TEGs

Immediate Actions

Once NIH policies for inclusion of gender, racial, and ethnic groups are finalized, it is anticipated that IRGs and TEGs will have significant responsibility for monitoring their implementation. As with any new policy, it is expected that in the initial stages of implementation guidance will be needed. **NIH should develop a mechanism for monitoring the actions taken by IRGs and TEGs in implementing policies for inclusion of gender, racial, and ethnic groups, and provide feedback to the IRGs and TEGs in order to ensure consistent and appropriate interpretation of these policies.** Among other tools for evaluation, NIH might consider taking a random sample of justifications for exclusions. Central review and evaluation can standardize the implementation of the policy, and it will correct both unnecessarily strict and overly lenient policy interpretations by the peer review system. It will also provide illustrative material for education of IRG and TEG members as recommended below.

As Soon as Feasible

Each IRG and TEG should recruit members with expertise in the area of gender, racial, and ethnic differences or persons sensitive to gender and racial and ethnic concerns. Furthermore, every member of IRGs and TEGs should receive training and education on evaluation of study population composition and gender, racial, and ethnic differences. The very presence of qualified males and females from different racial and ethnic backgrounds is one way of increasing the likelihood that the relevant questions and appropriate conceptualizations are considered by investigators. A rough measure of sensitivity could be based on professional activities, such as research agenda, participation in committees of professional associations, publications, and service at one's institution.

Scientific Advisory Councils

As Soon as Feasible

Mechanisms should be developed for ensuring that principles of justice are central considerations in the setting of the nation's research agenda. Because clinical research carries both benefits and burdens, justice requires that no one group—gender, racial, ethnic, or socioeconomic—receive disproportionate benefits or bear disproportionate burdens of research. For the overall biomedical research agenda to comply with the requirements

of justice, studies must not only include women as well as men, but also women and men from different age cohorts and different racial and ethnic groups. In addition, the health needs of all women and men should receive their fair share of research resources and attention. Scientific advisory councils have the ultimate responsibility for determining priorities in the research agenda for the subject matter area they cover. These decisions should move toward establishing equity in U.S. research efforts for all populations over time. Databases compiled by NIH can be used by scientific advisory councils in making decisions about research priorities within the available funding and in determining what areas require requests for proposals (RFPs) or requests for applications (RFAs) to improve the balance of research across diseases and subgroups. The heads of the councils should confer periodically to assess the application of principles of justice across research areas. In developing research priorities, these councils should give special consideration as to whether the health needs of pregnant women are being adequately addressed by their institutes.

NIH

Immediate Actions

NIH should maintain the current policy emphasis on the inclusion of women in NIH-supported clinical studies. NIH should continue the practice of identifying research concerns of various subgroups (gender, race, ethnicity, socioeconomic status) and offer RFAs and RFPs for such studies. **Where new requirements for subgroup analysis result in increases in study size and additional recruitment strategies, supplemental funds (e.g., from the NIH Office of Research on Women's Health) should be made available to meet these funding challenges.**

NIH should commission studies to determine the present state of scientific knowledge on gender, racial, and ethnic differences to help investigators determine where subgroup analysis would be likely to identify clinically significant differences. These efforts should culminate in the establishment of a database that includes such information as differences in disease incidence and prevalence, as well as relevant physiological and cultural differences in subgroups. Investigators would be able to consult this database in developing strategies to identify and detect gender, racial, and ethnic differences.

NIH should require that proposals for clinical studies include in their literature reviews the following: the extent to which an evidentiary base exists for suspecting gender or other subgroup differences relevant to the proposed research; the demographic characteristics of subjects in past similar research; groups for which the proposed study might have

s**pecial relevance; how the preceding information justifies the population selected for the proposed study; and how that choice will address gaps identified in the literature.** This requirement should be incorporated into the guidelines on the grant application (PHS 398 form).

NIH should widely disseminate to the scientific community methodological guidance on: (1) compliance with the legislative mandate regarding the inclusion of women and other subgroups in clinical research and (2) considerations for valid subgroup analysis.

As Soon as Feasible

NIH should pursue the current dialogue with Congress and the research community on the policy of inclusion and the commitment to justice. The objective is to develop mechanisms that merge public policy goals with scientific advice to promote legislation that is at once socially responsible, practical, and consistent with good science. Such action would extract the scientific community from a current dilemma: if NIH is strictly responsive to the law, clinical studies may become larger and more expensive in order to be in compliance, with no guarantee that this is either the most efficient or effective way to advance the health interests of women or other groups. If this results in an inability to fund an adequate range of biomedical research, it is likely that the health interests of all people will suffer, and thus justice will not be served.

As part of the registry of clinical studies it is currently evaluating, NIH should establish a database cross-referenced by: (1) categories of disease and physiological or psychological factors and (2) study population composition of ongoing and published studies. This database should be compiled in a way that ensures easy accessibility to the data included by subgroup classification. Reporting requirements for all studies should be comprehensive and uniform and at a minimum include: the research questions addressed and the gender, race, ethnicity, socioeconomic status, age, and hormonal status (i.e., pregnancy, stage of menstrual cycle) of the study population.

To facilitate the collection of data about inclusion and justice from non-federally supported research, NIH should encourage journal publishers to require presentation of data on demographic characteristics. Currently, there is no national norm that compels pharmaceutical manufacturers and other investigators to submit their data to a registry or other data repository.

NIH should assist investigators in the effort to detect gender differences by: (1) identifying, developing, and disseminating alternative methods for detecting or formulating hypotheses about gender differences and (2) providing guidance for the use of these methods by investigators, IRGs, and TEGs. The new legislative mandate makes it especially critical

that both investigators and review committees clearly understand the interrelationship of sample sizes and the power to draw statistically significant inferences about differences between subgroups. A proactive strategy of development and dissemination would help investigators in complying with regulations. It would also help to prevent the introduction into the literature of analyses based on insufficient data—analyses that could ultimately do a disservice to subgroups by fostering seemingly valid but erroneous conclusions.

and religious norms may also affect some subjects' willingness to use certain forms of contraception. Awareness of these subgroup differences has important implications for both recruitment and informed consent procedures; investigators may wish to modify protocols according to the demographic characteristics of the population to be studied.

Evaluating Drugs for Use in Lactating Women

Investigators must be especially concerned about developmental toxicity when testing drugs in the subset of the population of reproductive age that is composed of lactating women. Exposure to drugs and chemicals can lead to the presence of these agents in their breast milk, creating concern for: (1) exposure of the infant to the agent and (2) impact of the agent on the quantity and quality of breast milk. Partly as a result of these concerns, lactating women are rarely recruited into trials of new drugs. Therefore, when lactating women require treatment for a medical condition such as pain, infection, depression, constipation, or vitamin deficiency, they often must take medications that have not been systematically evaluated in lactating women. To avoid risk by ceasing lactation during treatment is in many cases not advisable, considering lactation's important benefits (e.g., maternal-infant bonding; transmission to the infant of antibacterial and antiviral substances; enhanced nutrition, growth, and development of the infant).

Factors influencing the presence and amount of a drug in breast milk include maternal and mammary physiology and pharmacokinetics, chemical properties (e.g., lipid solubility, and protein binding), and infant feeding characteristics (frequency, duration, and amount). The impact, if any, of a drug on the child will depend on the amount of drug ingested, the pharmacokinetics of the drug (absorption, distribution, metabolism, and elimination), and the mechanism of action and toxicity of the drug. Not all drugs on the market have been fully characterized for their presence in breast milk and effect on the nursing infant, but some data are available to guide the practitioner; most drugs are compatible with breastfeeding (Briggs et al., 1986). Less well studied is the impact of drugs on milk production. Drugs suspected to alter milk production include dopaminergic agents, estrogencontaining oral contraceptives and other estrogens, antiestrogens, nicotine, prostaglandins, and the thiazide diuretics.

Investigators designing clinical studies in which lactating women may be recruited should carefully advise these women of the risks to the nursing child, including those of or cessation of lactation. Where possible, efforts should be made to characterize risks to the nursing infant based on known pharmacologic and toxicologic properties of an agent in other populations.

Evaluating Drugs for Use in Pregnant Women

Studies have shown that an average of 3.8 medications are used during each pregnancy (Heinonen et al., 1983) and that 75 percent of pregnant women use between 3 and 10 drugs while they are pregnant (Quirk, 1986). Medications used most commonly during pregnancy include analgesics, antipyretics, antimicrobials, antiemetics, diuretics, cough medications, and psychoactive agents (Quirk, 1986). Yet despite their frequent need for medical treatment, few clinical trials of new drugs include pregnant women. Thus, the initial use of treatments in pregnant women often involves therapies developed in men (and women) who are physiologically different (see Chapter 4).

For clinical conditions that are sufficiently common, controlled trials may be conducted in pregnant women several years after a drug has been put on the market (and several years after pregnant women have been taking the drug on what amounts to an experimental basis). This was true for antihypertensive medications, a number of which were only recently tested in controlled trials for use in pregnancy-induced hypertension. It is not uncommon for physicians to prescribe drugs for pregnant women on the basis of substantial anecdotal information about such use, but reliance on information is risky given the number of cases necessary to identify an association between a drug and an adverse effect.

The testing of therapies in pregnant women often depends on the initiative of independent investigators rather than on the marketing intentions of pharmaceutical manufacturers. It is unusual for a drug to be brought to market for the express purpose of treating pregnancy conditions or pregnant women. An exception is ritodrine, an agent used to treat preterm labor, and which has been marketed expressly for this indication. Ironically, many practitioners use terbutaline or magnesium sulfate to stop preterm labor, although they have not received FDA indications for this purpose. In general, the indications for use restrict the way the drug can be marketed but not how a physician uses the drug. These agents and others (e.g., indomethacin, sulindac, nifedipine) have been tested in controlled trials of preterm labor, although these trials were not part of the drug development efforts for these compounds.

The committee recommends that NIH strongly encourage and facilitate clinical research to advance the medical management of preexisting medical conditions in women who become pregnant (e.g., lupus), medical conditions of pregnancy (e.g., gestational diabetes) and, conditions that threaten the successful course of pregnancy (e.g., preterm labor).

While the inclusion of pregnant women in clinical studies introduces new complications and risks, the dearth of proven-safe treatment options for ill pregnant women carries its own set of complications and risks. If a drug is going to be used in pregnant women, then the availability of safety and effectiveness information applicable to that population is critical. Reliance upon adverse event reporting by clinicians is not in and of itself a sufficient basis upon which to assess the safety and effectiveness of drugs in pregnant women. Clinical trials, however, also have limitations. Clinical trials have limited power to detect some adverse effects due to the relatively small numbers of subjects included in clinical trials compared with the number of persons who may eventually use the drug under study. Adverse effects may not become evident until the drug is in widespread use. Therefore, systematic surveillance for developmental effects is essential to any plan to include pregnant women in clinical trials. Together, both methods will further our understanding of the medical management of the ill pregnant woman.

Surveillance for Developmental Effects

Surveillance for reproductive and developmental effects in the offspring is essential to our understanding of the safety of drug use during pregnancy. Such screening assumes that there are tools available to identify developmental effects and that these tools can be economically applied for the surveillance of a healthy population. Procedures may be as simple as a clinical evaluation of the newborn to determine if the child has a structural birth defect that can be identified on physical examination. One of the most critical steps in surveillance is the recording of screening results in a database so that they can be combined with other results for a more comprehensive analysis. Several programs currently exist to monitor populations for congenital malformations; these programs may provide a starting point for surveillance efforts related to pregnant women in clinical studies.

Monitoring of populations for congenital malformations began in the mid-1960s, and by the mid-1970s 7 countries had nationwide monitoring systems and 12 other countries had regional monitoring systems. In addition, the International Clearinghouse for Birth Defects Monitoring was created in the mid-1970s to collect, collate, analyze, and share information on local trends in birth defects identified by the various participating programs; at present there are 26 participating programs.

Monitoring systems use one of two major monitoring strategies: (I) monitoring of all malformations as reported or (2) monitoring of selected "sentinel" malformations, so-called because they are generally detected within the first week of life. Examples of sentinel malformations include anencephaly, spina bifida, hydrocephaly, orofacial clefts, gastrointestinal atresia, deformities of the extremities, Down's syndrome, and congenital hip dislo

cation. Unfortunately, neither approach escapes the difficulty of ascertainment. Studies indicate that monitoring systems for congenital malformation experience substantial underreporting; in some cases, only one-third of infants with a given abnormality are identified by a monitoring system.

Most monitoring systems have established specific thresholds of malformation incidence that signal a significant increase in frequency (Holtzman and Khoury, 1986). These thresholds are characterized as excesses above an expected number (assumed to be a Poisson variable), excesses above a baseline rate determined from historical information, a decreasing time interval between consecutive births with the malformation (also determined from historical information), or changes in time-space clustering. As in all statistical analysis, it is important to avoid the erroneous assumption of causation when drugs are associated with birth defects. Given the large number of comparisons calculated for adverse developmental outcome, however, false positives are a continual problem.

As is the case with individual clinical trials, it is important to understand the capacity of a monitoring system to identify correctly a developmental toxicant, based on the number of births registered with the system. For example, cleft lip occurs in about I in every 1,000 births (incidence is 0.001). The ability to identify an exposure that increases the incidence of cleft lip varies with the size of the population monitored. If 75,000 births are monitored (half treated and half untreated), an increase of 1.3-fold over background could be identified; however, if 10,000 births are monitored (half treated and half untreated), the minimum increase that could be detected would be a 2.0-fold increase above background. In a related sense, the power of monitoring systems to detect adverse effects is also limited because few pregnant women will be exposed to a specific drug. While surveillance cannot guarantee detection of developmental toxicants, systematic collection of information about pregnancy outcomes in a wide range of situations, complemented with information gained through clinical trials that include pregnant women, provides an important element of protection for pregnant women and their offspring.

The committee recommends that a review be undertaken of existing birth defects monitoring programs to critically define what they are capable of doing and suggest improvements and reasonable expectations for their use.

Such a review would be of value in the development of reproductive and developmental screening systems and in further consideration of postmarketing surveillance for reproductive and developmental effects.

ETHICAL ISSUES: RISK-BENEFIT ANALYSIS

Assessing the potential risks and benefits of clinical research is not always an easy task. The very use of phrases such as "risk-benefit equation" and "balancing risks against benefits" has the misleading effect of making it seem that the process enjoys mathematical precision or scientific rigor. The task is made even more difficult because reasonable people disagree both in their evaluations of the magnitude of risks and benefits and how to weigh risks against potential benefits. Different people-be they medical scientists, patients, or healthy volunteers-may value the risks and benefits differently. They may consider some risks worth taking in relation to potential benefits, while other risks may be viewed as unacceptably high in relation to potential benefits.

Assessing risks and potential benefits has both a scientific component and a personal element that varies with the individual making the assessment. By "scientific" we mean that intersubjective agreement can be attained among scientists and researchers based on observations, previous studies, and clinical experience. For example, the identification of the risks and side effects of drugs and the probability of their occurrence is based on experience from earlier studies. Once a sufficiently large population has been studied, medical scientists should be able to agree on what risks might be expected, how likely they are to occur, and their impact on morbidity and mortality. The foregoing sections of this chapter illustrate the scientific dimension of assessing the risks of harm various substances are likely to produce. The same is true of benefits, when benefits are viewed in a relatively narrow, medical sense, best captured by the concept of efficacy: a drug does what it is designed to do-provide a cure, alleviate symptoms, produce a temporary remission, and so on.

But there also is an irreducibly personal element in risk-benefit assessments. By "personal" we mean the insertion of an individual's values, taken in the broadest sense, into the process of assessing the meaning of risks and benefits for one's life or the lives of others, as well as the weighing of risks against benefits. To take a common example, members of IRBs often disagree on how risky a particular procedure actually is.

A committee member who is a member of one IRB reports that heated disputes have arisen over how to characterize the level of risk of lumbar punctures in infants or demented elderly patients, insertion of urethral catheters in six-year-old boys, right-heart catheterization in cardiac patients, withdrawing medication from patients with mild-to-moderate hypertension, and withholding antipsychotic medication from patients with severe emotional disorders. Those who agree on the scientific facts concerning the magnitude and probability of side effects will bring different personal values and experiences to the question of whether the risks are acceptable.

Women's values can differ significantly from those of scientists (whether male or female) in assessing risk-benefit ratios. For example, women's health advocates tend to define the "safety" of contraceptive methods in terms different from those typically employed by biomedical scientists. According to one report:

> Scientists' concern is to establish safety of methods according to specific measurable parameters. They assess toxicity, first in animals and then in carefully controlled studies in human volunteers. Subsequent studies address efficacy and short- to medium-term safety. . . Women's health advocates . . . give more priority to methods that have fewer side effects and that protect against sexually transmitted diseases and their consequences such as infertility. While scientists have tended to give priority to methods which minimize users' control, women's health advocates prefer methods controlled by the users. [World Health Organization, 1991:11.]

New policies to encourage the inclusion of women, and in particular women of childbearing age, in clinical studies evidence a greater acknowledgment of individual values and a respect of individual autonomy (see, for example, Merkatz et al., 1993). These policies will affect the responsibilities of IRBs and potential participants. The changes will be most evident in the communication of risks to participants and in IRB risk-benefit assessments.

As with any potential participant, a thorough discussion of the risks and potential benefits of participation is a prerequisite for an individual's ability to make an informed decision to enroll in a clinical study. For men and women of reproductive age, reproductive issues affect the type of information included in the informed consent process.

It will be the IRBs' obligation, as with all research involving presumptively competent adults, to continue to ensure that: (1) the selection of potential participants is fair; (2) the informed consent process is adequate; and (3) the risks to participants are outweighed by the potential benefits. This first duty-fair selection-is the subject of the committee's report and thus requires no additional comment. The other two duties will be discussed below.

Women (Not Pregnant or Lactating) and Men of Reproductive Age

Significant changes have occurred during the committee's tenure, in policies that govern the inclusion of women of childbearing potential in clinical studies, particularly studies of FDA-regulated products (see Chapter 6). FDA issued new guidelines permitting the participation of women of childbearing potential in the early phases of drug trials, and offered three reasons for this decision: (1) scientific gains in study design related to the early identification of gender differences in trials; (2) the ability to reduce

the risk of fetal exposure through protocol design; and (3) recent social changes indicating respect for women's autonomy and decisionmaking capacity in reproductive issues. NIH guidelines are currently under revision. These policy changes should have the effect of including more women of reproductive age in clinical studies, with implications for risk-benefit assessments.

In a study that poses risks to potential offspring, women who are not pregnant at the outset of the investigation may become pregnant while they are still participants. The committee believes that the informed consent process for these women should include information about contraception and the alternatives of voluntarily withdrawing from the study and terminating a pregnancy should conception take place. Similar discussions should be held with men who could father a child while participating in the study. As in all research involving human participants, every effort should be made to ensure that the consent decision is fully voluntary. An example of language for consent forms proposed by Moreno (1994) in his presentation to the committee appears below, as modified by the committee:

> It is possible that your participation in this study may cause damage to children if you choose to have them. You have already been told what is known about this possibility, and you are encouraged to ask further questions. (Include as appropriate: We urge you or your partner not to become pregnant while you are part of this study.) You may want to discuss this with others before you agree to take part in this study. If you wish, we will arrange for a doctor, nurse or counselor who is not part of this study to discuss this possibility with you and anyone else you want to have present.

The committee recommends that investigators and IRBs not exclude persons of reproductive age from participation in clinical studies. In the case of women of reproductive age, the potential or prospect of becoming pregnant during the study may not be used as a justification for precluding or limiting participation. Risks to the reproductive system should be considered in the same manner as risks to other organ systems. Risks to possible offspring of both men and women who are not pregnant or lactating should not be considered in the risk-benefit calculation. It is the responsibility of investigators and IRBs to assure that the informed consent process include an adequate discussion of risks to reproduction and potential offspring, including, where appropriate, an adequate discussion of relevant considerations of birth control.

The committee recommends that the participant be permitted to select voluntarily the contraceptive method of his or her choice where there are no relevant study-dependent, scientific reasons to require

the exclusion of use of certain contraceptives (e.g., drug interaction).

The committee recommends that pregnancy termination options be discussed as part of the consent process in clinical studies that pose unknown or foreseeable risks to potential offspring.

Lactating Women

The possible transmission of drugs to nursing infants is a risk that must be considered when including lactating women in clinical studies. This additional consideration must be thoroughly discussed in the informed consent process.

The committee recommends that investigators and IRBs not exclude women who are lactating from participation in clinical studies. It is the responsibility of investigators and IRBs to ensure that the informed consent process includes, wherever appropriate, an advisory to potential participants that there may be special risks to their children if nursing mothers participate. No nursing mother should be permitted to agree to participate without first receiving additional information about these special risks.

Pregnant Women

As reflected in the recommendation presented earlier in this chapter, the committee wishes to encourage clinical research to advance the medical management of pregnant women who are or may become ill. In this context, the committee reviewed the current DHHS regulations concerning the involvement of pregnant women as research subjects. The committee's review was limited to situations in which the pregnant woman is the subject of the research (see Chapter 6). It did *not* include situations in which the fetus is the subject of the research (currently covered by the same regulation); fetal research was outside of the committee's charge.

The DHHS regulations begin with a presumption of exclusion-that is, "no pregnant woman may be a research subject" except under certain conditions. The regulations also require that IRBs ensure during their review of research protocols that the exclusionary standard enunciated in the regulations is met. In addition, the regulations classify pregnant women as a "vulnerable population" deserving of special protection. For the reasons discussed below, the committee concluded that the current regulatory scheme should be revised.

The committee acknowledges that the current regulations (45 C.F.R. 46

Subpart B) may reflect an inadvertent attribution of the vulnerability of the fetus (which obviously lacks autonomy) to the pregnant woman. Nonetheless, it is inappropriate for the regulations to retain a presumption of exclusion on the basis that pregnant women are a "vulnerable population" in need of special protection. In this context, "vulnerable" suggests that pregnant women are less autonomous or more easily exploited than other persons an inference that the committee has found no evidence to support. The labeling of pregnant women as a vulnerable population also might be viewed as suggesting that they cannot weigh the risks to a fetus or potential child in deciding whether to enroll in a clinical study; that pregnant women do not care sufficiently about the health or well-being of their future children to make sound decisions; and that the prevention of all potentially harmful outcomes of pregnancy is a goal that warrants governmental, regulatory, or other official intervention into the lives and free choices of women. The committee rejects these inferences as well. Removal of pregnant women from the regulatory category of "vulnerable" potential subjects would avoid any possible inference that pregnant women are less capable of making informed decisions by virtue of their pregnancy, than are other potential research participants.

For all potential research participants, risk-benefit assessment is a complex and difficult task. Nevertheless, it is no more difficult for pregnant women than it is for nonpregnant women or for men. Virtually all women desire healthy infants, even when their pregnancies are unplanned. While occasionally there may be pregnant women who are incapable of acting in the interests of their future children, it would be inappropriate to base a public policy on an atypical case, rather than a normative case.

There also is little public support for the proposition that the prevention of all potentially harmful outcomes of pregnancy is a goal that warrants governmental, regulatory, or other official intervention into the lives and free choices of women. Pregnant women may choose to work in stressful jobs, engage in recreational activities, drive automobiles, and do other things that could place their own or their fetuses' health or life in jeopardy.

The committee recommends that pregnant women be presumed to be eligible for participation in clinical studies. It is the responsibility of investigators and IRBs to ensure that pregnant women are provided with adequate information about the risks and benefits to themselves, their pregnancies and their potential offspring. Even when evidence concerning risks is unknown or ambiguous,[1] the decision about acceptability of risk to the pregnancy or to offspring should be made by the woman as part of the informed consent process.

The committee was unanimous in the view that pregnant women should be presumed to be eligible for participation in clinical studies. The committee also unanimously endorsed the importance of recognizing, in public policy as well as in the deliberations of IRBs and investigators, that pregnant women should be treated as competent adults capable of making their own decisions about participation in research. It should be emphasized that the committee is not recommending that NIH impose an affirmative obligation on investigators to recruit pregnant women into every clinical study. What follows is further explication of the committee's intent with respect to the implementation of this recommendation.

Adequate Information

With respect to the obligation to ensure that pregnant women are provided with adequate information about the risks and benefits to their pregnancy and potential offspring, the committee recommends the following strengthened informed consent procedure. The disclosure statement of consent forms for all studies that pose a risk to pregnancy or potential offspring should include, highlighted in bold type, a statement such as: *If you are pregnant or contemplating pregnancy, we urge you to consult your obstetrical care provider before deciding about participation in this study. Participation in this study may (does) pose a risk of (significant) harm to your pregnancy and/or your potential baby.*

Investigators should ask all potential participants if they are pregnant as part of the initial screening phase of recruitment. If a woman is pregnant, her attention should be drawn to this bolded statement. This process should include a special disclosure statement that details in easily understood lay language what is known about the risks and potential benefits to her pregnancy and potential offspring, resulting from participation in the study. This statement should be reviewed with the pregnant woman, and she should be encouraged to consult with her obstetrical care provider before proceeding further in the consent process. It is important for a pregnant woman to have benefit of the advice of her obstetrical care provider in deciding whether to participate in a study. (In the case where the woman's own obstetrical care provider is the study investigator, the pregnant woman should be offered the opportunity to discuss her participation with a similarly qualified individual who is not associated with the study.) If the pregnant woman does not wish to consult with her obstetrical care provider, and even if she has had such a consultation, specific procedures should be instituted to ensure that she understands the relevant risks and benefits. For example, the potential participant could be asked to describe in her own words what the risks and benefits are. It should be clear that the pregnant woman understands

that no drug or other intervention can improve on normal pregnancy in a healthy woman. Alternatively, the pregnant woman could be asked to complete a knowledge test. Deficiencies in understanding discovered through either method should be addressed through continued discussion and education. Only after the woman demonstrates an adequate understanding should consent be solicited. These are procedures that are generally advocated to improve the quality and the meaningfulness of the informed consent process (Faden and Beauchamp, 1986; Appelbaum et al., 1987). They are particularly important when the stakes associated with participation are high, as is the case for pregnant women if participation entails significant risks to pregnancy or potential offspring.

Paternal Consent

It is appropriate for investigators to encourage a potential participant who is pregnant to discuss her participation in clinical studies and risks to potential offspring with the potential baby's father, but the committee rejects any requirement that the consent of the potential baby's father be a condition of the participation of a pregnant woman in research. The committee recognizes that the husbands of pregnant women, as well as future fathers who are not husbands, have an interest in the health of their children and that these men may have a deep emotional attachment toward their offspring prior to birth. Until a child is born, however, the future father can only protect the health of the potential child by controlling the decisions and actions of the woman. To give men the authority to veto the decisions of their wives or partners to participate in research grants men unacceptable power over women. It also would accord greater protection to fetuses than to children; only one parent's permission is required to enroll an infant or child in clinical research.

Scientific Criteria for Exclusion

The committee recognizes that, as in all clinical studies, there may be scientifically and medically valid reasons for excluding pregnant women from a particular study. A pregnant woman would be excluded if the medical condition of pregnancy disqualifies her as a subject in the same sense that anyone else, pregnant or nonpregnant, male or female, would be disqualified based on medical conditions that would interfere scientifically with the study. For example, a pregnant woman would be excluded from a study of hormone replacement or contraception. A pregnant woman also would be excluded from a study of weight loss, as would any person who, for example, was already very underweight; scientifically, it would not make sense to include either type of person in such a study. Similarly, a pregnant

woman would be excluded from a study when the condition of pregnancy places the *woman* in a risk category (because pregnancy increases the risk of harm to the woman) that would exclude others due to an unacceptable risk/benefit ratio.

Other Criteria for Exclusion

There was considerable discussion within the committee about whether there are any exceptional instances in which IRBs can be given the discretion to exclude pregnant women from participation for other than scientific reasons. Most committee members ultimately endorsed the following recommendation:

Investigators and IRBs may exclude pregnant women from participation only when the IRB finds, and records its finding in writing, that the following standard has been met: (1) there is no prospect of medical benefit to the pregnant woman, and (2) a risk of significant harm to potential offspring is known or can be plausibly inferred.

A finding that a risk of significant harm to potential offspring is "known or can be plausibly inferred" may be based on evidence from animal studies, in vitro studies, structure-activity relationship data, or previous clinical experience.

Under this standard, IRBs may exclude pregnant women from the earliest phases of many drug trials, but most clinical studies would remain open to pregnant women. Committee members adopting this standard were motivated by a desire to be true to the underlying principle that pregnant women should be treated no differently than other presumptively competent adults in the context of IRB deliberations. In addition, these committee members were particularly concerned that if the exceptive case was not narrowly constructed, variation in interpretation could open the door to widespread exclusions of pregnant women.

A few members of the committee, however, were not able to endorse the above mentioned standard. They wished to reserve for the IRB the discretion to exclude pregnant women from participation not only when there is no prospect of medical benefit to the women but also when there is only potential for benefit to them that could be characterized as minimal or insignificant. The intent here is to allow the IRB more room for judgment about the appropriateness of exclusion. An example of a situation in which these members believed that IRBs should have the discretion to exclude pregnant women was that of a clinical trial of a medication thought to be helpful in the management of severe acne but known to cause malformations in offspring if taken during pregnancy. The standard endorsed by most

committee members would not permit a blanket exclusion of pregnant women from such a study, as it could not be claimed that there is no prospect of medical benefit to the pregnant participant.

The committee also struggled with how to accommodate within its support for the shift of the presumption to *inclusion* of pregnant women (from that of exclusion) a role for conscience and an individual investigator's moral commitments. It was agreed that, at a minimum, such a mechanism would require that the investigator provide the IRB with a written explanation of his or her concerns of conscience and that the IRB review any such requests in light of a presumption that favors the inclusion of pregnant women in clinical studies. It also would require the IRB to guard against any abuse of conscience claims, and, in particular, against circumstances in which a request for exemption on the basis of conscience is offered in lieu of other reasons not based in moral commitment. It is precisely because of the potential for abuse of a "conscience" exemption that the committee could not resolve whether or under what conditions such an exemption should be constructed. Appeals to conscience are in many respects unassailable; in some contexts, the force of such appeals has had a chilling effect on public policy.

Documentation and Monitoring of Exclusions

An IRB must record in writing both its reasons for permitting any exception to the general presumption of inclusion of pregnant women and the frequency with which it grants such exceptions. It is anticipated that IRBs would record such information in the minutes of their meetings and that the act of documentation would help the IRBs to properly implement the standard. Such record keeping also would provide a source of information should OPRR desire to evaluate the performance of an IRB on this issue.

Conclusion

The committee recognizes that its recommendation concerning the participation of pregnant women in clinical studies cannot ensure the prevention of a small, theoretical risk of harm to offspring. Pregnancy and the controversial moral and legal standing of the fetus or potential child raise unique considerations. We do not wish to dismiss or evade these important considerations. However, the committee was persuaded of the overriding value of ensuring that all women-pregnant or otherwise-be treated justly with respect to the opportunity to derive the benefits of research. The shifting of the presumption to one of *inclusion* of pregnant women in clinical studies from one of *exclusion* is an important step in that direction.

The committee believes that given the safeguards described above, holding IRBs and investigators to the presumption of including pregnant women in research is not a significant threat to the health of future generations. Except for studies specifically designed to investigate outcomes in pregnant women-which the committee strongly endorses-it is exceedingly unlikely that investigators will seek out pregnant women for recruitment. It should be emphasized that the committee is not recommending that NIH impose an affirmative obligation on investigators to recruit pregnant women into every clinical study. Moreover, the committee's conclusions are consistent with the position that women who are or who might become pregnant have a moral obligation to weigh risks to a future child when deciding whether to participate as research subjects. It is unlikely that pregnant women will seek admission into studies that pose a significant risk of harm to their offspring, unless there is some offsetting benefit to the health of the pregnant woman that in turn advances the interests of the potential child by its having a healthy mother. A policy of presuming that pregnant women are eligible to participate in clinical research, although introducing a possibility of harm to a potential child, is in fact likely to produce health dividends for mothers that will inure to their children. Although the committee is not indifferent to the risk of harm to even one potential child, the committee felt compelled to consider as primary the interests of all women in being treated justly and with dignity.

The committee recommends that OPRR revise and reissue Subpart B of the DHHS regulations for the Protection of Human Subjects, titled "Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In vitro Fertilization [45 C.F.R. 46, subpart B] in accordance with the committee's recommendations.

At least a technical amendment to Subpart A, sec. 46.111(a)(3), eliminating the reference to pregnant women as a "vulnerable population" will be required by this revision to Subpart B.

NOTE

1. There is historical precedent for classification of unknown or ambiguous risks to the fetus as more than minimal. This policy was developed with respect to fetoscopy in a decision by the Department of Health, Education, and Welfare Ethics Advisory Board in 1979 (DHEW, 1979) and by the NIH with respect to chorion villi sampling in the 1980s (C. McCarthy, former director of NIH Office of Protection from Research Risks, personal communication, October 1993). In both cases, it proved to be an appropriate

WOMEN AND HEALTH RESEARCH

Ethical and Legal Issues of Including Women in Clinical Studies

Volume 2

Workshop and Commissioned Papers

Anna C. Mastroianni, Ruth Faden, and Daniel Federman, *Editors*

Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies
Division of Health Sciences Policy
INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C. 1994

Ethical Issues Related to the Inclusion of Pregnant Women in Clinical Trials (I)

John Robertson

Researchers, institutional review boards (IRBs) and others reviewing clinical research including pregnant women must assess the effect of proposed research on the pregnant woman, on the developing fetus, and on the child whom the fetus, if carried to term, will become. In most instances concern with fetal effects is not by virtue of the fetus's interests in its own right, but by virtue of the effect which prenatal interventions affecting the fetus will have on offspring.

A set of guidelines for such research was developed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Science Research in 1974. These guidelines were incorporated into federal regulations for research with human subjects in 1975, and continue to apply today (45 C.F.R. §§ 46.201–46.211). They are generally sound with the specifications and modifications discussed below.

THE PREGNANT WOMAN AS SUBJECT

Both the National Commission and the federal regulations distinguish clinical research involving pregnant women on the basis of whether the woman or the fetus is the subject of the research. In each case they make a further distinction between research that is therapeutic—the purpose of the activity is to meet the "health needs of the mother" or "the health needs of the particular fetus"—and research that is nontherapeutic.[1] The amount of risk which may be

accepted depends on this set of distinctions.

Therapeutic: To Meet the Health Needs of the Mother

Pregnant women may participate in clinical research where the "purpose of the activity is to meet the health needs of the mother" regardless of the degree of risk to the fetus and offspring. If the purpose of the research is not to meet her health needs, she may participate only if "the risk to the fetus is minimal."

While this rule is generally sound, it conceals some problems. The main problem concerns the broad phrase "health needs of the mother." Consider an established treatment for a disease or condition that is safe and effective for women whenever it is given, but also has a very high risk of affecting future offspring if given during pregnancy. Ethical judgment of whether the woman should be able to have the treatment during pregnancy will depend not merely on whether the treatment will affect her "health," but also on the burdens and benefits to her of having treatment during pregnancy or after. The type of benefit to her alone is not determinative, but the magnitude is. The more minor the benefits the less discretion the woman should have to accept treatment, if there is any risk beyond minimal to offspring.

Such a standard requires weighing the importance to the woman of the health need in question versus the risk to offspring. Treating morning sickness or a cold during pregnancy is certainly a health need. But if the drug used to treat those conditions is teratogenic, it would be unethical to take it even though it is directed at treating her "health." If this is true about established therapies, then it is even more true about experimental therapies. If use of an experimental drug poses more than minimal risks to the fetus and offspring, a woman should have even less of a moral right to take such a drug to treat a cold, morning sickness, or any condition that is not life-threatening or very serious, where the primary purpose of the research is to meet her health needs. Thus a researcher, an IRB, or other review body should make a judgment about the degree of the benefits or burdens of taking or forgoing the experimental treatment relative to the harm to the fetus and offspring if it is given. A purpose of treating the "health needs" alone of the pregnant woman is not ethical when the benefits to her are greatly outweighed by the risks to fetus and offspring. The current federal regulations are overbroad to the extent that they would permit such research to occur.

Nontherapeutic Research: Not Meeting the Health Needs of the Pregnant Woman

Where the purpose of clinical research involving a pregnant woman is not

to meet her health needs, the regulations limit such research only to instances where "the risk to the fetus is minimal." The implicit ethical assessment is that a pregnant woman may not harm expected offspring when there is no health benefit to her.

The first thing to note about this regulation is the ambiguity inherent in "risk to the fetus." Strictly speaking, "risk to the fetus" could be interpreted to mean only those risks that will prevent the fetus from being born alive, i.e., that might induce miscarriage. But that meaning does not make sense because women do not have moral duties to bring previable fetuses to term. Hence, they would be morally entitled to engage in activity which has a risk of inducing miscarriage, because the fetus itself lacks interests or rights. Except for persons who view the fetus as a person or moral subject in its own right, the moral concern with research or other impacts on fetuses arises because fetuses generally go to term and become offspring. More than minimal risk to a fetus is of ethical concern because of the impact which that risk will have on the resulting child. Thus it is necessary to understand "risk to the fetus" as "risk to the fetus that will be carried to term." The only qualification to this understanding would arise with research involving viable fetuses. In those cases risk to the fetus might also be of concern because it prevented an entity with interests in itself from being born.[2]

Thus understood, the point of the regulation is to protect expected offspring from experimental prenatal harms that are not justified by important health needs of the woman. The woman is not free to sacrifice the interests of expected offspring by her interest in serving the needs of science or of other women. She is free to make a martyr of herself, but she is not free to make a martyr of her children, whether the martydom occurs by prenatal or postnatal conduct.

This understanding of the regulation is ethically sound. The only argument against it would be the claim made by some feminists that a pregnant woman should be free to do what she wants with her body, and that any restrictions on her behavior is an intolerable restriction of her freedom. The very issue being discussed shows that this position is unsound, even if one believes that coercive state interventions to prevent prenatal harm to offspring are rarely justified on policy grounds. The regulation, however, is ethically sound. No one, not even the pregnant woman, has a moral right to engage in experimental clinical research not necessary to meet her own substantial health needs when there will be a major impact on offspring.

THE FETUS AS SUBJECT

Clinical research involving pregnant women may also be directed at the fetus as the subject of the research. Again, the major ethical distinction in this category is between therapeutic and nontherapeutic fetal research, the former

being cases where the "purpose of the activity [is] to meet the health needs of the particular fetus" (45 C.F.R. § 46.208(a)).

Therapeutic: To Meet the Health Needs of the Fetus

The federal regulations permit research with the fetus as subject when "the purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs."

This standard is ethically unexceptional once the ambiguity mentioned earlier in "health needs of the fetus" is resolved. The term in this context would apply to procedures that will enable the fetus to survive, i.e., come to term, and survive in a healthy or undamaged way. Thus experimental procedures designed to prevent or treat handicap or disease in offspring would be permitted, because the health needs of the fetus include the health needs of the child that the fetus will become. Prenatal procedures on the fetus are necessary to safeguard the welfare of offspring. Thus experimental *in utero* fetal surgery to correct diaphragmatic hernia in the fetus may be done because of the impact which that condition will have on offspring.

Note that there is no obligation to include the fetus in experimental research. Parents have no duty to subject their fetuses and offspring to experimental procedures, even when there is no alternative treatment available, precisely because it is experimental and thus not clearly a benefit. On the other hand, parents should be free to have experimental *in utero* therapies used when they reasonably believe that the benefits of the procedure to offspring outweigh the risks.

Nontherapeutic Fetal Research: Not to Meet the Fetus's Health Needs

The federal regulations restrict research not directed to meet the health needs of the fetus to situations in which "the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means" (45 C.F.R. § 46.209(b)).

This rule is ethically sound—indeed, is morally obligatory—in situations in which the pregnancy may or will go to term. In that case research not designed to benefit offspring would occur that has more than minimal risk of harming offspring. Because parents have no right to harm their offspring, whether by prenatal or postnatal conduct, they have no more right to include their offspring in prenatal experiments that carry a risk of harm than they do to include them

in postnatal research. Note, however, that they would have the right to include them in minimally risky research on the ground that no ethical or legal duty would be violated in doing so.

However, this regulation is not justified in situations where the pregnancy will not go to term. In such cases, strictly speaking, there is no risk of harm to the fetus, because a previable fetus is insufficiently developed to have interests in its own right, and thus cannot be harmed. The National Commission, however, took the position that all fetuses should be treated equally—those going to be aborted should be treated the same as those going to term. Under the Commission's understanding no research could be done on fetuses going to be aborted that could not be done on fetuses going to term. Treating all fetuses the same overlooks the fact that nontherapeutic research on fetuses going to term could affect the interests of offspring, whereas research on fetuses to be aborted cannot hurt future offspring, much less previable fetuses, which are nonsentient and do not have interests.

There is one possible risk with nontherapeutic research on fetuses going to be aborted that is of ethical concern. That risk is that the woman who consents to that research might change her mind about abortion after the experimental procedure has begun. If so, research begun with no intention of harming offspring could end up harming children who are later born. Of course, once the experimental procedure has begun, the woman might be reluctant to change her mind precisely because of risk of harm to offspring. To make research ethically acceptable on fetuses going to be aborted, the experimental procedure should be administered shortly before the abortion or in other circumstances in which it is very clear that the pregnancy will in fact be terminated, and that the woman has had sufficient opportunity to contemplate that decision. Researchers and reviewers should assure that this condition is met.

NOTES

1. § 46.207(a); § 46.208(a).
2. This statement assumes a certain view of why viable fetuses are protected. If protection is based on sentience alone—an interest in avoiding pain and suffering—they may not also have an interest in coming to term.

Ethical Issues Related to the Inclusion of Pregnant Women in Clinical Trials (II)

Bonnie Steinbock

More than a billion drug prescriptions are written every year, there is unlimited self-administration of "over-the-counter" drugs, and approximately 500 new pharmaceutical products are introduced annually (Briggs et al., 1983, cited in Elias & Annas, 1987, p. 196). Moreover, a surprisingly high number of pregnant women use legal drugs; 40 percent in the first trimester, according to one study (Heinonen et al., 1977, cited in Elias and Annas, 1987, p. 196). These facts lead to the conclusion that "the potential for drug teratogenicity is thus truly remarkable" (Elias and Annas, 1987, p. 196).

Much information about the pharmacology of the maternal—fetal unit has been derived from animal studies, but it is extremely difficult to predict whether observations made in animals will have relevance to human beings. For example, preliminary testing of the rubella vaccine in monkeys indicated that the vaccine did not cross the placenta. However, when human studies were undertaken with women about to undergo abortions, it was found that the vaccine virus did cross the placenta and infect the fetus. Thalidomide is another dramatic example that negative animal data do not prove that a drug is innocuous to humans. This presents a dilemma. If we include pregnant women in clinical trials, we risk exposing fetuses to the risk of teratogenicity. If we exclude pregnant women from clinical trials, we will not have information about the effects of various drugs on the maternal/placental/fetal unit. We must therefore steer between Scylla and Charybdis, and we need appropriate guidelines to help.

This issue was addressed by the National Commission for the Protection of

Human Subjects of Biomedical and Behavioral Research, the first of whose mandates was to review and report on research involving living fetuses. The result was a report, *Research on the Fetus*. Among its recommendations were the following: nontherapeutic research on the pregnant woman or on the fetus *in utero* may be conducted or supported, provided it will impose minimal or no risk to the fetus, the woman's informed consent has been obtained, and the father has not objected (*Research on the Fetus,* pp. 73–76).

Several key concepts are included in this recommendation. The first is nontherapeutic research, that is, research that does not benefit the research subject, in this case, either the pregnant woman or the fetus. Placing restrictions on the use of pregnant women in nontherapeutic research limits their freedom of choice, but it cannot be said to harm them as individuals. Women taken as a class may be harmed by the exclusion of women from clinical trials. Indeed, such exclusion is likely to affect adversely society as a whole, as important knowledge that might have been acquired may not be gained. The situation is quite different for therapeutic research, to which I will return shortly.

The next key concept is that of risk to the fetus. The National Commission required that the risk to the fetus from the research be minimal or nonexistent. It maintained that all fetuses should be protected from potentially harmful research, regardless of whether they were going to be aborted or going to be born: ". . . the same principles apply whether or not abortion is contemplated; in both cases, only minimal risk is acceptable" (*Research on the Fetus,* p. 66). This requirement was referred to as "the principle of equality."

I disagree. In my view, because of the difference between children and early-gestation fetuses, it is crucially important whether the woman is going to abort or going to term. Early-gestation fetuses are not sentient or conscious or aware of anything. No matter what is done to them, they feel nothing. Nonsentient fetuses cannot be harmed in the way that sentient beings can be harmed; that is, they can't be hurt or made to suffer. Treatment that would cause a sentient being to experience pain is not necessarily harmful to nonsentient fetuses.

However, pain isn't the only way in which a being can be harmed. What if a fetus is exposed to substances that prevent it from developing normally, such as the rubella virus, thalidomide, alcohol, and so forth. Here, however, the harm is not to the fetus, but to the born child. It is the child who must go through life deaf and mentally retarded when the fetus has been harmed by prenatal exposure to rubella. It is the child who must go through life without limbs when the fetus has been harmed by thalidomide. It is the child who must go through life with learning disabilities when the fetus has been harmed by prenatal exposure to alcohol. If the woman aborts in the first trimester, before the fetus becomes sentient or conscious, there is no one who can be harmed. That is why a woman who plans to abort has only her own health to consider regarding drinking or

smoking, while the woman who plans to go to term has the health of her future child to consider, as well as her own health.

If this is right, then it makes no sense to insist, as did most of the Commissioners, that no procedures should be applied to a fetus-to-be-aborted that would not be applied to a fetus-going-to-term. The reason for banning potentially harmful nontherapeutic research on fetuses-going-to-term is not to protect the fetus per se, but rather to protect the future child. If the woman is going to abort, there won't be any future child, and literally no one who can be harmed or protected. Moreover, if women who are scheduled to abort are willing to participate in clinical trials, and give their informed consent, much useful information that will serve to protect future children may be gained. What if the woman is going to term? In this case, the interests of the surviving child must be considered. Could there be any objection if there are only minimal or no risks to the future child? Paul Ramsey opposed *all* nontherapeutic research on children, on the ground that they have not given informed consent (Ramsey, 1976). Richard McCormick thinks that some nontherapeutic research on children can be justified, and that parents can give proxy consent for their children where there is no discernible risk or undue comfort. Proxy consent is morally legitimate insofar as it represents what the child *ought* to choose—and everyone ought to be willing to participate in experiments that benefit the human community (McCormick, 1974). Both Ramsey and McCormick regard informed consent, either given directly or through a proxy, as morally required. However, it is hard to see the point of requiring informed consent in situations when it is literally impossible. Surely the important point is whether the research is likely to harm the children, either after or before birth. I am assuming that the question of whether research will impose more than minimal risks upon offspring is an objective and scientific matter. If so, then this is not a matter for potential participants in nontherapeutic research to assess. Rather, it is the duty of researchers to determine if the research poses more than minimal risks to offspring. If it does not, then there doesn't seem to be any objection to it.

What if the risks are either significant or unknown? Should a woman be allowed to expose her not-yet-born child to such risks? It is difficult to imagine a situation in which a woman would want to expose her future child to risks, when there is no benefit either to herself or to the child. But imagine a woman with a Mother Theresa complex. She wants to volunteer for medical research to help humanity, and she's willing to take the risk that it might harm either her or her baby. It seems entirely reasonable for us to tell her that while she is permitted to take such risks on her own behalf, she is not entitled to impose such risks on her not-yet-born child. After all, preventing her from participating in an experiment isn't infringing her bodily integrity. It isn't monitoring her lifestyle. So I see no objection to regulations preventing pregnant women who plan to go to term from participating in risky nontherapeutic research.

Restrictions are harder to justify where the research offers a potential benefit to the pregnant woman. Experimental therapy may offer the only hope to individuals who are sick and cannot be helped by tested methods, such as people who have AIDS. They have a direct personal interest in being included in clinical trials. Not allowing them to participate does not merely infringe their autonomy and right to decide for themselves; it may foreclose the only hope they have of survival. It seems, therefore, that it would be wrong to exclude pregnant women who are not going to term from experimental trials that might benefit them.

What about women who wish to continue their pregnancies? I don't think it matters much if the therapy is experimental or conventional. The question is the same: does a woman who is planning on-going to term have the right to undergo therapy that poses a risk to her fetus?

A recent story in the *New York Times* described an Italian woman who refused cancer therapy out of concern that it would harm the fetus she was carrying. She was willing to die in order to avoid harming her fetus. If one views the fetus as having the same status as a born child, then this may seem like a noble act of self-sacrifice. (This is how the Vatican regards it. I believe that they are taking steps to canonize her.) My own view is that her refusal of therapy is certainly permissible, but not morally required. No one is morally required to sacrifice her own life or health to sustain the life of a fetus (Thomson, 1971).

But what if the therapy isn't likely to be lethal to the fetus, but rather risks causing it to be born with severe handicaps? If the risk is great enough, and the handicaps severe enough, terminating the pregnancy might be morally required. For abortion is not a harm to the nonconscious fetus, but being born with very severe impairments may be unfair to the child (Steinbock and McClamrock, in press).

What if the potential benefit is to the fetus, that is, the surviving child? In general, parents have the responsibility for deciding whether to impose experimental treatment on their minor children. Similarly, the prospective parents should be allowed to decide, within comparable limits, whether the potential benefits to the fetus outweigh the risks. However, there is one glaring difference between the two situations. Prenatal treatment of a fetus can be done only through the body of its mother. So the risks to her are an important part of the decision. In recent years, fetal therapy and surgery has grown by leaps and bounds. In one dramatic case (which by now has no doubt been repeated several times) a surgeon removed a previable fetus from the uterus, repaired his diaphragmatic hernia, put the fetus back in the womb, and delivered him six weeks later by cesarean section (Kolata, 1990). The mother had no obligation to try the therapy, given the risks and burdens to her from two cesareans and six weeks of enforced bed rest, especially since it was very experimental and carried

no guarantee of success. Even if such therapy should become "routine," it still should never be compulsory. But neither should anyone deny a pregnant woman the chance to save her baby's life.

Finally, I'd like to consider the role of the woman's partner in making these decisions. By partner, I mean the man who is not only the genetic father, but who also intends to be a rearing parent. It seems to me that if the woman is planning to abort, the man should have no say in whether she participates in a clinical trial. For while a man has a legitimate interest in the well-being of his offspring, if the woman decides to abort, there won't be any offspring. The decision to participate in a clinical trial belongs solely to the pregnant woman.

A man would have a legitimate interest in preventing a woman who did not plan to abort from participating in nontherapeutic research that posed some risk to the not-yet-born child. However, there's a strong case for society's banning pregnant women who plan to go to term from such clinical trials, whether or not the father objects.

Men have legitimate interests in the health of their not-yet-born children. It is not unreasonable for them to be concerned if their pregnant wives smoke or abuse alcohol or drugs. It seems unfair that a man who intends to parent a child should have to stand by and watch behavior that risks harming his future child. He is certainly justified in trying to persuade his wife to get treatment, for the sake of their baby. He might even be justified in coercing her to get treatment, since this will benefit both her and the baby. But he would not be justified in preventing his pregnant wife from getting therapy necessary for her own life and health, to protect the future child. Being a Good—or Splendid—Samaritan may be noble and praiseworthy; it is not something one individual has any right to demand of another.

REFERENCES

Briggs, G. G., Bodendorter T. W., Freeman R. K., et al. 1983. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Baltimore: Williams & Wilkins.

Elias, S., and Annas, G. 1987. Reproductive Genetics and the Law. Chicago: Year Book Medical Publishers.

Heinonen, O. P., Slone, D., and Shapiro, S. 1977. Birth Defects and Drugs in Pregnancy. Littleton, Mass.: Publishing Science Group.

Kolata, G. 1990. Lifesaving surgery on a fetus works for the first time. *The New York Times,* Thursday, May 31, A1.

McCormick, R. A. 1974. Proxy consent in the experimentation situation. *Perspectives in Biology and Medicine* 18:2–20.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1975. Research on the Fetus: Report and Recommendations (cited as Research on the Fetus), DHEW Pub. No. (OS) 76-127.

Ramsey, P. 1976. The enforcement of morals: Nontherapeutic research on children. *Hastings Center Report* 6(4):21–30.
Steinbock, B., and McClamrock, R. In press. When is birth unfair to the child? *Bioethics*.
Thomson, J. J. 1971. A defense of abortion. *Philosophy and Public Affairs* 1:1.

Published in final edited form as:

Hastings Cent Rep. 2017 May ; 47(3): 38–45. doi:10.1002/hast.706.

Research with Pregnant Women: New Insights on Legal Decision-Making

Anna C. Mastroianni,
University of Washington School of Law

Leslie Meltzer Henry,
University of Maryland Carey School of Law; Johns Hopkins Berman Institute of Bioethics

David Robinson,
Wyoming Attorney General's Office

Theodore Bailey,
Johns Hopkins Berman Institute of Bioethics; Lancaster Regional Medical Center, Lancaster, PA; Heart of Lancaster Regional Medical Center, Lititz, PA

Ruth R. Faden,
Johns Hopkins Berman Institute of Bioethics

Margaret O. Little, and
Georgetown University

Anne Drapkin Lyerly
University of North Carolina School of Medicine

Abstract

Although pregnant women rely on medical interventions to treat and prevent a wide variety of health conditions, they are frequently excluded or underrepresented in clinical research. The resulting dearth of pregnancy-specific evidence to guide clinical decisionmaking routinely exposes pregnant women, and their future offspring, to risk of uncertain harms for uncertain benefits. The two legal factors regularly cited as obstacles to such research are the federal regulatory scheme and fear of liability. This article reveals a far more nuanced and complex view of the legal context. First, legal professionals may—at any time from product conception to marketing—influence decisions about research with pregnant women. Second, factors not previously articulated in the literature may prompt legal professionals to slow or halt such research. They include: financial interests, regulatory ambiguity, obstacles to risk management, and site-specific laws unrelated to research. Any efforts to promote the ethical inclusion of pregnant women in research must acknowledge the role of legal decisionmakers and address their professional concerns.

Corresponding Author: Anna C. Mastroianni, amastroi@uw.edu.

Conflicts of Interest: The authors report no conflicts of interest.

Keywords

clinical research; pregnancy; law; liability

INTRODUCTION

Pregnancy does not protect women from experiencing illness and disease. Like everyone, pregnant women face medical challenges—including pregnancy-specific conditions like preeclampsia; serious chronic diseases like diabetes and depression; infectious diseases like HIV, and now Zika; and life-threatening conditions like hemorrhage, stroke, and cancer—that can benefit from safe and effective biomedical interventions. Pregnant women, however, confront a paradox: Although they may need to take prescription medications to treat or prevent serious health conditions, their frequent underrepresentation in—or complete exclusion from—clinical research has resulted in U.S. Food and Drug Administration (FDA) approvals of very few products for use during pregnancy. Nevertheless, women do use medications during pregnancy, and physicians do prescribe medications to pregnant women.[1] In the absence of adequate clinical evidence to inform treatment decisions, both women and their future offspring are subjected to risk of uncertain harms for uncertain benefits. For example, because pregnancy can affect both the way drugs are metabolized by the body and the way the body responds to drugs, standard dosing of medications can lead to under-treatment of disease, or to drug levels that are unsafe for a pregnant woman, a fetus, or both.[2]

U.S. researchers and scholars often point to two legal factors as significant obstacles to the inclusion of pregnant women in clinical research: Department of Health and Human Services' (DHHS) regulatory limitations specific to pregnant women's research participation, and fear of liability for potential harm to children born following a pregnant woman's research participation.[3] This article offers a more nuanced view of the potential legal complexities that can impede research with pregnant women than has previously been reflected in the literature. It reveals new insights into the role of legal professionals throughout the research pathway, from product conception to market, and it highlights a variety of legal factors influencing decisionmaking that may slow or halt research involving pregnant women. Following a brief background, we discuss those insights, concluding that any attempts to close the evidence gap created by the underrepresentation and exclusion of pregnant women in research, will require targeted attention to the role of legal professionals and the legal factors that influence their decisions.

BACKGROUND

The work presented in this article is a component of the PHASES project (Pregnancy and HIV/AIDS: Seeking Equitable Study). PHASES is a multidisciplinary, National Institutes of Health-funded grant committed to developing engagement-driven ethics guidance for conducting research with pregnant women that is responsive to the range of ethical and legal challenges arising in studies with this population.[4] Using HIV research as an anchoring context, the project aims to articulate research pathways that permit and promote the ethical

collection of clinical data that will benefit the health needs of pregnant women and, by extension, their families. An important aspect of that effort is in-depth examination of the legal context, policies, and practices that can pose obstacles to the conduct of research with pregnant women conducted or originating in the United States. Identification and analysis of those hurdles can illuminate and inform the content and type of guidance that would be most valuable to those in the research enterprise. As other aspects of our project have demonstrated in the context of HIV,[5] guidance will be especially helpful for researchers and institutional review boards (IRBs). Researchers report experiencing legal barriers, whether real or perceived, in attempting to plan or conduct clinical research with pregnant women, and IRBs lacking guidance may decline to approve ethically justifiable research with pregnant women out of an abundance of caution.

In an effort to supplement our knowledge and deepen our understanding of those legal claims and the role that legal decisionmakers play throughout the clinical research pathway, we invited a diverse group of legal professionals with intimate knowledge about different facets of the research enterprise to share their expertise with us in a day-long meeting.[6] The attendees represented the public, private, and academic sectors, and included prominent legal practitioners, legal scholars, and regulators with extensive experience or scholarship in clinical research law and policy. They included: former and current general counsels and outside legal counsel to major pharmaceutical companies, prominent academic research institutions, and nonprofit research organizations; former government regulators; and legal academics with directly applicable scholarship and policy experience.[7] This group informed our insights and provided a unique opportunity to learn from legal insiders about their understanding of, and experiences with, legal obstacles to the inclusion of pregnant women in clinical research.

The discussion below summarizes and analyzes major insights from our work to date on legal obstacles to clinical research with pregnant women, incorporating what we learned at the meeting with legal experts. We highlight factors influencing legal decisionmaking that may have the potential to impede research with pregnant women, including financial factors, regulatory ambiguity and inconsistency, obstacles to risk management, and venue-specific laws that may not otherwise be directly relevant to research.

LAWYERS ARE ACTIVE AND INFLUENTIAL PARTICIPANTS IN DECISIONMAKING THROUGHOUT RESEARCH PATHWAYS

Overlooked in the literature to date is the role of lawyers as active participants in decision-making at every step in the research pathway, whether the research is conducted in or sponsored by the private, public, or academic sectors. Meeting attendees emphasized that lawyers may be involved team members at each stage of product development—from pre-clinical conceptualization, to clinical trials, to manufacturing, and ultimately to marketing. As examples, a commercial entity can embed an in-house lawyer in a product-specific team to guide a product idea through each step of the research pathway, or can rely on a lawyer as a member of the executive team who participates in strategic planning at the highest levels. In the academic setting, attendees explained that academic departments, research

investigators, and IRBs take their legal cues from their institution's Office of General Counsel. That office, which is the legal nerve center of a research institution, makes risk/benefit calculations about a variety of institutional activities, often including decisions about research with pregnant women. While some general counsels defer decisions about whether to permit research with pregnant women to IRBs, others set an institutional policy about research with pregnant women that either expressly or tacitly precludes it.

Importantly, legally trained professionals do not speak with one voice. Indeed, the plain language of written laws cannot anticipate their every context and application, and thus laws can be subject to varying interpretations. Two or more lawyers may interpret the same legal language differently, and as further discussed below, their judgments about proceeding, delaying, or halting a clinical trial may be influenced by factors external to the written law. The potential for variable interpretations is enhanced by the fact that there is always more than one lawyer or regulator involved in decisionmaking throughout the research pathway. For example, a lawyer on the IRB may view a study with pregnant women as legally appropriate, while a university general counsel may interpret the law differently, or conclude that a more liberal interpretation would be viewed unfavorably within or outside the institution. Ultimately, legal decisionmakers along the research pathway wield significant power: as one attendee anecdotally shared, even one FDA regulator may be in a position to derail a study, even one that has been approved by the IRB and survived scrutiny from internal or external legal counsel, because of different interpretations about legally (or perhaps institutionally) acceptable levels of risk.

FINANCIAL FACTORS IMPACT LEGAL DECISIONMAKING

Regardless of lawyers' specific roles, because they may be working alongside others committed to the product's financial success, their decisionmaking processes are not just driven by the law, but are also significantly impacted by financial factors. Financial interests of the pharmaceutical industry are best served when a product is taken to market with a clear safety and efficacy profile, for an indicated use, in the general adult population rather than a population that raises interconnected legal-financial concerns. Attendees shared the view that in-house and external legal counsel frequently consider the inclusion of pregnant women in pre-approval clinical trials "taboo" for at least three legal-financial reasons.

First, attendees noted that because the FDA does not require the inclusion of pregnant women in research studies for basic drug approval, it makes no "commercial sense" to expand the clinical trial population beyond what the FDA requires. Second, because pregnancy is widely perceived as adding "background noise" to clinical trial data, which might "complicate" or "mess up" the safety and efficacy profile of a potentially lucrative product, legal decisionmakers might perceive the inclusion of pregnant women as jeopardizing or delaying FDA approval, while also adding cost and time to the research development process. Third, there is "no financial incentive" to conduct studies with pregnant women, and there is a legal disincentive for doing so. Specifically, the market for drugs that treat pregnancy-related conditions is small, and drugs for general medical conditions that may arise or persist during pregnancy, such as diabetes or hypertension, are frequently prescribed to pregnant women despite the absence of pregnancy-specific

"indication and usage" labeling. This regulatory bypass mechanism not only allows the product to reach pregnant women without any financial investment in researching the safety or efficacy of the product in that population, it can also buffer the pharmaceutical industry from liability by shifting responsibility to the prescribing physician for any resulting harms. (See further discussion of liability, below.) As the three articulated legal-financial factors demonstrate, the regulatory framework and traditional concerns about legal liability intersect with efforts to safeguard industry's financial interests in a way that can discourage research with pregnant women.

The entwinement of legal and financial considerations is not limited to the private sector. The attendees emphasized that when clinical research is conducted at an academic institution, a distinct set of obstacles for including pregnant women in clinical trials arises. At academic institutions that are willing to consider clinical trials with pregnant women, such research still may not move forward because the legal and financial incentives that promote partnerships with industry sponsors do not align with the participation of pregnant women in research. Those partnerships are promoted by the federal Bayh-Dole Act, which authorizes academic researchers and institutions to transfer intellectual property from NIH-funded research to private industry.[8] The purpose of that technology transfer is to ensure that the fruits of government-funded research are commercialized and made available to the public. To attract industry sponsors, academic researchers and institutions thus have a strong incentive to conduct research that serves the business interests of private industry. For the reasons described earlier, including pregnant women in clinical trials is perceived to be at odds with those financial objectives.

REGULATORY AMBIGUITY AND INCONSISTENCY PROMOTES CAUTIOUS OR NARROW LEGAL INTERPRETATIONS

Not surprisingly, attendees identified federal regulations as obstacles, targeting a set of DHHS regulations commonly referred to collectively as "Subpart B" that place additional review requirements on research involving pregnant women and fetuses.[9] When pressed for more specificity, attendees homed in on what they viewed as Subpart B's ambiguous and inconsistent language and a corresponding lack of guidance from regulators.

The relevant regulations in Subpart B provide a two-part standard of acceptable imposition of fetal risk in research involving pregnant women. If the proposed research carries no "prospect of direct benefit" to the woman or fetus, then the research may proceed only if the risk to the fetus is "not greater than minimal." If the proposed research does offer a "prospect of direct benefit" to the pregnant woman, the fetus, or both, then the permissible level of fetal risk may move above minimal risk. Attendees noted, however, that in practice, the terms "minimal" risk and "prospect of direct benefit" prompt narrow, and arguably overcautious, interpretations by legal decisionmakers, which ultimately harm efforts to collect research data that benefit clinical care of pregnant women.

Minimal risk, as defined in the regulations that apply to all human subjects research, limits risk to no more than that "ordinarily encountered in daily life."[10] The definition is subject to a wide range of interpretations, particularly in attempts to apply the concept to a fetus as

required by Subpart B: there is no common understanding of risk encountered in the daily life of a fetus. Further, Subpart B does not provide guidance on whether those risks should be understood differently when the woman has a disease or condition, such as HIV, that may have an impact on fetal well-being.

The attendees expressly highlighted those ambiguities. They also questioned whether minimal risk should be interpreted to apply equally to all phases of pregnancy—a "one-size-fits-all" approach—or whether it instead should acknowledge the changing risks to the fetus over the course of the pregnancy (e.g., increased fetal susceptibility to certain risks earlier in pregnancy as compared to later in pregnancy, and vice versa). Attendees also indicated that, because there is often little evidence that bears directly on the likelihood or nature of fetal risk, from a legal perspective the resulting uncertainty becomes controlling, and translates into a conservative interpretation of "more than minimal risk." That regulatory interpretation means that, in practice, research involving pregnant women is much more likely to be justified when there is a prospect of direct benefit to the woman or the fetus. But, even in circumstances where there are arguments to support potential benefit to the pregnant woman or fetus, there is no regulatory definition or guidance about the term "prospect of direct benefit." In addition, there is no express articulation or common understanding of when, how, or whether the prospect of societal benefit can factor into a maternal-fetal risk-benefit assessment. Narrow interpretations of risk and benefit can operate as important red lights in any stage of the drug development process.

Lack of regulatory clarity is magnified in practice, where, as one attendee suggested, decisionmakers can respond to a proposed research protocol by using any uncertainty to preference risk and discount any assertions of benefit. One consequence is a failure to systematically collect data in pregnancy, which also results in a "catch-22" of sorts: The regulations are interpreted in a way that constrains the ability to collect data, but the regulations require data to assess the risks and benefits of research. The lack of data thus stymies attempts to assess with any confidence whether protocols meet the regulatory requirements of minimal fetal risk or prospect of direct benefit to the woman or fetus.

Lastly, legal experts from every research sector—pharmaceutical companies, research institutions, academia, and government—raised questions about federal regulatory inconsistencies related to the biological father's role in consent to research. In the context of research with pregnant participants, Subpart B mandates paternal consent, with some exceptions, where the "research holds out the prospect of benefit solely to the fetus."[11] In research involving neonates, however, only one parent must consent to research involving neonates of uncertain viability,[12] while both parents must consent, with limited exceptions, to research involving nonviable neonates.[13] And finally, for research with children, the regulations require the permission of both parents for certain types of research, while they only require permission of one parent for others.[14] The attendees commented that the confusing and often discordant nature of these rules, coupled with the perceived difficulty in obtaining paternal consent, factor into legal decisionmaking that can influence pregnant women's exclusion from research.

Notably, attendees explained that the lack of definitional clarity and regulatory guidance with respect to Subpart B compels legal decisionmakers to approach research with pregnant women cautiously, if at all. Lawyers must carefully consider the potential for exposing a client to regulatory scrutiny, financial penalties, and reputational damage. Interpretation of a protocol's risks, benefits, or paternal consent requirements that is at variance with a regulator's interpretation could result in institutional sanctions and reputational harm from public attention.

Attendees also described the challenge of conducting research with pregnant women in the absence of a federal regulator's affirmative authorization to proceed, and where regulators can appear to discourage the research or promulgate what are in fact myths about its ethical and legal permissibility. For example, at the time the meeting was convened, an FDA website describing and promoting registries to track pregnancy outcomes in the clinical setting proclaimed that "drug companies can't test medicine on pregnant women."[15] That information, which is factually incorrect, has since been removed from the website. Nevertheless, because there is a paucity of relevant and easily accessible precedents of approved research with pregnant women that might serve as a guide through regulatory pathways, legal decisionmakers have scant knowledge of what others in the same or similar position are doing. All of the foregoing uncertainties can lead legal decisionmakers to default to advising their clients not to initiate or otherwise support research on pregnant women.

OBSTACLES TO LEGAL RISK MANAGEMENT MAGNIFY LAWYERS' CONCERNS ABOUT LIABILITY

The literature has long suggested that the primary factor contributing to the exclusion of pregnant women from clinical trials is fear of liability.[16] The attendees confirmed that pharmaceutical sponsors, IRBs, and research institutions they work with are sensitive to what they perceive as heightened legal risk associated with conducting research with pregnant women. But, they also stressed that fear of liability is neither the primary nor the only obstacle to including pregnant women in research. In fact, lawyers are accustomed to developing strategies to manage liability risk for those clients who desire to pursue ventures that are considered "risky." In the context of research with pregnant women, however, attendees identified a number of impediments to robust risk management. These obstacles to risk mitigation can magnify concerns that legal decisionmakers have about liability related to the inclusion of pregnant women in clinical research. We begin with the attendees' insights regarding legal risk assessment, followed by their views concerning risk management.

The attendees emphasized that when legal decisionmakers consider the liability risks posed by research, their assessment is shaped by a number of considerations. First is so-called "long-tail liability." Long-tail liability describes a legal claim that arises when an alleged harm occurs continuously or progressively over a number of years or even decades. The liability concern is not simply that a pregnant woman or her potential offspring may be harmed by an experimental agent, but rather that these harms may take years to manifest, or

may appear in future generations. In this context, attendees pointed to the American experience with diethylstilbestrol (DES), a drug prescribed to an estimated 5–10 million pregnant women between the 1950s and 1970s, before the FDA determined in 1971 that DES is strongly associated with the risk of clear cell adenocarcinoma and reproductive abnormalities in female offspring. As a consequence, the manufacturers of DES faced enormous lawsuits over a lengthy period of time, not only from the women who had taken DES, but from their daughters as well.[17] Manufacturers have also faced the threat of litigation from injured women whose grandmothers had taken DES, although those plaintiffs generally have been unsuccessful.[18] Nonetheless, as several attendees explained, the potential for a long-tail of liability means that for decades after a research study concludes, there are at least two categories of "potential future litigants": the woman and her potential offspring.

The second, and related, liability consideration that attendees emphasized was that history and context influence the legal advice that lawyers offer. The thalidomide tragedy of the 1950s and 1960s, in which thousands of European babies were born with birth defects linked to the widely available anti-nausea drug their mothers took while pregnant, has had a lasting impact on risk perception. Although the tragedy arguably could have been mitigated had pregnant women been included in early testing of thalidomide—a point frequently made in the literature urging the early inclusion of pregnant women in clinical trials[19]—the episode was more often cited by attendees for the proposition that research with pregnant women requires special legal attention because of the *magnitude* of potential harm to offspring from pharmaceutical interventions. As one attendee noted, no one wants to be responsible for "the next thalidomide."

The third liability-related consideration that influences legal decisionmakers is the existing liability profile of a research institution or pharmaceutical sponsor. If an institution or sponsor recently experienced litigation, its lawyers and high-level executives may be "gun-shy" about entering research perceived to involve greater than standard liability risk. This may be particularly true if the institution or sponsor "is under the microscope" following adverse publicity from a prior legal decision or settlement. One attendee explained that in such cases, "everything related to risk [is then] colored through the prism of [prior] litigation."

Liability is not, however, considered a complete barrier to research with pregnant women. Lawyers are trained to assess risk and offer strategies to mitigate that risk. Attendees highlighted two factors currently challenging their management of liability-related risk. First is the difficulty in obtaining clinical trial insurance to cover potential research-related injuries incurred by a pregnant woman and/or her potential offspring. Although some representatives of pharmaceutical companies, academic research institutions, and non-profit research organizations indicated they had successfully procured such insurance—for example, for HIV-related trials of pre-exposure prophylaxis (PrEP) and for HIV prevention of mother-to-child transmission—others reported that self-insurance was the only option available to cover any legal or medical costs associated with research-related injuries, regardless of whether the trial included pregnant women.

The second risk-management challenge that attendees described relates to legal risk exposure for pharmaceutical manufacturers that test, and ultimately label, drugs for use in pregnant women. Attendees explained that once a pharmaceutical manufacturer conducts research with pregnant women and labels a product for use in that population, their "liability becomes real" for any drug-related harms experienced by pregnant women or their potential offspring. Pharmaceutical manufacturers therefore prefer to categorize drugs as untested in pregnant women, which is permissible under current regulations, and leave prescribing decisions to a pregnant woman's health care provider. If the health care provider prescribes such a drug with a resulting teratogenic or other harmful effect, the consequences may be litigated in a medical malpractice claim against the provider, referred to as the "learned intermediary," but most likely not in a legal claim against the manufacturer.[20] As a matter of legal risk management, legal advisors therefore recommend that pharmaceutical sponsors "keep their hands off" of clinical research with pregnant women. The practical effect is that potential legal risk for pharmaceutical interventions is thereby shifted downstream to health care providers who prescribe needed drugs to their pregnant patients, and those drugs have not been tested in that population.

LEGAL DECISIONMAKERS CONSIDER VENUE-SPECIFIC LAWS THAT MAY NOT BE RESEARCH-SPECIFIC

In their advisory role, lawyers must specifically account for laws of the jurisdiction—whether international, national or local—in which the research will be conducted. Relevant laws include those related to the conduct of research as well as all other laws that could possibly be implicated by the proposed research. Attendees commented that some jurisdictions have laws that might make research with pregnant women more difficult, for example, compensation requirements for research-related injuries and heightened paternal consent laws. Other jurisdictions have laws that might lead a lawyer to advise against any research with pregnant women in that jurisdiction, for example, fetal protection laws.

The prospect of conducting research with any population in international venues prompts a number of legal considerations that were highlighted by the attendees. Not only must lawyers become intimately familiar with the legal complexity of foreign laws, but they also may need to resolve conflicts between U.S. laws, international guidelines, and country-specific legal norms. The laws of foreign jurisdictions may be more or less strict than those of the United States, and the perspectives of legal decisionmakers in each country add yet an additional layer of complexity. Attendees focused on two legal issues related to research with pregnant women, the complexities of which are amplified in the international setting. The first involves international and country-specific legal norms pertaining to compensation for research-related injuries, and the second concerns differing requirements for paternal consent.

On the topic of compensation, attendees noted that while U.S. federal research regulations are silent on whether compensation is owed to participants for research-related injuries, international guidelines specifically address the issue. The Declaration of Helsinki states that "appropriate compensation … for subjects who are harmed as the result of participating in

research must be ensured."[21] Similarly, the International Council on Harmonisation's "Good Clinical Practice" guideline states that sponsors should make provisions to compensate individuals who suffer injuries as a consequence of their participation in research.[22] The positive obligation to compensate participants for research-related injuries, which is echoed in the laws of many foreign countries, factors into legal decisionmaking about whether to include pregnant women in research. Research with pregnant women is associated with a lengthy period of risk exposure (described above as long-tail liability) because research-related injuries can emerge in a pregnant participant, her immediate offspring, and even future generations. Although some compensation schemes limit the class of possible claimants to individuals who have enrolled in research and suffered related harms, other compensation schemes stipulate that offspring who are injured in utero are entitled to the same compensation as enrolled research participants.[23] Meeting attendees stressed the financial unpredictability of long-tail liability and the related difficulties of obtaining clinical trial insurance to cover compensation requirements. They suggested that legal decisionmakers are likely to advise against conducting research with pregnant women in jurisdictions mandating compensation schemes for both pregnant women and their potential offspring.

With regard to paternal consent, the attendees noted that regional and local laws could negatively impact the willingness of pharmaceutical sponsors and research institutions to include pregnant women in clinical trials abroad. Although the *International Ethical Guidelines for Health-related Research Involving Humans* —issued by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)—state that "only the informed consent of the woman herself is required for her participation" in research,[24] attendees anecdotally noted that local cultural and legal norms about consent often hold more authority "on the ground." These norms, which may require a pregnant woman's husband or village leader to consent to her participation in research, can further discourage legal decisionmakers from supporting the inclusion of pregnant women in research.

Attendees also identified laws outside of the human subjects research context that are implicated by research with pregnant women. They highlighted three types of laws related to the legal status of the fetus that may influence how lawyers reason through decisions about whether and where to undertake clinical research with pregnant women: (1) fetal homicide laws, which impose criminal penalties for acts that cause the death of a fetus other than (in most such laws) legal abortion[25] ; (2) personhood laws, which similarly aim to provide legal protection to fetuses, but do so by declaring that fertilized eggs, zygotes, and fetuses are persons with full legal rights[26] ; and (3) child abuse, child neglect, and substance abuse laws. To our knowledge, none of those types of laws have been applied in the context of research, e.g., to criminally charge a research institution, pharmaceutical sponsor, or investigator for a miscarriage or stillbirth following a pregnant woman's participation in a trial. But their attempted use in non-research contexts,[27] (e.g., charging pregnant women with child neglect for refusing to follow doctor's orders or with child abuse for ingesting drugs) can affect legal decisionmaking about whether and where to pursue research with pregnant women.

CONCLUSION

The ever challenging HIV epidemic and recent Zika crisis are reminders of the urgent need for clear guidance about the conditions under which clinical research with pregnant women can—and should—proceed. A first step in that process is articulating and understanding the variety of moral, political, practical, and legal concerns about such research. This article—which is part of a larger project that also examines how clinical researchers, institutional review boards, pregnant women, and ethicists perceive HIV research with pregnant women—focuses on the role of legal decisionmakers and the factors that influence their decisions. It illuminates a number of legal considerations that go beyond those reported to date in the academic literature, and it challenges the perception, generally cited in the literature, that regulatory limitations pertaining to pregnant women in research and fear of liability are the critical legal obstacles to such research.

In this article we reveal a more complex legal context for research in pregnancy. Most importantly, legal professionals are—or have the potential to be—involved in decisionmaking that influences the conduct of research at every stage of the research process, from conception of the study question and product idea, through to reporting of findings, and ultimately to final product approval and marketing. We emphasize that focusing solely on federal regulations and liability fails to acknowledge the variety of factors that may prompt legal decisionmakers to prevent or halt research with pregnant women at various junctures along research pathways. Notably, institutional policies, customs, and practices – so-called “soft law” – shape risk-averse interpretations of statutes, regulations, and legal cases related to research with pregnant women. Looking forward, examining those “soft law” areas can assist in identifying not only the extent of their reach, but importantly, also the areas of flexibility that might permit research with pregnant women to proceed.

Although this article highlights why legal professionals may “red light” research with pregnant women, it does not foreclose the possibility that legal decisionmakers can “green light” such research. Clinical trials that actively enroll pregnant women, while uncommon, are in fact approved, and may generate data important to the health of women and their offspring. Future efforts to ensure that pregnant women benefit from evidence-based clinical interventions should therefore consider not only the layers of legal complexity that can pose obstacles to their inclusion in research, but also the analytical mechanisms by which some legal decisionmakers have successfully surmounted those hurdles. Our future work involves analyzing and sharing what we learn about those facilitative approaches. In the meantime, the insights provided in this article, at a minimum, point to a need for greater sharing of legal strategies that can successfully address the complex legal environment surrounding research with pregnant women. Clearly a critical and important first step would involve information sharing by and among legal professionals about the legal reasoning they applied to currently approved research with pregnant women. We are hopeful that our legal findings—combined with insights gained from other stakeholders we are engaging as part of the PHASES project—will inform crafting of guidance to facilitate ethical conduct of research with pregnant women that is capable of implementation in real-world settings. Doing so is critical to the ultimate objective of benefiting the health of pregnant women and the children they bear.

Acknowledgments

We are grateful to the legal professionals who either attended an in-person meeting held at the Johns Hopkins Berman Institute of Bioethics on November 21, 2014 or were consulted by telephone during October and November 2014, and whose expertise informed our analysis. We also thank the three anonymous peer reviewers for their helpful comments. The work reported in this article was supported by the National Institutes of Health under award numbers R01AI108368 and R56AI108368 (Lyerly PI).

References

1. Lyerly AD, Little MO, Faden R. The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research. International Journal of Feminist Approaches to Bioethics. 2008; 1(2):5–22. [PubMed: 19774226]
2. Andrew MA. Amoxicillin Pharmacokinetics in Pregnant Women: Modeling and Simulations of Dosage Strategies. Journal of Clinical Pharmacology and Therapeutics. 2007; 81(4):547–56. [PubMed: 17329990]
3. See, e.g., Institute of Medicine. Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Mastroianni AC, Faden R, Federman D. Vols. 1 and 2Washington, DCNational Academy Press1994;
4. PHASES (Pregnancy and HIV/AIDS: Seeking Equitable Study). http://www.hivpregnancyethics.org/
5. Krubiner CB, et al. Advancing HIV Research with Pregnant Women: Navigating Challenges and Opportunities. AIDS. 2016; 30(15):2261–65. [PubMed: 27490637]
6. Many of this article's authors have a long history of scholarly involvement in analyzing and addressing ethical and legal issues related to the inclusion of women (including pregnant women) in research. The meeting, which was intended to build on that expertise, was held at the Johns Hopkins Berman Institute of Bioethics and led by Mastroianni, Henry, Bailey, and Robinson. Eleven legal experts were able to attend in person in November 2014. Nine legal experts were reached by telephone either before or after that meeting, during October and November 2014. (Throughout this article, all experts are referred to collectively as meeting attendees.) The meeting was structured as a dialogue on three questions to assist the authors in mapping known obstacles throughout the research pathway: (1) What legal considerations (including incentives and disincentives) arise in decisions to include or exclude pregnant women from research generally? From HIV-related trials? (2) When does each of those legal considerations arise in the research process and by whom are they raised? (3) Who provides legal advice on each of those legal considerations and what sources of legal authority are used to provide answers or direction? Where are the "red lights"? Attendees were also provided with a set of facts and asked to map legal obstacles.
7. We provided anonymity to the attendees in order to encourage frank discussion and information sharing.
8. Bayh-Dole Act, 35 U.S.C. §§ 200–212 (1980).
9. Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research. 2001. 45 C.F.R. §§ 46.201–46.207http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.204. Subpart B has been adopted by the Central Intelligence Agency, Department of Defense, Department of Health and Human Services, Department of Homeland Security, and Environmental Protection Agency, and is applicable to research conducted or funded by those agencies. Institutional research that is not funded by those agencies may also be subject to the provisions of subpart B by a Federalwide Assurance (FWA) agreement. Terms of the Federalwide Assurance for the Protection of Human Subjects are available at http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html
10. 45 C.F.R. § 46.102(i) provides: "Minimal risk means that 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."
11. Exceptions to the paternal consent requirement include circumstances in which the biological father is "unable to consent because of unavailability, incompetence, or temporary incapacity or [when] the pregnancy resulted from rape or incest." 45 C.F.R § 46.204(e).

12. 45 C.F.R. § 46.205(b)(2).
13. 45 C.F.R. § 46.205(c)(5).
14. 45 C.F.R. § 46.408(b).
15. Pregnancy Registries. United States Food and Drug Administration; http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm. This language has since been removed [accessed May 4, 2015]
16. Rothenberg KH. Gender Matters: Implications for Clinical Research and Women's Health Care. Houston Law Review. 1996; 32:1201–72. [PubMed: 11660524] Mastroianni, AC.Faden, R., Federman, D., editors. Institute of Medicine. Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Vol. 1 and 2. Washington, DC: National Academy Press; 1994.
17. See, e.g., In re DES Cases, 789 F. Supp. 552 (E.D.N.Y. 1992).
18. Although companies have incurred legal expenses for defending against third generation tort claims, recovery for third generation DES claims has been denied in most reported decisions. See, e.g., Enright v. Eli Lilly & Co., 570 N.E.2d 198 (N.Y. 1991); Grover v. Eli Lilly & Co., 591 N.E.2d 696 (Ohio 1992); Marks v. Abbott Labs. & Co., No. 11-cv-4147, 2012 WL 1004874 (E.D.N.Y. Mar. 23, 2012). Nonetheless, claims for third-generation DES claims have been recognized in limited circumstances. See, e.g., E.R. Squibb & Sons, Inc. v. Lloyd's & Cos., 241 F.3d 154 (2d Cir. 2001) (excess liability contract interpreted to permit indemnification for third-generation DES claims); DeMayo v. Schmitt, No. 625, 1989 WL 234501 (C.P. Phila. Cty. Dec. 28, 1989) (allowing third-generation DES claim to proceed on negligence grounds, but not on strict liability grounds).
19. Levine, C. Women as Research Subjects: New Priorities, New Questions. In: Blank, RH., Bonnicksen, A., editors. Emerging Issues in Biomedical Policy: An Annual Review. Vol. 2. New York: Columbia University Press; 1993. Greenwood K. The Mysteries of Pregnancy: The Role of Law in Solving the Problem of Unknown but Knowable Maternal-Fetal Medication Risk. Cincinnati Law Review. 2010; 79(267):267–322.
20. The success of the learned intermediary doctrine as a liability defense for pharmaceutical manufacturers depends on the legal jurisdiction in which it is raised. Trasatti MA, Lanzendorfer LN. Defending Products Liability Suits Involving Off-Label Use: Does the Learned Intermediary Doctrine Apply?. Feb. 2011http://www.semmes.com/publications_archive/litigation/pdf/off-label-use.PDF.
21. World Medical Association. Declaration of Helsinki. § 15, October 2013, http://www.wma.net/en/30publications/10policies/b3/
22. International Council on Harmonisation. Good Clinical Practice. Jun 10.1996 E6(R1) https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.
23. Association of the British Pharmaceutical Industry. Clinical Trial Compensation Guidelines. Nov 12. 2014 http://www.abpi.org.uk/our-work/library/guidelines/Documents/compensation_guidelines_2014.pdf
24. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Health-related Research Involving Humans. Guideline 18, http://cioms.ch/ethical-guidelines-2016/WEB-CIOMS-EthicalGuidelines.pdf
25. At least 38 U.S. states now have fetal homicide laws, 23 of which apply to pregnancies from "conception" or "fertilization." National Conference of State Legislatures, "Fetal Homicide Laws," last modified March 4, 2015, accessed October 16, 2016, at http://www.ncsl.org/research/health/fetal-homicide-state-laws.aspx.
26. At the federal level, personhood initiatives like the Sanctity of Human Life Act and the Life at Conception Act have been unsuccessful. See, e.g., Life at Conception Act, H.R. 1091, 113th Cong. (2013); Sanctity of Human Life Act, H.R. 23, 113th Cong. (2013). At the state level, Kansas, for instance, legally protects fetuses as persons (Kan. Stat. Ann. § 21-5419 (2012)) and personhood laws are under consideration in seven additional states (Alabama, Colorado, Georgia, Iowa, Maryland, Missouri, and Virginia).
27. Several U.S. states have prosecuted women under these laws for engaging in behavior during pregnancy that is known or suspected to pose risk to a fetus. Paltrow L, Flavin J. Arrests of and Forced Intervention on Pregnant Women in the United States (1973–2005): The Implications for

Women's Legal Status and Public Health. Journal of Health Politics, Policy & Law. 2013; 38(2): 299.

Published in final edited form as:
Womens Health Issues. 2013 January ; 23(1): e39–e45. doi:10.1016/j.whi.2012.10.003.

Enrolling Pregnant Women: Issues in Clinical Research

Mary C. Blehar, PhD
Office of Research on Women's Health, NIH

Catherine Spong, MD
Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH

Christine Grady, PhD
Department of Bioethics, Warren G Magnuson Clinical Center, NIH

Sara F. Goldkind, MD, MA
Office of Good Clinical Practice, Office of the Commissioner, FDA

Leyla Sahin, MD
Pediatric and Maternal Health Staff, Maternal Health Team, Office of New Drugs, Center for Drug Evaluation and Research, FDA

Janine A Clayton, MD
Office of Research on Women's Health, NIH

Introduction

The NIH Office of Research on Women's Health (ORWH) was established in 1990 in response to Congressional, scientific and advocacy group concern that a lack of systematic and consistent inclusion of women in NIH-supported clinical research could result in clinical decisions made for women based on findings from studies of men—without evidence that they were applicable to women. The establishment of ORWH also heralded earnest efforts by NIH to develop a research agenda addressing gaps in scientific knowledge about women's health across the lifespan. In 1993, the Office's role in monitoring inclusion of women in NIH clinical research was codified by the NIH Revitalization Act. Over the past 20 years, much progress has been made in inclusion, so that females are currently 49 percent of subjects in NIH funded studies that include both male and female participants.

Over its 22 year history, ORWH has played a major role in coordinating and advancing a women's health research agenda at NIH. Based on a national collaborative effort that involved scientists, advocates, and other stakeholders, ORWH released a report, “Agenda for Research on Women's Health for the 21st Century: A Report of the Task Force on the NIH Women's Health Research Agenda for the 21st Century.” (DHHS, 1999) In 2009, the Office embarked on an update of the 1999 report through a series of scientific regional workshops and public hearings. The product of this effort was “Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research” released in September 2010 (DHHS, 2010). From the recommendations of 40 topic-focused scientific

Corresponding Author: Mary C. Blehar PhD, Office of Research on Women's Health National Institutes of Health, Department of Health and Human Services 6707 Democracy Blvd. Suite 400, MSC 5484, Bethesda, Maryland 20892-5484 Telephone: 301-402-1770 Fax: 301-402-1798 mary.blehar@nih.gov.

workgroups at five regional meetings, the agenda distilled six cross-cutting and overarching goals to advance women's health and sex/gender research. One goal, to “actualize personalized prevention diagnostics and therapeutics for women and girls”, included specific objectives for research on conditions affecting pregnant women and research on the effects of pregnancy-related conditions on the subsequent health of women and their offspring. In October 2010, ORWH convened a workshop to address ethical, regulatory, and scientific issues raised by the enrollment of pregnant women in clinical research.

Defining the Need

In 1994 an Institute of Medicine report (Mastroianni, Faden & Federman, 1994) on challenges and barriers to the inclusion of women in clinical research recommended that pregnant women be presumed eligible for participation in clinical studies. The majority of members of the report's authorship committee also endorsed a recommendation that investigators and institutional review boards (IRBs) exclude pregnant women from participation only when (1) there was no prospect of medical benefit to the pregnant woman, and (2) a risk of significant harm to the offspring was known or could be plausibly inferred. Despite the report, today pregnant women continue to be excluded from the vast majority of pharmacological therapeutic or preventive trials.

This exclusion is highly consequential. Over 4 million women in the United States give birth annually. Among them are women affected by serious illnesses such as hypertension, diabetes, asthma, mental disorders, autoimmune disorders, cancers and others that require ongoing or urgent treatment during pregnancy. Approximately 64 percent of pregnant women are prescribed one or more medications for chronic illnesses or for conditions that arise during pregnancy (Andrade et al. 2004). Nonetheless, very few drugs are approved for use during pregnancy. In addition, most drug labels have little pregnancy data to inform prescribing decisions. Efforts to address this problem have resulted in a draft FDA rule[1], which will improve the information in labeling after it publishes as a final rule. Although there are significant physiologic changes in pregnancy, including near doubling of maternal blood volume and alterations in binding proteins, the pharmacokinetics and efficacy of drugs in pregnancy are, by and large, unknown. Toxicity and teratology studies of pregnant animals imperfectly or inconsistently predict human effects. As a result, therapeutic decisions for pregnant women are often made without an evidence base. Treatment of the mother may be inadequate, exposing the fetus to therapies at a dose which does not provide a benefit to the mother (Lyerly, Little & Faden, 2008).

As an example, in 2001, in response to concern over the public health consequences of anthrax exposure, the CDC recommended a 60-day course of ciprofloxacin for pregnant women, because the high risk associated with developing anthrax was judged to outweigh possible teratogenic risk of the drug. Based on amoxicillin's superior safety profile in pregnancy, the American College of Obstetrics and Gynecologists recommended that clinicians treating at risk pregnant women exposed to anthrax switch to amoxicillin if the anthrax was found to be penicillin-responsive (ACOG 2002). This strategy may have exposed pregnant women to under-treatment. A 2007 study funded partly by the FDA and NIH, indicated that amoxicillin concentrations adequate to prevent anthrax were most likely unachievable during pregnancy due to increased metabolism of the drug (Andrew et al., 2007).

In 2009, when the H1N1 pandemic occurred and pregnant women were identified as a high risk population, no immunogenicity data were available in pregnant women to inform dosing

[1] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

of the H1N1 vaccine, and no pharmacokinetic data in pregnant women were available to inform dosing of antivirals (Goldkind, Sahin & Gallauresi, 2010). Due to the threat posed by H1N1 during pregnancy, clinical trials in pregnant women are subsequently being conducted.

Pregnancy Research: Historical Background of Exclusion

With such compelling needs, why are pregnant women largely excluded from clinical research? This is an important area for further study because the reasons for exclusion are not well documented. However, reasons include at least fear of harm to the fetus and threat of legal liability; concern about the complicated physiology of pregnant women; uncertainty whether pregnant women would be willing to participate; regulations which classify pregnant women as a "vulnerable" population in need of special protections in research; and vague, ambiguous, and restrictive wording of regulations, which IRBs in turn interpret conservatively for pregnant subjects.

In 1974 Congress asked the newly established National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to make recommendations for the conduct of research involving pregnant women and fetuses. In its work, the Commission was influenced by a number of contemporaneous events such as the 1973 *Roe v. Wade* decision, the subsequent emergence of a notion of a "maternal-fetal conflict" (Markens, Browner & Press, 1997) and the occurrence of serious birth defects as a consequence of pregnancy exposures to thalidomide and diethylstilbestrol. The recommendations of the Commission were codified in Federal Regulations at Subpart B of 45 CFR 46.

Pregnant women, fetuses and neonates are often considered vulnerable and are protected by additional regulations, along with children and prisoners. In 2001, the wording of Subpart B was changed from a prior more proscriptive approach to a more inclusive approach. The new language states that pregnant women or fetuses *may be involved* in research if all of ten conditions are met. The current wording of Subpart B is given in Table 1. Despite these modifications, pregnant women continue to be excluded from clinical trials.

As part of the effort to develop scientifically rigorous and evidence-based treatment options for pregnant women, FDA reviews protocols for clinical research involving this study population, on a case-by-case basis. Based on this experience, FDA has developed guidance to help researchers and IRBs understand the Agency's current thinking in this regard. For example, FDA has issued guidance on pharmacokinetic studies during pregnancy,[2] clinical lactation studies[3] and pregnancy exposure registries[4]. Recognizing the additional ethical and scientific complexities associated with studying pregnant women in the setting of a clinical trial, FDA is developing guidance on this topic[5].

In 2009, the *Second Wave Initiative* was founded at Georgetown University to promote the responsible inclusion of pregnant women in clinical research based on ethical reasons and medical need (Little, Lyerly & Faden, 2011). During the October 2010 ORWH workshop the current status of research involving pregnant women and future needs were discussed in light of the above issues and concerns. A workshop summary report (Foulkes, Grady, Spong, Bates & Clayton, 2011) and a more extensive report of workshop proceedings (ORWH, 2011) provide detail on presentations and topics. Below is a focus on three major

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072133.pdf
[3] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127505.pdf
[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071639.pdf
[5] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm314767.htm

interrelated scientific and science regulatory issues that emerged as important concerns at that meeting.

Recommendation 1: Define Pregnant Women as a Scientifically "Complex" Population and Change the Presumption of Exclusion

In order to appropriately address health needs, pregnant women should be reclassified from their current status as a "vulnerable" population to that of a medically complex population, necessitating special scientific and ethical considerations. A corollary is the need to change the presumption of exclusion of pregnant women to one of inclusion. These issues are discussed below.

Ethical Issues

Ethical issues in pregnancy research have received extensive consideration elsewhere (McCullough, Coverdale, Chervenak, 2006; Lyerly, Little, Faden, 2008, 2011; Macklin, 2010). Macklin (2010) stated that "the most compelling reason to justify the inclusion of pregnant women in studies is the need for evidence gathered under rigorous scientific conditions that place fewer women and their fetuses at risk than the much larger number of pregnant women who will be exposed to the medications once they come to market."

Groups are considered vulnerable when they have a compromised ability to protect their interests and provide informed consent. In general, pregnant women are capable of protecting their own interests and giving their own informed consent. However, because they are also responsible for protecting the interests of the growing fetus, who cannot consent to research or may have unique susceptibility to risks, there are additional distinctive issues that a pregnant woman needs to consider with regard to the risks and benefits of participation in clinical research, resulting from the interdependence of the maternal-fetal unit. Even though the interests of the mother and the fetus are conceptually separable, in practice, the notion of maternal-fetal conflict poses a false dichotomy. If a pregnant woman affected by a serious debilitating or life-threatening disease is enrolled in a trial with therapeutic benefit potential for her, her health is closely linked to the health of the baby and later to the health of the child who will receive benefit from maternal care. Those benefits and direct maternal therapeutic benefit need to be weighed against any possible risks to the fetus of maternal treatment or non-treatment.

A major impediment in moving forward with enrolling pregnant women in research is a concern that an intervention could cause harm resulting in birth defects. There is a baseline rate of approximately 3 percent for birth defects, although it is difficult to predict which babies will have birth defects. In research that includes pregnant women, the mother's health status coming into the study is known and the assumption is usually that the fetus is healthy. An adverse fetal outcome tends to be attributed to the research intervention despite the baseline rate of birth defects. There is a need to develop special scientific models that address the baseline rate issue and attribution of causation in clinical interventional research in pregnancy.

The Physiology of Pregnancy

Pregnant women are an especially dynamic subset of women, in whom pregnancy related physiological changes occur that can potentially alter a drug's pharmacokinetics and efficacy. Not only is the pregnant state physiologically different than the non-pregnant state, but also physiology changes over the course of the pregnancy. When blood volume doubles in pregnancy, the effects on drug metabolism are significant. Dosing and interval recommendations established for non-pregnant women cannot automatically be extrapolated

to pregnant women (Little 1999; Chambers, Polifka & Friedman, 2008). In 2004, the FDA issued draft guidance on pharmacokinetic studies in pregnancy. The guidance emphasized that treatment of conditions in pregnant women ought to optimize results for the maternal-fetal pair. In order to do that it is important to obtain pharmacokinetic data that reflect changes in drug metabolism and are relevant across pregnancy.

Moving from a Presumption of Exclusion to One of Inclusion

The need to reclassify pregnant women as a complex population was recognized in the 1994 IOM report. This reclassification is an important step toward engaging more scientific and ethical dialogue on pregnancy research. However, reclassification needs to proceed along with a change in the presumption of exclusion of pregnant women to one of inclusion.

Currently researchers must justify the inclusion of pregnant women and specify what special protections are going to be put in place. Interestingly, there is no requirement to justify their exclusion from a protocol. Since the NIH began to require inclusion of women, ethnic minorities, and children in research, pregnant women are the only population for which justification for exclusion does not need to be given.

A 1998 NIH directive on children in clinical research, for example, called for a presumption of inclusion, consistent with subpart D of the human subjects' regulations and a need to justify exclusion. Following that directive and with further impetus from the Pediatric Research Equity Act (Public Law 108–55, 2003), there has been a marked increase in the number of clinical trials and studies that include pediatric subjects. A similar NIH directive for the inclusion of pregnant women would move the field to a more balanced scientific consideration of issues.

Recommendation 2: Clarify Existing Regulations and Focus on IRB Behavior as it Facilitates or Impedes Pregnancy Research

There are several factors leading to reluctance to include pregnant women in clinical research. Researchers are sometimes concerned about the physiologic complexity in pregnancy, and possible legal liability. Existing regulations governing the inclusion of pregnant women in clinical research are somewhat ambiguous, imposing another significant barrier to their implementation. Additionally, IRBs may go beyond regulatory requirements when the proposed subjects are pregnant women. Although not specific to pregnancy research, variation among IRBs in the interpretation of regulations for the same protocol is a further impediment, especially in multisite studies.

Problems have been identified with IRB interpretation of regulations governing clinical research that includes pregnant women as subjects (Levine, 2011). As an example, wording in Subpart B states that pregnant women or fetuses may be involved in research if all of ten enumerated conditions are met. Condition (a) specifies that research may be conducted where scientifically appropriate, preclinical and clinical studies on non-pregnant women provide an adequate basis for assessing potential risks to pregnant women and fetuses. IRBs are left to interpret how much prior research is sufficient and they typically interpret this directive conservatively.

The interpretation of “minimal risk to the fetus” in condition (d) of Subpart B is particularly problematic. Despite clarifications in 2005 by the Secretary's Advisory Committee on Human Subjects Research, as well as clarifications from the IOM and other organizations, arguments continue about the meaning of minimal risk and interpretations vary widely.

Testing of drug therapies in a pediatric population presents an analogous situation to testing of drugs in a pregnant population. Several studies reveal inconsistencies among IRBs in

applying regulations governing clinical research to studies involving children (Whittle et al, 2004; Kimberly et al., 2006). A survey (Shah et al., 2004) asked IRB chairs to evaluate the degree of risk for various kinds of research on children. For a study in children testing a drug already found safe in adults, only five percent of IRB chairs said that the study presented minimal risk and 72 percent felt that this was greater than a minor increase above minimal risk. Even for a pharmacokinetic study, in which the risk of death is estimated to be less than one in a million, 53 percent of IRB chairs evaluated it as greater than a minor increase over minimal risk.

Although IRB inconsistency is likely due in large part to differences in interpreting regulatory requirements and ethical standards, it might also stem from some IRB members' lack of necessary expertise regarding research ethics and regulations for research with special populations of children or pregnant women. Specialized committees as well as training of IRB members in the specific requirements of regulations for such populations may be helpful.

A July 2011 Federal Register Announcement sought input on possible changes to the Common Rule and to Federal Regulations 21 CFR Parts 50 and 56 Human Subjects in order to enhance protections for research subjects and reduce burden, delay, and ambiguity for investigators. The announcement noted that regulations have not kept pace with the evolving human research enterprise, the proliferation of multi-site clinical trials and observational studies, the expansion of health services research, research in the social and behavioral sciences, and research involving databases, the Internet, and biological specimens in repositories, and the use of advanced technologies, such as genomics.

Proposed revisions included those to reduce impediments to IRB approval for multisite protocols. Although the changes discussed did not specifically address regulatory-defined “vulnerable” populations such as pregnant women, it was noted that regulations for these populations will likely be affected by changes and will need to be harmonized, as appropriate, with any changes made to the Common Rule.

In summary, there is wide agreement about the need to clarify regulations governing the inclusion of pregnant women and fetuses in clinical research and to increase consistency among IRBs in decision making procedures. More transparency in IRB decision processes concerning pregnancy research is needed. In this regard, surveys of IRBs similar to those conducted for pediatric research would be useful. The NIH should consider the value of adopting a policy of inclusion and a need to justify exclusion for pregnant women similar to the policy adopted for pediatric research.

Recommendation 3: Develop a Pregnancy Research Agenda

A research agenda on pregnancy should address both areas of high clinical need as well as scientific opportunities while at the same time capitalizing on existing resources. Among major elements to be included in such an agenda are: (1) research to promote evidence-based clinical practice; (2) identification of questions that can be addressed with existing data and through ongoing studies; (3) identification of new studies in high scientific impact areas.

Promote Evidence-Based Clinical Practice

Studies of the effects of interventions in pregnancy are clearly a priority to move forward to inform evidence-based clinical practice. It is important to consider including pregnant women in certain ongoing clinical trials addressing interventions for conditions that are not related to pregnancy but that pregnant women suffer from, such as hypertension and asthma.

However, inclusion of pregnant women in such trials has to be planned for reasons of safety and interpretation of expected differences. FDA and NIH encourage researchers to engage in early discussions with appropriate FDA and NIH staff when a trial enrolling pregnant women is considered. The physiologic changes occurring in pregnancy may require greater numbers across gestational ages to clearly identify and define optimal treatment regimens. In addition, there is a need for more trials specific to pregnancy. Although in these trials, exclusion is not a relevant concern, as all participants are pregnant, the size, number, and type of these trials need to be augmented.

Capitalize on Existing Studies and Resources

Opportunistic study designs such as pharmacokinetic studies and pregnancy registries, which collect data on dosing and pregnancy outcome, respectively, are encouraged when appropriate. In these types of studies, enrolling pregnant women who are already using the medication of interest, that is, have already been prescribed the drug for therapeutic purposes by their physician, obviates the need to begin a medication in the research setting. (Healthcare providers and patients can access a list of available pregnancy registries at the FDA's Office of Women's Health website[6].) Furthermore, with little or no additional risk to the pregnant woman or her fetus and without changes to the regulatory environment, a wealth of data may also be available from ongoing studies that include cohorts of pregnant women. Input from clinical and health services researchers, ethicists and policymakers is needed to identify and prioritize existing studies that may be readily mined or adapted to address questions of importance to pregnant women and their health concerns.

Pregnancy Research: New Opportunities

Currently, the majority of research on pregnancy confines itself to issues of the pregnancy and extends to early neurodevelopmental outcomes of the child. Although these areas continue to be highly important, a new paradigm is emerging that views pregnancy in terms of its implications for later health and seeks to understand the longer term effects of treatment or non-treatment of illness during pregnancy on later maternal and child health and even the health of offspring as adults.

Pregnancy may unmask chronic disease; pregnancy outcomes may predict future disease; and pregnancy may provide an opportunity to identify health risks and disease. Normal changes in pregnancy present a picture of a “metabolic syndrome”, with insulin resistance, hyperlipidemia, increased coagulation factors, upregulation of the inflammatory cascade and increased white blood cells. Most women tolerate these changes with no problems but others develop diseases such as gestational diabetes and thromboembolisms.

Severe preeclampsia leading to preterm birth is a major cause of maternal and fetal morbidity and mortality. Recent epidemiological findings have challenged a long-held view that preeclampsia is inconsequential for later health (Ray, Vermeulen, Schull, Redelmeier, 2005). Rather it is now recognized as an early indicator of a woman's risk for later vascular disease --hypertension, myocardial infarction, stroke, and renal disease. Pregnancy is a metabolic and vascular `stress test' for women and those who `fail' are at increased risk of long-term cardiovascular complications. The risk is highest among women who develop both maternal (e.g., hypertension and proteinuria) and fetal (e.g., intrauterine growth restriction) manifestations of abnormal placentation, especially with preterm delivery. Translational research should continue to increase fundamental understanding of the mechanisms linking pathological syndromes of pregnancy to later disease and to provide new therapeutic and preventive targets.

[6] http://www.fda.gov/scienceresearch/specialtopics/womenshealthresearch/ucm134848.htm

Furthermore, it is hypothesized that, in response to intrauterine stresses, the fetus makes adaptations that persist into postnatal life. These changes include epigenetic modifications of gene expression. Prenatal programming of the epigenome is viewed as a critical determinant of offspring outcome and stands at the interface between environment and genetics. Maternal experiences such as stress and obesity are associated with a host of neurodevelopmental and metabolic diseases, some of which have been characterized into the second and third generations. The mechanism through which determinants such as maternal diet or stress contribute to disease development in the child likely involves a complex interaction between the maternal environment, placental changes, and epigenetic programming of the embryo. Changes in epigenetic programming provide the developmental link between prenatal risk exposure and later outcomes (De Boo & Harding, 2006). A small number of studies have identified heritable epigenetic effects of environmental perturbations on offspring that may provide a mechanism for explaining trans-generational influences (Anway et al., 2005; Crews et al., 2007).

Moving into the Future with Pregnancy Research

A 2011 review of the policy implications of the NIH Agenda for Women's Health research noted that women's health research is at a scientific turning point for the 21st Century with the incorporation of new scientific approaches and technologies into the agenda. However, women's health research must also address important clinical care and public health issues (Wood, Blehar & Mauery, 2011).

Despite substantial progress over the past two decades in increasing the inclusion of minorities and children in clinical research, pregnant women remain highly under-served in this regard. Due to the complexity of issues raised by efforts to increase their inclusion, a multidisciplinary collaborative approach is required, consisting of scientists, ethicists, clinician researchers, clinicians and pregnant women themselves as advocates for their health interests.

There is a clear and compelling rationale for increased pregnancy research in order to address the pressing therapeutic needs of pregnant women. Additionally, there is accumulating evidence that pregnancy provides a unique window into understanding fundamental mechanisms underlying observed links between a pregnant woman's health and her later health and the health of her children. While pregnancy research raises myriad complex issues and challenges, its clinical value and its potential for generating new scientific knowledge about lifespan and intergenerational development demand that the challenges be met.

Acknowledgments

The opinions expressed in this commentary are those of the authors and do not necessarily reflect the position of the Department of Health and Human Services, the National Institutes of Health and the Food and Drug Administration.

References

ACOG Committee of Obstetric Practice. ACOG Committee Opinion number 268, Management of asymptomatic pregnant or lactating women exposed to anthrax. Obstetrics and Gynecology. 2002; 99(2):366–8. [PubMed: 11814522]

Andrew MA, Easterling TR, Carr DB, Shen D, Buchanan ML, Rutherford T, Hebert MF. Amoxicillin pharmacokinetics in pregnant women: modeling and simulations of dosage strategies. Clinical Pharmacology and Therapeutics. 2007; 81(4):547–556. [PubMed: 17329990]

Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science. 2005; 308:1466–1469. [PubMed: 15933200]

Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet. 1986; 1(8489):1077–1081. [PubMed: 2871345]

Chambers CD, Polifka JE, Friedman JM. Drug safety in pregnant women and their babies: ignorance not bliss. Clinical Pharmacology and Therapeutics. 2008; 83(1):181–183. [PubMed: 18073777]

Crews D, Gore AC, Hsu TS, Dangleben NL, Spinetta M, Schallert T, Anway MD, Skinner MK. Transgenerational epigenetic imprints on mate preference. Proceedings of the National Academy of Science USA. 2007; 104:5942–5946.

De Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2006; 46:4–14. [PubMed: 16441686]

Foulkes M, Grady C, Spong CY, Bates A, Clayton JA. Clinical research enrolling pregnant women. A workshop summary. Journal of Women's Health. Aug 5.2011 e-pub ahead of print.

Goldkind SF, Sahin L, Gallauresi B. Enrolling pregnant women in research---lessons from the H1N1 influenza pandemic. New England Journal of Medicine. 2010; 326(24):2241–2243. [PubMed: 20554981]

Kaposy C, Baylis F. Ethical evidence based guidelines for contraceptive use in research. IRB. 2010; 32(5):1–9. [PubMed: 21033603]

Kimberly MB, Hoehn KS, Feudtner C, Nelson RM, Schreiner M. Variation in standards of research compensation and child assent practices: a comparison of 69 institutional review board-approved informed permission and assent forms for 3 multicenter pediatric clinical trials. Pediatrics. 2006; 117(5):1706–11. [PubMed: 16651328]

Levine RJ. IRB perspective on inclusion of pregnant women in clinical research. Issues in Clinical Research: Enrolling Pregnant. A workshop report. 2011

Women Little BB. Pharmacokinetics during pregnancy: evidence-based maternal dose formulation. Obstetrics and Gynecology. 1999; 93(5 Pt 2):858–868. [PubMed: 10912434]

Lyerly AD, Little MO, Faden RR. Reframing the framework: toward fair inclusion of pregnant women as participants in research. American Journal of Bioethics. 2011; 11(5):50–52. [PubMed: 21534152]

Lyerly AD, Little MO, Faden RR. The second wave: Toward responsible inclusion of pregnant women in research. International Journal of Feminist Approaches to Bioethics. 2008; 1(2):5–22. [PubMed: 19774226]

Lyerly AD, Little MO, Faden RR. The National Children's Study: A golden opportunity to address the health needs of pregnant women. American Journal of Public Health. 2009; 99(10):1742–1745. [PubMed: 19592606]

Macklin R. The art of medicine: Enrolling pregnant women in biomedical research. The Lancet. 2010; 375(9715):632–633.

McCullough LB, Coverdale JH, Chervenak FA. A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves pregnant women. American Journal of Obstetrics and Gynecology. 2005; 193(3 Part 2):901–907. [PubMed: 16157085]

Markens S, Browner CH, Press N. Feeding the fetus: on interrogating the notion of maternal-fetal conflict. Feminist Studies. 1997; Vol. 23(No. 2):351–372. Feminists and Fetuses (Summer, 1997). [PubMed: 11656819]

Mastroianni, AC.; Faden, RR.; Federman, DD., editors. Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Institute of Medicine; Washington D.C.: 1994.

National Institutes of Health Revitalization Act. Public Law 103-43.42 USC 289 (a)(1). 1993. Retrieved September 25 2011 from http://grants.nih.gov/grants/olaw/pl103-43.pdf

NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. 59 Fed. Reg. 1994. p. 14508-14513.Retrieved September 22, 2011 from http://grants.nih.gov/grants/olaw/pl103-43.pdf

Office of Research on Women's Health. Monitoring Adherence to the NIH Policy on the Inclusion of women and minorities as subjects in clinical research: 2009-2010. 2010. Retrieved 9/26/2011 from http://orwh.od.nih.gov/inclusion/inclreports

Pediatric Research Equity Act. Public Law. 2003. p. 108-155.Retrieved September 23, 2011 from http://www.gpo.gov/fdsys/pkg/PLAW-108publ155/pdf/PLAW-108publ155.pdf

Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet. 2005; 366(9499): 1797–803. [PubMed: 16298217]

Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do institutional review boards apply the federal risk and benefit standards for pediatric research? Journal of the American Medical Association. 2004; 291(4):476–482. [PubMed: 14747505]

U. S. Department of Health and Human Services (DHHS). Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators. 2011. Retrieved September 26 2011. From http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/pdf/2011-18792.pdf

U. S. Department of Health and Human Services, (DHHS). National Institutes of Health, Office of Research on Women's Health. Issues in Clinical Research: Enrolling Pregnant Women: A Workshop Report. 2011.

U. S. Department of Health and Human Services (DHHS); Public Health Service, National Institutes of Health. Agenda for Research on Women's Health for the 21st Century. A report of the Task Force on the NIH Women's Health Research Agenda for the 21st Century. 1999; volume 1

U. S. Department of Health and Human Services (DHHS). National Institutes of Health. Office of Research on Women's Health. Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research. 2010.

Whittle A, Shah S, Wilfond B, Gensler G, Wendler D. Institutional review board practices regarding assent in pediatric research. Pediatrics. 2004; 113(6):1747–52. [PubMed: 15173501]

Wood SF, Blehar MC, Mauery R. Policy Implications of a New National Institutes of Health Agenda for Women's Health Research, 2010-2020. Women's Health Issues. 2011; 21–2(2011):99–103.

Table 1

The Current Wording of §46.204 Subpart B

45 CFR46 Subpart B	Category	Explanation
§46.46.204	**Pregnant women or fetuses may be involved in research if *ALL* of the following conditions are met**	a. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses; b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means; c. Any risk is the least possible for achieving the objectives of the research; d. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions; e. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest. f. Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate; g. For children as defined in Sec. 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of the Protections for Children Involved as Subjects (Subpart D); h. No inducements, monetary or otherwise, will be offered to terminate a pregnancy; i. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; ***AND*** j. Individuals engaged in the research will have no part in determining the viability of a neonate.

BMC Pregnancy and Childbirth

RESEARCH Open Access

A Learning Healthcare System for pregnant and breastfeeding women: what do women during preconception, pregnancy, and nursing think? – A qualitative study

A contribution from the ConcePTION project

Marieke J. Hollestelle[1*], Rieke van der Graaf[1], Sarah Dewi Hartman[1], Miriam C. J. M. Sturkenboom[2] and Johannes J. M. van Delden[1]

Abstract

Background: Most medications lack evidence-based information about its safety and efficacy during pregnancy and breastfeeding, because pregnant women are often not included in clinical research. Another way to generate evidence is by using a Learning Healthcare System (LHS) approach. In an LHS, care and research are aligned in such a way that it can accelerate evidence generation and outcomes for patients, based on real-life medication use. For the development of an ethically responsible and sustainable LHS, it is of crucial importance to understand what women think of such an alternative approach to knowledge generation. Therefore, this paper explores their views on an LHS for pregnant and breastfeeding women.

Method: For this qualitative study, we interviewed 20 women during preconception, pregnancy, or nursing to explore their views on an ethically responsible LHS for pregnant and breastfeeding women. The pseudonymized transcripts were analyzed thematically.

Results: We identified four main themes describing women's views on LHSs. The first theme describes that respondents were positive about learning healthcare systems, and considered them to function as a central point for information about their medication, which they felt is currently lacking. The second theme shows that respondents want to contribute to and engage in generating new information because they want to help others and contribute to scientific research. Respondents also mentioned that, currently, not every woman is aware of the risks of the lack of evidence for medication used in pregnancy. The third theme shows that respondents regard their healthcare professional as essential for the translation and interpretation of information, regardless of a learning healthcare system. The last theme describes that respondents will trust a learning healthcare system more if the medical community supports it, and when data collection and processing is transparent.

*Correspondence: m.j.hollestelle-2@umcutrecht.nl
[1] Department of Medical Humanities, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
Full list of author information is available at the end of the article

Conclusion: Women during preconception, pregnancy and nursing agree that an LHS could be a viable alternative to help close the knowledge gap on the safety of medication used during pregnancy and breastfeeding. The obtained insights from our interviews provide valuable stepping-stones for the development of an ethically responsible and sustainable LHS, as well as for the engagement of women in an LHS.

Keywords: Ethics, Qualitative research, Learning healthcare systems, Pregnant and breastfeeding women

Background

Every year more than 5 million women[1] become pregnant in the European Union and the majority takes at least one medication during a pregnancy [1, 2]. Yet, most medications lack evidence-based information about safety and efficacy during pregnancy, because pregnant women are routinely excluded from most clinical research, due to a fear of harming the developing fetus [3, 4]. Even less information is available about the exposure of the newborn to the medication through breastfeeding. Only 5% of the available medications have been adequately monitored, tested, and labelled for use in pregnancy and breastfeeding and often long-term effects remain unknown [5].

In real life, numerous medications have been used safely and effectively in pregnancy with minimal risk to the fetus and mother, but we are not systematically learning from these experiences [6, 7]. There are strong ethical reasons to change the way evidence is currently being generated and disseminated. In the literature, multiple solutions for conducting research with pregnant women have been suggested, such as, routine inclusion of pregnant women in clinical trials or using an adaptive trail design to support safe and efficient inclusion of pregnant women in different stages of medication development [3, 8]. However, pregnant women hesitate to participate in trials, and medicines manufacturers hesitate to have them included, because of potential liability issues. Given the vast availability of real-world data on medicines prescriptions and health outcomes, an alternative way to generate evidence is to learn from previous and current medication use, by transforming the field of pregnant and breastfeeding women into a Learning Healthcare System (LHS) [4]. In an LHS, healthcare and research are aligned to accelerate research and outcomes for patients. LHSs have the potential to develop scientific knowledge based on health information and research data, and by directly implementing new insights from analyses to the clinical practice [9].

Currently, information on the safety and efficacy of medications used during pregnancy and breastfeeding is fragmented and spread across different data sources, pregnancy or medicines cohorts, registries, and research groups with unique data regarding pregnancies, adverse drug reactions and the like. Examples are the European system for the evaluation of safety of medication use in pregnancy in relation to risk of congenital anomalies (EUROmediCAT) and the European Network of Teratology Information Services (ENTIS). Combining these unique data sources in a system of continuous learning could help clarify how medications impact pregnancy outcomes and breastfeeding exposures [4, 7].

Although an LHS approach may broaden the opportunities to strengthen the evidence base of medications used during pregnancies and breastfeeding, multiple ethical issues arise when establishing and sustaining an LHS [10]. These ethical issues are for a large part the result of the sharp distinction that is currently visible between research and practice. In general, there is the question of quality and usability of the results from the learning activities flowing from an LHS, and therefore, the classification of the learning activities as (scientific) research. Furthermore, LHSs might struggle with ethical oversight, especially when the boundary between research and care is becoming less clear. Other important issues involve notifying participants and asking informed consent, creating transparency regarding data analyses, commercial interests, and unintended negative consequences from implementation of new insights into practice [11]. Furthermore, transforming the field of pregnant and breastfeeding women into an LHS will, besides overcoming the ethical issues, also depend on the support of a broad range of key stakeholders within the health system [12]. For example, women need to trust there is significant value and quality in the alternative approach so that they can rely on this evidence, and they need to believe their concerns about this new approach are taken seriously [12]. However, there is not much knowledge of patients' perspectives, let alone women of childbearing age, on LHSs. Currently, we do not know what their concerns are and when they would trust and support an LHS. Understanding what women think of this alternative approach and what their concerns are, will be of crucial importance for the success of the implementation of new insights into care and the collection of new health-related data within the LHS. Therefore, this paper aims to explore

[1] This also includes transgender men, non-binary and gender fluid people who want to become pregnant or are pregnant.

Table 1 General topic list

1. Attitude towards the status quo and the goal of ConcePTION
2. Participatory engagement
3. Respect for autonomy
4. Perceived risks
5. Need for return of results
6. Inclusion and freeriding
7. Sustainability

the views of women on an ethically responsible and sustainable LHS for pregnant and breastfeeding women. To deepen our understanding of the views of women whose data may become part of such an LHS for pregnant and breastfeeding women, we conducted semi-structured in-depth interviews with women during preconception, pregnancy, and nursing. During our interviews, we used the Innovative Medicine Initiative (IMI) ConcePTION-project as a case study. ConcePTION aims to develop an LHS mechanism for pregnant and breastfeeding women. In this way, the questions and answers are less hypothetical and can already be placed in real life context.

Method

Design

We employed a qualitative study design to explore women's views on an ethically responsible LHS for pregnant and breastfeeding women. The study is reported in accordance with the consolidated criteria for reporting qualitative studies (COREQ) [13]. This qualitative interview study is a sub study of the IMI ConcePTION-project. Our study focused solely on women, since we were interested in the primary target population of the LHS specifically, which accordingly could be aligned with the opinion of other relevant stakeholders within IMI ConcePTION. For example, other researchers within the ConcePTION-project conducted a survey study and focus groups with healthcare professionals (HCPs) to understand their needs regarding medication use during pregnancy.

We performed semi-structured interviews with a topic list (see Table 1), which came from two sources. We used some of the items from guideline 12 of the 2016 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-related Research Involving Humans [14]. The CIOMS guideline 12 covers essential elements for governing the collection, storage, and analysis of data in health-related research. A parallel can be drawn between data analysis within an LHS and health-related research in general, and therefore, the CIOMS guideline is very relevant for an LHS. We also used the results of a narrative review on patient and public views and attitudes towards the sharing of health data for research [15]. This review gave insight into key conditions for the use of health data in general, which were used as topics in the interviews.

Sample and setting

We aimed to include women whose data may become part of an LHS for pregnant and breastfeeding women. We therefore included women who wanted to become pregnant, were pregnant at the time of the interview, or were nursing[2] up to 6 months after giving birth. Furthermore, to obtain a broad range of perspectives on the topics, we aimed to include women with different medical backgrounds and diverse characteristics. Respondents were recruited by purposeful sampling with the help of our contact persons from the University Medical Center Utrecht, the Amsterdam University Medical Center, The Netherlands Pharmacovigilance Center Lareb, Eurocat Northern Netherlands, and by means of snowball sampling. Potential respondents were then approached and informed about the set-up of the study by e-mail or by phone.

Since an effective LHS for the treatment of pregnant and breastfeeding women is currently lacking, respondents were unfamiliar with the concept of an LHS. To collect valuable answers from the respondents, we decided to give them additional information at the start of the interview. With the additional information, we introduced IMI ConcePTION (see Table 2) as a case study to explain the lack of scientific knowledge and to explain the alternative way to help close the knowledge gap. We assumed all respondents were unfamiliar with the concept of an LHS, and therefore choose to explain the approach ConcePTION is taking and further explained the term LHS as an ecosystem of continuous learning from routinely collected health data. During the interviews, the term ecosystem was used to refer to an LHS, since an LHS is mostly an academic term. In this paper,

[2] We use the word "nursing" instead of "breastfeeding" to respect all different ways women can nurse their newborn, that is for example: breastfeeding, using a breast pump, or using formula milk.

Table 2 IMI-ConcePTION

In April 2019, the Innovative Medicines Initiative (IMI) launched the ConcePTION project (Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now). ConcePTION is a European public-private partnership that aims to develop a Learning Healthcare System (called "an ecosystem") that can generate and disseminate reliable evidence-based information about medication safety and efficacy during pregnancy and breastfeeding by learning from routinely collected data and research data across Europe [7].
During the interviews we introduced ConcePTION, and made a distinction between ConcePTION as a five-year project, which aims to build a system of continuous learning, and ConcePTION as a sustainable ecosystem, which can eventually share new scientific knowledge. A way of sharing new knowledge is through a knowledge bank, which ConcePTION aims to build for both women and their HCPs [7].

we will use the term LHS, since it is a commonly used term for systems of continuous learning in healthcare settings in the medical literature. To further explain and to help visualize all the different components of the ConcePTION ecosystem, we used a diagram (see supplementary file 1). The diagram allowed us to emphasize the circular flow in an LHS and to show the important steps in an LHS: data collection, analysis and interpretation, and output. After this short introduction, we started with the first two7 topics. Once these topics were discussed, we made sure the respondents understood what was meant with health data and explained how currently in the Netherlands data is being collected, stored, and used. Then we continued with the rest of the interview.

Data collection

The semi-structured interviews were conducted by MH (trained qualitative researcher, female, MA, PhD candidate) with a topic list. The topic list was refined after two pilot interviews. According to the technique of constant comparative analysis, the interview topics evolved as the interviews progressed alongside the data analysis [16]. Data was collected from February 2020 to January 2021. In 19 out of 20 interviews, there had been no previous contact between the interviewer and the respondents beforehand. In 1 out of 20 interviews, the interviewer and the respondent had met each other prior to the interview in an informal setting. Five interviews were performed in person in rooms at the UMC Utrecht or at the respondent's home. Due to Covid-19 restrictions, 15 interviews took place via a secure online platform. The interviews took 41 to 94 min with a median duration of 64 min. During the interviews, the order of questions was adapted to the narrative flow and the openness of the individual respondent. During and after the interviews, MH made notes to enhance the data and to provide a clear context for data analysis. The interviews were audiotaped and transcribed verbatim, coded and stored anonymously. Written consent was obtained from all respondents. Because no intervention was imposed on the participants, the Medical Research Ethics Committee (MREC) Utrecht determined that the study was exempt from ethics review under Dutch law.

Data analysis

After transcription, we analyzed the interviews according to the thematic analysis method and by going back and forth between data collection and analysis to develop codes [16]. MH coded the transcripts using software program NVivo 12. The interpretations and suitability of the codes were discussed and compared amongst the research team. During analysis, codes were adapted and combined, and new codes were added to the coding list where necessary. A meaning pattern was identified across the data set, leading to the formulation of higher order themes. To enhance the validity of our results, an intern, SDH (female medical student, BSc) read the full transcripts to check the consistency of the thematic framework and critically (re)read the coding list. The findings, including the coding list and formulated higher order themes, were discussed within the complete research team (MH, RG, MS, HD). Furthermore, a member check was executed in the last phase of data analysis to discuss the accuracy and interpretation of our preliminary results [17]. Thematic saturation was reached when the occurrence of new findings ended after 20 interviews.

Results

Out of the 30 people that were approached, 22 agreed to participate in the study, 2 were excluded, 6 were unable to participate and 2 did not respond. A total of 20 semi-structured interviews were conducted with women who varied in medical indication, stage of pregnancy, and reproductive history. Table 3 shows all relevant characteristics of the respondents.

Based on the interviews we formulated four main themes characterizing women's views and moral intuitions regarding LHSs. The themes emerged consistently across all interviews. We provide representative quotations to illustrate the themes (see Table 4).

We started the interviews by asking the respondents about their experiences with the use of medication and with the search for information about their medication. Most respondents mentioned that they experienced difficulties in finding reliable and consistent information and that drug labels lack any useful information on the safety of the medication they wanted or needed to take. We also asked healthy women whether they had taken any

Table 3 Demographic characteristics of the respondents

Respondent	Age	Education	Medical indication	Gravida Para Mater (GPM)[a]	Stage pregnancy
1	31–35	Graduate degree	Chronic condition	G3P0M0	Third trimester
2	31–35	Graduate degree	Chronic condition	G1P1M1	Nursing
3	26–30	Lower vocational (MBO)	Chronic condition	G2P1M1	Second trimester
4	36–40	Graduate degree	Acute condition pregnancy related	G4P1M1	Third trimester
5	31–35	Lower vocational (MBO)	Chronic condition	G3P3M2	Nursing
6	31–35	College (HBO)	Acute condition pregnancy related	G1P1M1	Nursing
7	31–35	Graduate degree	Acute condition pregnancy related	G3P2M2	Nursing
8	26–30	Graduate degree	Healthy	G1P0M0	Second trimester
9	36–40	College (HBO)	Acute condition	G2P2M2	Nursing
10	21–25	Lower vocational (MBO)	Chronic condition	G1P1M1	Wish to become pregnant
11	31–35	College (HBO)	Healthy	G1P0M0	Second trimester
12	36–40	Graduate degree	Anomaly	G1P1M1	nursing
13	41–45	Graduate degree	Healthy	G3P2M0	Third trimester
14	31–35	Graduate degree	Acute condition	G3P2M2	Third trimester
15	31–35	Highschool	Chronic condition	G1G0M0	Second trimester
16	31–35	Graduate degree	Healthy	G3P1M1	Nursing
17	31–35	Graduate degree	Healthy	G2P2M2	Nursing
18	36–40	Lower vocational (MBO)	Chronic condition	G8P0M0	Second trimester
19	41–45	College (HBO)	Chronic condition	G3P1M1	Wish to become pregnant
20	36–40	Graduate degree	Healthy	G2P1M1	Nursing

[a] Gravida Para Mater (GPM) represents the reproductive history by indicating the number of pregnancies (G), births (P), and children (M) of the respondents

medication during pregnancy or breastfeeding. Interestingly, most respondents replied they had not. Only after we asked whether they had looked for information online about medication and we discussed the return of results, did it become apparent that these women had in fact taken multiple medications for milder complications or conditions, during their pregnancy or during birth and/or recovery.

Theme 1: views on an LHS

In principle, all respondents expressed a positive attitude towards ConcePTION as a project and as an LHS (Q1). Most respondents considered an LHS to function as a central point for data analysis and/ or as a central point for information. Some respondents emphasized the need for such a central point to help overcome the problem of contradictory information available online or from their HCPs. Some respondents argued that the information that flows from an LHS could increase their confidence regarding the safety and efficacy of medications and would allow them to take control over their own medication intake. They mentioned that they often do not know whether a medication is safe, and therefore, they rather not take any medication at all (Q2).

Some respondents stressed the importance of organizations, experts, HCPs, and patients working together within an LHS. They argued that working together oftentimes means learning from each other through knowledge sharing. Combining knowledge was seen by some of the respondents as an improvement for the generation of new knowledge about the safety and efficacy of medications for, for example, different types of patients, event congenital anomalies, and women in general.

Some respondents immediately addressed the potential risks and hurdles that are associated with large data projects. They argued that they were in favor of collecting health data and the use of their health data in an LHS, as long as their privacy can be protected.

Another initial response of some respondents, was that an LHS is very complicated to understand. Some respondents said that they did not understand how an LHS would work in reality, but argued that it was not up to them to fully grasp it. Furthermore, respondents thought that building an LHS must be very challenging, labor-intensive, and above all highly ambitious, because it involves many stakeholders, and it concerns a lot of data (Q3). A few respondents compared an LHS with big

Table 4 Representative quotations

Views on an LHS	Q1	R13: It is making me happy, the fact that you can merge information from different places to create new knowledge. I get that it is complicated and that you need to think about the methods for analysis and interpretation of results. I think it is a good development, also for the users. In this way, HCPs and women can get unambiguous information.
	Q2	R18: I think [ConcePTION] is very good, because it is just great for future patients and others to easily find good information. […] Because it can be very frustrating right now. […] There is a lot of contradictory and unreliable information on the internet.
	Q3	R4: It is ambitious, because you need to gather a lot of data, you need the right data and the right method for data analysis. Then you also need to interpret results and translate the results into accessible information. Not only in jargon, so that nobody understands the information.
Willingness to contribute and engage in an LHS	Q4	R2: For others, yes. [The LHS] is of little use to me, but [contributing] is more to help others in the future.
	Q5	R4: I think it is important that [consent] is asked. And that everything is not just lying around all over the place. Especially when it concerns medical data, I don't think that's being careful. So, I think this should be handled with care. Certainly. [..] At least consent should be asked [before data is shared] and it should not be just assumed that people consent to sharing data.
	Q6	R15: I am doing pregnancy-yoga, there I am in a group with all big baby bellies. And I also find it useful that I hear various tips regarding the pregnancy. I like that.
	Q7	R20: I don't think a lot of people, or pregnant women know that they can contribute to scientific research. If they would know about it, I believe they will contribute. It would help to at least give women information about the possibilities [and about the burdens and benefits of contributing].
The role of the HCP in an LHS	Q8	R8: It is better to discuss the interpretation [of results] with a GP or gynecologist. Especially on how does this [medicine] influence me and my body?
	Q9	R3: [regarding medication intake during pregnancy] It depends on the choice you make. That goes for everything in life. You are the one to decide. And if your decision turns out wrong, that mistake is yours not someone else's.
	Q10	R18: Despite the fact that you can suffer from the same condition, everybody is different, every woman is different, and every pregnancy is different. So, what works for one person, does not necessarily work for the other.
Trust in an LHS	Q11	R7: I actually trust that [research] will be conducted in a good and competent way and that my data is being used for scientific research and for improving clinical practice. That would be in line with my own goal, which is nice. So, I do not necessarily need to be informed about every detail of the research process. I don't think that is problematic.
	Q12	R13: Once there is this additional goal of making profit, you cannot be objective. Even as a researcher you cannot. The pharmaceutical industry can ask researchers for certain results in exchange for a trip to Haiti. In that situation, you are no longer transparent, honest, and objective. Commercial purposes cloud that.
	Q13	R19: It should be promoted by the right people. When I would go to my doctor, for example, my doctor would say to me this is a great website to go to. I go to the midwife and she would say to me this is a great website to go to, etc. I think that's important.

data projects or information technology systems, which according to them, is complex and takes years to set up properly.

Theme 2: willingness to contribute to an LHS

Motivations for contributing

The respondents considered helping other people or helping future generations to be one of the most important reasons to contribute to the development of new information. Respondents emphasized that they want to help with preventing people from experiencing the same struggles they experienced when searching for information on medication and the struggles with becoming pregnant while also dealing with a chronic condition (Q4). Another reason mentioned was to advance scientific research, even if there is no direct benefit for themselves. Respondents highly valued scientific research and argued that it would facilitate the progress in this little explored field.

Perceived barriers and facilitators

The respondents emphasized that contributing to the creation of new information within an LHS should be non-invasive and not too time consuming. Examples of invasive and time-consuming contributions mainly had to do with undertaking a complex action, such as having to arrange your own supplies to collect for example milk or urine. Many respondents suggested combining already planned hospital visits, or other pregnancy-related check-ups with research activities to make it more accessible to pregnant and breastfeeding women. Furthermore, most respondents emphasized that the aim of the project or an LHS should be relevant to their own situation, or should be in line with their own

health needs and priorities, such as fighting an illness or condition and sharing experiences.

Respect for autonomy

Most respondents argued that it is important to at least notify people about collecting and using health data. A small group of respondents wanted to give informed consent for the use of their health data for a study within an LHS. They argued that consent would allow for some control regarding the use of their own data. According to these respondents, data are something personal that should be treated with caution (Q5). Other respondents argued that giving informed consent every time a new study is performed with their data is too invasive and could negatively influence a person's willingness to contribute. Being (re)contacted for research was sometimes experienced as annoying and was not considered a priority. Furthermore, respondents put forward that when data is anonymous, then there is no added personal value in knowing or giving consent. Furthermore, multiple respondents suggested that when an LHS has been developed it would suffice to have a clear statement on the website explaining how and by whom data is collected, analyzed, and stored. Having information available online allows people to look for the information when they want to know more.

Responsibility

All respondents felt a level of responsibility to participate in or contribute to an LHS, if possible. Reasons included: to help prevent other women from experiencing the lack of information about a chronic condition, an adverse drug reaction, the pregnancy, the newborn, doing 'the right thing', and helping with research progressing (Q6). Most respondents with a chronic condition explained that they wanted to help other women by sharing their experiences and information, because they felt part of another group or felt connected to other women because of a shared chronic disease or other shared pregnancy or maternal features. Some healthy respondents argued that they did not feel more connected to other pregnant or nursing women and did not need another group to affiliate with and/ or did not want the opinion of other women on how to be pregnant. Some of the healthy respondents also mentioned that the feeling of being connected to other pregnant women was less present during their second pregnancy. A few respondents had the opinion that, unfortunately, some women were not always aware of the knowledge gap, and therefore, do not feel as responsible to participate in research activities (Q7). Further to this, they suggested that more awareness needs to be raised to also reach these women.

Theme 3: the role of the healthcare professional in an LHS

While the interviews did not specifically focus on the role of the HCPs in the creation of new knowledge, most respondents emphasized the importance of the HCP in both the search for and dissemination of information about medication and treatments while pregnant or breastfeeding.

Searching for information

Most respondents found interpreting medical information and research results to be extremely difficult and trying medication by yourself undesirable. Most respondents felt they should consult their HCP (Q8). Many respondents consulted drug labels, the internet, and their HCP for information on the medication they were considering taking. According to them, the internet can be used for personal research prior to a consult or after to read the information again at a slower pace.

Dissemination of information

When asked about the return of results in an LHS, most respondents expressed the wish for personalized information. Many respondents valued privacy as an important principle to protect, and therefore, it was acknowledged by a few respondents that personalized information would be difficult to realize without sharing personal information. Respondents mentioned that to fully depend on the information in a knowledge bank, it needs to be able to give decisive advice. Some respondents emphasized the need for a "yes" or "no" answer. Other respondents argued that, if personalized information is not an option, it would still be useful to have information to guide a decision regarding medication intake. A small group of respondents argued that it is always one's own responsibility to make a good and informed decision (Q9).

Most respondents asked their HCP for advice about the safety and efficacy of medication. Respondents who visit their HCP regularly because of a chronic illness or condition, argued that they rely on their doctors to give them advice on what is desirable for their specific condition. Other respondents emphasized that "everybody is different" and could respond differently to treatment (Q10). Therefore, applying the little information available to one's own situation is difficult. In general, all respondents trusted their HCP to have the knowledge or to help with deciding what is best for them. Respondents also argued that the HCP probably knows how to interpret the latest news about medication safety, because of their expertise. Some respondents emphasized that in an LHS the benefits for the HCP are much higher in comparison to the direct benefits for themselves. Respondents argued

that regardless of an LHS, they would still rather rely on the information from the HCP, because they know more about their specific condition and their context.

Theme 4: trust in an LHS

Trust in research

Most respondents view research as objective, structured and believe there is no conflict of interest. Respondents explained that they trust researchers to handle data correctly and that they trust researchers to follow the rules and regulations regarding data protection. Furthermore, some respondents argued that because they trust researchers, they do not need to be informed about every detail of the research project (Q11).

Commercial use and purposes

Commercial use and purposes were also discussed by a group of respondents. Some respondents expressed a cautious or negative attitude towards public-private partnerships in an LHS. Respondents argued that such partnerships could jeopardize the neutrality of the information, since they feel that commercially interested parties' main objective is to make money (Q12). Some respondents explained that companies like Facebook, news articles on privacy breaches and the negative reputation of the pharma industry make them more cautious of data collection and analysis in general. Respondents emphasized that they would rather not share their personal information with private organizations that make a profit from it. Respondents questioned the level of objectivity of those companies. Respondents expressed that the interference of commercial interests in any system, negatively influences their trust in that system, and therefore, in the information that flows from that system. A small group of respondents argued that although commercial parties have an additional goal, they also stimulate and realize important progress. These respondents expressed a more positive attitude towards collaboration with private organizations in an LHS.

Transparency

Most respondents argued that transparency is of great importance for the sustainability of an LHS and for earning their trust in such a system. Respondents explained that to be transparent includes honesty about data collection, data analyses, public-private partnerships, and the way privacy is protected. Transparency also makes the information that flows from it seem more reliable and solid, because it shows that there is "nothing to hide" and all relevant information on how the LHS works is available to anyone who is interested.

Broad support from the medical community and the government

Respondents emphasized the need for support of the LHS from the medical community and the government. Having broad support by different authoritative institutions shows that the LHS is well established, and that multiple authoritative people acknowledge and trust the value of the information developed by the LHS. The interviews demonstrated that the respondents considered the research and medical community to be the experts in the assessment of new information, and therefore, respondents rely on their opinion (Q13). Many respondents argued that they would not hesitate using ConcePTION as a source themselves when their HCP would recommend it. Respondents suggested that for ConcePTION to become a sustainable LHS, it should strive to become highly trusted by the medical community.

Discussion

Our study with 20 women during preconception, pregnancy, or nursing, showed that these women 1) are positive about an LHS for pregnant and breastfeeding women to help diminish the knowledge gap, 2) want to contribute to the development of new information and engage in an LHS, 3) view their HCPs essential in the translation and interpretation of information, regardless of the establishment of an LHS and 4) see trust and transparency as essential for the realization and sustainability of an LHS.

To our knowledge, this is the first study that conducted in-depth interviews with pregnant and nursing women to explore their views on LHSs. In addition to the literature on patients' and stakeholders' views on health data research or health information networks, these interviews provide for an extensive understanding of how women view medication intake during pregnancy and breastfeeding, from what perspective women argue for or against contributing to an LHS, and what women of childbearing age need and wish for regarding the return of results in an LHS.

Interestingly, although this is not a quantitative study, all our respondents had taken at least one medication during their pregnancy or during breastfeeding. This finding is in line with what is described in the literature about medication use among pregnant and breastfeeding women [1]. At first, most healthy respondents, who mainly used over-the-counter medication, seemed to think their medication was irrelevant to mention or not as serious compared to medication used for chronic or acute diseases. It seemed that these respondents did not entirely realize that they may be vulnerable when it comes to the risks of a lack of knowledge on medication. At the same

time, all respondents experienced difficulties with finding reliable and straightforward information about their medication. These experiences underline the current lack of knowledge and contradicting information, described in the literature [18].

Solidarity

Earlier studies identified multiple motivators for pregnant women to contribute to clinical research. Similar to our interview study, main motivators are improving medical research, helping others, and having a personal connection to the research subject [19–22]. Interestingly, our respondents also mentioned they felt responsible to contribute and engage to help others with whom they share a specific experience, like having a chronic condition, being in the same stage of the pregnancy, and being a new and young or older mother. In the literature, acting upon this feeling of responsibility to assist others with whom one shares a specific experience, is described as solidarity [23]. Barbara Prainsack and Alena Buyx understand solidarity as a relational practice, where being able to identify with and care for another person in a similar context are of key importance in suggesting new practical solutions to existing problems [23]. Perhaps a solidarity approach in the field of pregnant and breastfeeding women is necessary to include women in the discussion and to allow them to be actively involved in closing the knowledge gap.

Another interesting observation from our study is that women with a chronic condition seemed to experience this personal connection with the research subject and with other women more intensively. A reason for this might be that they already belong to a group of patients with a specific chronic disease or condition. It might, therefore, have been easier for them to picture other women who are going through the same experience of managing their condition and their pregnancy, and they might already have a group of women with whom they share their experiences about having to deal with a chronic disease. Furthermore, their affinity with medical research can possibly be explained by the fact that their pregnancy is medicalized early on [24, 25]. Although, pregnancy and childbirth increasingly have become medically defined phenomena due to medical technology and surveillance focused on risks, women's experiences with pregnancy-related risks are determined by the interactions with a HCP [25]. Women who suffer from a chronic condition have interactions with their HCP at an early stage, often before their pregnancy. For healthy women, this is probably different, since there are fewer interactions with HCPs and their pregnancy is not fully depended on medical care.

Dissemination of information

In general, there is a cautious attitude towards medication use during pregnancy or breastfeeding [26]. Our interviews, as well as the literature, showed that women are concerned about the impact of medication on both foetal development and their own health [22, 27]. Our interviews showed that regardless of an LHS, respondents want to know from their HCP whether a medication is safe to use in their situation. The anxiety towards medication use and the difficulty with interpreting medical information, results in a feeling of insecurity [28]. The question is whether an LHS can take away these insecurities. Not only are HCPs important in the dissemination of information among women, but they are also important in the interpretation and translation of new insights that are generated through an LHS. Therefore, the help of HCPs in validating research outcomes and deciding what type of knowledge would be useful to pregnant and breastfeeding women is necessary. Respondents explained they wish to have information that is applicable to their specific situation. It seems that an HCP is of crucial importance in making sure the results generated through an LHS flow back to the patient in understandable language.

Subsequently, pharmaceutical companies have the duty to monitor the safety and efficacy of their medication and to update drug labels once new information becomes available. Unfortunately, it has proven to be extremely difficult to stimulate the progress of updating labels. The European Medicine Agency (EMA) has set up post-authorisation measures (PAM) to make sure drug agencies collect and provide data to enable further assessment on the safety or efficacy of medication in the post-approval setting [29]. Despite these regulations, it still takes too long before labels are updated or the assessments are not completed because of a lack of data [5, 30]. However, providing readable and solid evidence on the safety and efficacy of medication is the task of drug manufacturers. Furthermore, labels are an important source for making an informed decision. Our interviews showed that almost all respondents read the labels before taking any medication during pregnancy or breastfeeding.

Public-private partnerships and LHSs

Even though we avoided using the term LHS, respondents associated the concept of an LHS mainly with big data, information technology systems, Facebook-like platforms, and medical research in general. Although their associations are not entirely surprising, it did influence their attitude towards ConcePTION as an LHS. The overall negative attitude regarding partnerships with private parties is also often described in the literature as a perceived barrier for

sharing health data for research [27, 31]. Individuals seem to be opposed to data sharing if it is motivated by financial gain or profit, or if data is shared with private or commercial companies [31]. To earn the trust of women in an LHS, it seems important to be transparent about the collaboration with private organizations, and to explain why this is vital for the realization and sustainability of an LHS.

Engagement of pregnant and breastfeeding women

Because there are only a few effective LHSs in practice and because ConcePTION is still an ongoing project, it is not surprising that many respondents did not fully grasp the concept of an LHS. However, for the sustainability and for the willingness of women to engage in an LHS for pregnant and breastfeeding women, it is of crucial importance that women understand what it is, how it works and how certain issues, like privacy, informed consent, and private partnerships are regulated. As Seid et al. (2014) explain, an LHS depends on collaboration and engagement to really improve health care and health outcomes. According to them, engagement can be understood as the extent to which an individual takes part in the generation of new information, knowledge, and know-how, and exists along a continuum ranging from awareness, to participation, to contribution and to ownership of the knowledge generating system [32]. They continue that awareness is the first building block that introduces the individuals with the system and could lead to them becoming participants (using the tools within the system) or eventually contributors (helping with improving the knowledge and resources) [32]. The same could work for women of childbearing age. Meaning that clear information about the LHS, additional tools (sources for more information, research activities, survey studies), and ways for them to be involved (joining a pregnancy advocacy group) need to become available to them. The way to reach women might be, again, different for the group of chronically ill women in comparison to healthy women. As mentioned earlier, women who suffer from a chronic condition, might already be aware of their vulnerable position and might already be involved in patient's advocacy groups or already participate in research activities.

Limitations

Our study has a number of limitations. First, we have tried to purposefully include women of all different educational levels, however, we received more responses of highly educated women. Therefore, the possibility of selection bias exists, which challenges the generalizability of the findings. Furthermore, as the results show, we interviewed women who have a positive attitude towards scientific research. This general positive attitude might not be a good reflection of the total population. Second, due to Covid-19 restrictions most of our interviews were held via an online platform instead of face to face. Third, during some of the interviews the subject of privacy was brought up by one of the researchers to help the respondents reflect upon possible risks of an LHS. Bringing up privacy as a possible risk might have altered the answers of the respondents in such a way that privacy became a concern after hearing about it. Fourth, the graph used to visualize the ConcePTION ecosystem was designed with very bright colours. Using these colours might have triggered positive responses to the explanation of the ConcePTION ecosystem, and therefore, the concept of an LHS in general. Fifth, the interviews were conducted with Dutch women only who are in a heterosexual relationship. The Netherlands might reflect a different culture and attitude towards research and health data than other countries. Follow-up research could explore the possible variety of views of women across Europe. In addition, a more inclusive approach is necessary to make sure the (health) interests of all pregnant and breastfeeding people with different sexual orientations and gender identities get equal weight. Despite the limitations of this study, we believe the insights from the study can be used in the development of a sustainable and ethically responsible LHS for pregnant and breastfeeding women.

Conclusion

To conclude, women during preconception, pregnancy and nursing agree that an LHS could be a viable alternative to generate evidence on medication safety in pregnancy and breastfeeding, which they feel is currently lacking. The obtained insights provide valuable steppingstones for the development of a sustainable and ethically responsible LHS. Furthermore, the results from this interview study inform the implementation of real-time results flowing from an LHS, as well as encourage the engagement of women in the development of an LHS.

Abbreviations

LHS: Learning Healthcare System; HCP: Healthcare Professional; ConcePTION: Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now; COREQ: COnsolidated criteria for REporting Qualitative studies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-022-04675-2.

Additional file 1.

Acknowledgements
We are grateful to all respondents for their contribution to this study. We would like to thank our contact persons for the support and recruitment of respondents for this interview study.

Authors' contributions
MH, RG, HD and MS were responsible for the concept and design of the study. MH and RG were responsible for the recruitment of participants. MH was responsible for data collection, initial drafting of the article and conducted the thematic analysis, to which RG, HD, SDH provided substantial input along the way. RG, MS and HD critically revised the manuscript. All authors approved the final version of the article. The research leading to these results was conducted as part of the ConcePTION consortium. This paper reflects the personal views of the stated authors and not necessarily IMI ConcePTION.

Funding
The ConcePTION project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 821520. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA.

Availability of data and materials
The datasets generated and analyzed during the current study are not publicly available because individual privacy could be compromised. Additionally, no permission was asked from the participants for public availability. The dataset is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Participants were informed about the study and agreed to participate verbally or via e-mail. Prior to the start of the interview, participants were informed about the interview study, its recording and the pseudonymized analysis of the interview data. All women who participated in this study gave written and verbal consent. The research protocol including the procedure for informed consent was submitted to the research ethics committee of the University Medical Center Utrecht for review prior to the initiation of the research. Because no intervention was imposed on the participants, the MREC Utrecht determined that the study was exempt from ethics review under Dutch law.

Consent for publication
Not applicable.

Competing interests
Author MS is leading a department that conducts regulatory required research for COVID-19 vaccine manufacturers based on the ENCePP code of conduct and is project coordinator of IMI ConcePTION. The other co-authors declared no competing interests for this work.

Author details
[1]Department of Medical Humanities, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands. [2]Department Data science & Biostatistics, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands.

Received: 1 November 2021 Accepted: 8 April 2022
Published online: 18 April 2022

References

1. Lupattelli A, Spigset O, Twigg MJ, Zagorodnikova K, Mårdby AC, Moretti ME, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014;4(2).
2. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernández-Díaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51.e1–8.
3. Baylis F. Pregnant women deserve better. Nature. 2010;465(7299):689–90.
4. van der Graaf R, van der Zande ISE, van Delden JJM. How the CIOMS guidelines contribute to fair inclusion of pregnant women in research. Bioethics. 2019;33(3):367–73.
5. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. Am J Med Genet Part C Semin Med Genet. 2011;157(3):175–82.
6. Polifka JE, Friedman JM. Developmental toxicity of ribavirin/IFα combination therapy: is the label more dangerous than the drugs? Birth Defects Res Part A - Clin Mol Teratol. 2003;67(1):8–12.
7. Innovative Medicine Initiative ConcePTION. Description: Key objectives of the project. [Internet]. Available from: https://www.imi-conception.eu/description/.
8. Roes KCB, van der Zande ISE, van Smeden M, van der Graaf R. Towards an appropriate framework to facilitate responsible inclusion of pregnant women in drug development programs. Trials. 2018;19(1):1–9.
9. Foley T, Fairmichael F. The potential of learning health care systems. J Am Coll Cardiol. 2015;66(5):4–19.
10. Wouters RHP, van der Graaf R, Voest EE, Bredenoord AL. Learning health care systems: highly needed but challenging. Learn Heal Syst. 2020;2019:1–6.
11. Mclennan S, Kahrass H, Wieschowski S, Strech D, Langhof H. The spectrum of ethical issues in a learning health care system: a systematic qualitative review. Int J Qual Heal Care. 2018;30(3):161–8.
12. Moloney RM, Tambor ES, Tunis SR. Patient and clinician support for the learning healthcare system: recommendations for enhancing value. J Comp Eff Res. 2016;5(2):123–8.
13. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Heal Care. 2007;19(6):349–57.
14. Council for International Organizations of Medical Sciences & World Health Organization. CIOMS Guidelines. International Ethical Guidelines for Health-related Research Involving Humans. [Internet]. 2016. Available from: https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/.
15. Kalkman S, Mostert M, Gerlinger C, Van Delden JJM, Van Thiel GJMW. Responsible data sharing in international health research: a systematic review of principles and norms. BMC Med Ethics. 2019;20(1):1–13.
16. Charmaz K. Constructing Grounded theory: a practical guide through qualitative analysis: SAGE Publications; 2006.
17. Birt L, Scott S, Cavers D, Campbell C, Walter F. Member checking: a tool to enhance trustworthiness or merely a nod to validation? Qual Health Res. 2016;26(13):1802–11.
18. Byrne JJ, Saucedo AM, Spong CY. Task force on research specific to pregnant and lactating women. Semin Perinatol. 2020;44(3).
19. van Der Zande ISE, Van Der Graaf R, Oudijk MA, Van Vliet-Lachotzki EH, Van Delden JJM. A qualitative study on stakeholders' views on the participation of pregnant women in the APOSTEL VI study: a low-risk obstetrical RCT. BMC Pregnancy Childbirth. 2019;19(1):1–11.
20. Mohanna K, Tuna K. Withholding consent to participate in clinical trials: decisions of pregnant women. BJOG An Int J Obstet Gynaecol. 1999;106(9):892–7.
21. Meshaka R, Jeffares S, Sadrudin F, Huisman N, Saravanan P. Why do pregnant women participate in research? A patient participation investigation using Q-methodology. Health Expect. 2016;20(2):188–97.
22. Lyerly AD, Namey EE, Gray B, Swamy G, Faden RR. Women's views about participating in research while pregnant. IRB Ethics Hum Res. 2012;34(4):1–8.
23. Prainsack B, Buyx A. Solidarity in biomedicine and beyond. (Cambridge bioethics and law), editor. Solidarity in biomedicine and beyond. Cambridge: Cambridge University Press; 2017.
24. Christiaens W, van Teijlingen E. Four meanings of medicalization: childbirth as a case study. Salut E Soc. 2009;8(2):123–41.
25. Prosen M, Krajnc MT. Perspectives and experiences of healthcare professionals regarding the medicalisation of pregnancy and childbirth. Women Birth. 2019;32(2):173–81.
26. Lynch MM, Squiers LB, Kosa KM, Dolina S, Gard J, Broussard CS, et al. Implications for communication. Strategies. 2019;22(1):92–100.
27. van der Zande ISE, van der Graaf R, Hooft L, van Delden JJM. Facilitators and barriers to pregnant women's participation in research: a systematic review. Women Birth. 2018;31(5):350–61.

28. Little MO, Lyerly AD, Faden RR. Pregnant women and medical research: a moral imperative. Bioethica Forum. 2009;2(2):60–5 Available from: http://www.bioethica-forum.ch/docs/09_2/Bioethica_01_focus.pdf.
29. European Medicines Agency. Post-authorization measures: questions and answers. [internet]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-measures-questions-answers
30. Pereira LR, Durán CE, Layton D, Poulentzas G, Lalagkas PN, Kontogiorgis C, et al. A landscape analysis of post-marketing studies registered in EU PAS register and clinicaltrials.gov focusing on pregnancy outcomes or breastfeeding effects: a contribution from the ConcePTION project. Drug Saf. 2022.
31. Kalkman S, van Delden J, Banerjee A, Tyl B, Mostert M, van Thiel G. Patients' and public views and attitudes towards the sharing of health data for research: a narrative review of the empirical evidence. J Med Ethics. 2019;0:1–11.
32. Seid M, Margolis PA, Opipari-Arrigan L. Engagement, peer production, and the learning healthcare system. JAMA Pediatr. 2014;168(3):201–2.

Publisher's Note

PHASES
PREGNANCY + HIV/AIDS
SEEKING EQUITABLE STUDY

EXECUTIVE SUMMARY

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

This work is a product of The PHASES Working Group. PHASES is a grant-funded project led by faculty at the University of North Carolina at Chapel Hill alongside co-investigators at Georgetown University and Johns Hopkins University with contributions from Working Group members.

PHASES Core Team:
Anne Drapkin Lyerly, MD, MA (Principal Investigator); Maggie Little, BPhil, PhD (Co-Principal Investigator); Ruth Faden, MPH, PhD (Co-Principal Investigator); Kristen Sullivan, PhD, MSW, MBA, MA (Project Director); Elana Jaffe, BA (Project Manager); Marisha Wickremsinhe, MSc (Research Associate)

The recommendations, interpretations, and conclusions expressed in this work do not necessarily reflect the views of the institutions with which Working Group members are affiliated.

PHASES is funded by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award number R01AI108368 (Lyerly, PI). Dr. Rid is supported by the Clinical Center Department of Bioethics, which is in the Intramural Program of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Suggested citation:
The PHASES Working Group. Ending the evidence gap for pregnant women around HIV & co-infections: A call to action. Executive Summary. Chapel Hill, NC: July, 2020.

* Corresponding Author: Anne Drapkin Lyerly (alyerly@email.unc.edu)

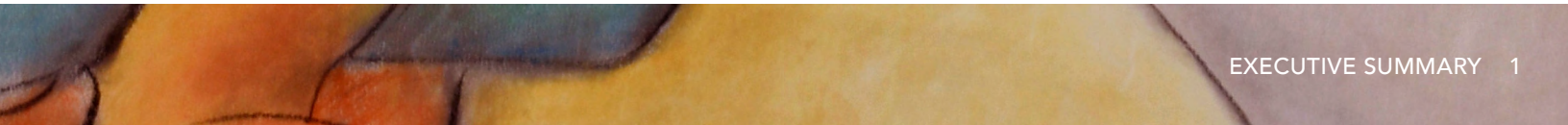
Ending the evidence gap for pregnant women around HIV & co-infections: A call to action

EXECUTIVE SUMMARY

The PHASES Working Group

Pregnancy and HIV/AIDS: Seeking Equitable Study

Richard Beigi MD MSc
Linda-Gail Bekker MD PhD
Benjamin Chi MD MSc
Susan E. Cohn MD MPH
Dazon Dixon Diallo DHL MPH
Joseph Eron MD
Ruth Faden PhD MPH
Angela Kashuba BScPhm PharmD DABCP FCP
Mary Kasule PhD
Carleigh Krubiner PhD
Maggie Little BPhil PhD
Anne Drapkin Lyerly MD MA
Joseph Mfutso-Bengo PhD MA
Lynne Mofenson MD
Victor Mwapasa PhD MPH
Lillian Mworeko
Landon Myer MBChB PhD
Martina Penazzato MD DTMH MSc PhD
Annette Rid MD PhD
Roger Shapiro MD MPH
Jerome Amir Singh BA LLB LLM PhD MHSc
Kristen Sullivan PhD MSW MBA MA
Marissa Vicari MS
Jacque Wambui
Amina White MD MA
Leslie E. Wolf JD MPH



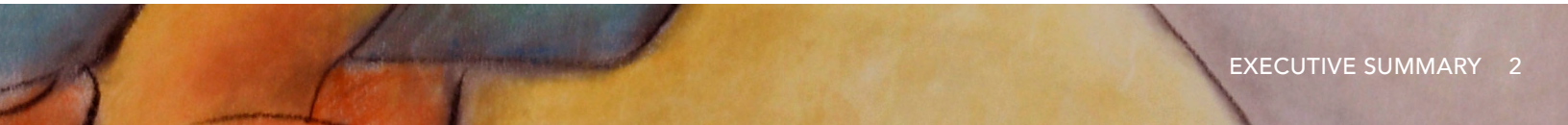
Introduction

Globally, at any given time, 1.3 million women are living with HIV while pregnant.[1] HIV brings special risks during pregnancy. The risk of perinatal transmission is the most well known, and its prevention is widely recognized as a continuing, critical goal for global health.[2] More recent evidence has also pointed to the risks maternal HIV carries to offspring even when the child does not become infected: higher rates of preterm birth, poor fetal growth, stillbirth,[3] and worse outcomes that may stretch into childhood.[4–7]

For women living with HIV, pregnancy is also a time of heightened risk for their own health. HIV increases the risk of deadly obstetrical complications, such as sepsis—a life-threatening reaction to infection—after delivery.[8,9] Pregnancy-specific changes to heart function, lung capacity, and immune response make pregnant women more susceptible to some of HIV's most deadly co-infections. Tuberculosis is a leading cause of maternal mortality among women living with HIV; malaria, HIV, and pregnancy together form a deadly combination.[9] Overall, women living with HIV face up to a tenfold increase in the risk of dying during pregnancy and the postpartum period compared with women not living with the virus.[9]

For women living in areas of high HIV prevalence, pregnancy is also a time of heightened risk for acquiring HIV in the first place.[10] Biological changes in pregnancy, as well as challenges in negotiating partner condom use during pregnancy, increase the likelihood of infection upon exposure to the virus and put pregnant women at especially high risk.[10,11]

Pregnant women, in short, are among those most in need of safe and effective preventives and treatments for HIV and co-infections. Yet they are among the least likely to have robust, timely evidence to inform decisions around use of medications. While the HIV research community has a notable history of conducting research with pregnant women—from efforts in the 1990s to address prevention of perinatal transmission to more recent vanguard studies—critical and systemic patterns of exclusion in the broad HIV/co-infection space nonetheless persist.



Pregnant women have been excluded from most drug development trials of new interventions, including most large trials of pre-exposure prophylaxis (PrEP) to prevent HIV,[12–15] new antiretroviral therapies,[16,17] and drugs for HIV's deadliest co-infections: tuberculosis (TB) and malaria.[18–20] Most post-approval research continues to exclude pregnant women and to remove women who become pregnant during a clinical trial from the study drug. Research specifically dedicated to pregnant women, while increasing, remains highly uneven across areas of need and often occurs only years after the drug in question is approved. And when the research agenda does attend to pregnancy, attention can focus disproportionately on fetal outcomes, without equal or adequate attention to issues around the pregnant woman's own health.

"Pregnant women are among the least likely to have robust, timely evidence to inform decisions around medication.

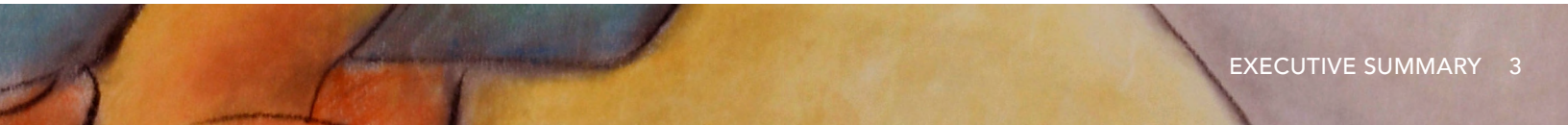
Key evidence gaps and their costs

The resulting evidence gaps and delays are significant—and put pregnant women and their children in harm's way.

First are issues of dosing. Most HIV and co-infection drugs come to market with no pregnancy-specific dosing information—despite the fact that the pregnant body can radically change how drugs are processed.[21–24] When data are gathered in studies conducted after the drugs are approved, it is usually with long lag times, years after being prescribed to pregnant women.[22,25] Other times, they are lacking still. Pregnancy-specific dosing data are almost completely lacking for combinations of antimalarials and antiretrovirals in pregnant women,[26,27] and again for TB treatment during pregnancy.[18,28]

"The resulting evidence gaps and delays are significant—and put pregnant women and their children in harm's way.

➔ Guesswork on dosing can be costly. Pregnant women are sometimes inadvertently underdosed—prescribed a regimen that will inadequately reduce HIV viral load.[29,30] In other cases, doses may leave a pregnant woman with more medicine in her system than is needed, exposing her to heightened toxicities, drug interactions, or side effects that can lead her to switch to a less optimal regimen.[31,32]



Second are issues of fetal safety. Most HIV and co-infection drugs come to market with only animal data to inform questions of fetal safety. In-human data is left to be gathered in postmarketing registries or potential independent research that may occur, and remains starkly limited and marked by extensive delay.[33,34]

➔ Gaps and delays in fetal safety assessment matter—for two reasons. Of most obvious concern is the possibility that medications prescribed to pregnant women may be unsafe for the fetus, carrying elevated risk of birth defects (teratogenicity) or potential effects on the fetus's growth. A second cost exists even when—as often happens—the drug in question turns out to have a favorable risk-benefit balance: barriers to pregnant women accessing the benefits of new drugs. Providers and policymakers are often reticent to endorse the use of a drug during pregnancy until robust in-human data on fetal safety are available—which can take many years after drug approval. Gaps and delays in evidence leave pregnant women among those last in line to receive the benefits of next-generation drugs.

Third are issues of maternal outcomes. Few drugs used in HIV, TB, or malaria have a well-evidenced assessment of potential pregnancy-specific risks. Drugs prescribed for the benefit of fetal health may carry risks that are specific to—or specifically heightened for—pregnant and delivering women, such as elevated risks of life-threatening preeclampsia, dangerous liver toxicities, or hemorrhage after delivery.[35]

➔ This is problematic not only as an issue of potential harm, but also of respect for the independent value of the woman's health. Without adequate research attention to maternal outcomes, a drug that is deemed safe and effective in terms of fetal health may in fact be harmful to the pregnant woman. A focus on fetal outcomes tells only half the story.

fig 1
Key evidence gaps

Ethical foundations

The ethical responsibility to address inequities in the evidence base for the use of medications during pregnancy is based on three ethical foundations.

Equitable protection from drug-related risks. An animating mission of all research is to gather evidence under carefully controlled and regulated contexts to decrease risks in the clinical care setting. Pregnant women, no less than any other population, deserve this protection against risks to themselves and their future offspring. Adequate research is essential to realizing the fundamental public health obligation of ensuring that the drugs taken by people—including pregnant women—meet an acceptable safety threshold.

Equitable access to first-line medications. Pregnant women deserve timely access to the most effective advances medicine can offer, both for their health and the health of the children they bear. Delays and gaps in evidence are a major barrier to meeting this goal. A commitment to better, earlier evidence is critical to ensuring pregnant women's equitable access to needed preventives and treatments.

Equitable respect for pregnant women's own health. When research is conducted, it is crucial that attention to fetal and child outcomes do not overshadow attention to maternal outcomes. Drugs used during pregnancy are often prescribed or chosen in part to benefit the child. It is critical to ensure that such decisions reflect due consideration of the woman's health as well. Not to do so inadvertently treats a woman as a mere vector of disease or vessel for her child, not a person whose health and well-being matter in their own right.

fig 2
Three ethical foundations

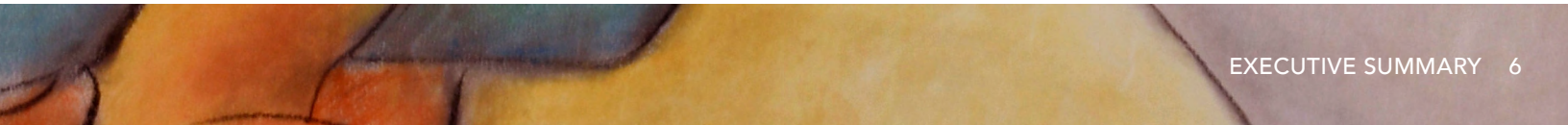
A pathway to progress

The purpose of this Guidance is to provide concrete and immediately actionable recommendations, grounded in ethical principles and consistent with current regulations, for better advancing timely, needed, responsible research with pregnant women in the HIV/co-infection research agenda.

The Guidance represents the efforts of a 26-member international, interdisciplinary, and intersectoral working group, convened as part of the PHASES (Pregnancy and HIV/AIDS: Seeking Equitable Study) Project, a seven-year effort funded by the U.S. National Institutes of Health. The Working Group includes experts in bioethics, public health, law, obstetrics and maternal-fetal medicine, pediatrics, HIV research, infectious disease, and pharmacology, as well as community advocates for women living with HIV; and includes members from Botswana, Kenya, Malawi, South Africa, Switzerland, Uganda, the United Kingdom, and the United States.

The Working Group's deliberations were informed by extensive research conducted by the PHASES Project. Project-based efforts include a qualitative study with 140 pregnant and recently pregnant women in the United States and Malawi; commissioned country-specific legal briefs; a series of workshops with representatives from North America, South America, sub-Saharan Africa, Southeast Asia, and Europe; and consultations with over 150 subject area experts, including HIV and co-infection researchers, clinicians, research oversight officials, legal scholars, regulators, and policymakers from around the world.

The 12 resulting recommendations are directed to multiple stakeholders in the research and advocacy communities addressing HIV and key co-infections, including pharmaceutical companies and regulatory agencies, research agenda setters and funders, researchers and those involved in research oversight, and community research advisors. Together, these recommendations aim to advance the three key ethical objectives of equitable protection, access, and respect.



RECOMMENDATIONS

Building capacity

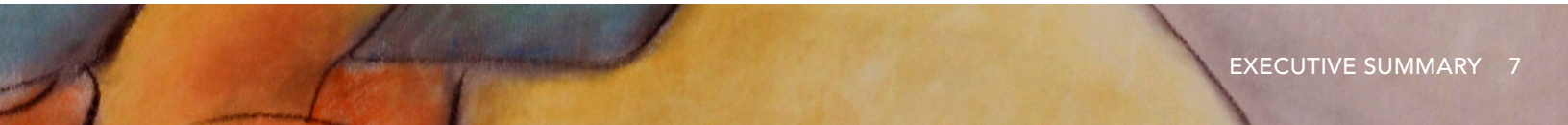
1. Affirm the need for research with pregnant women

Organizations with influence over the development, research, regulatory approval, guidance development, and use of HIV/co-infection drugs should affirm the imperative for responsible research with pregnant women to achieve a timely and equitable evidence base.

Common misperceptions about pregnant women's eligibility for research participation, coupled with a historical culture of risk aversion around pregnancy, have led to patterns of excluding pregnant women from research that far outstrip regulatory restrictions and ethical constraints. Anticipating difficulty in approval, researchers and funders who might otherwise be interested in conducting such research may be discouraged from conceiving or proposing research with pregnant women. While resources, both human and financial, will be needed to enable such research, affirmation of the critical need for and ethical appropriateness of such research is thus a critical effort in its own right. Key stakeholders and agenda-setters can play a key role in changing the research culture from exclusion to integration of pregnant women in the HIV/co-infection research agenda.

2. Formalize a global network for advocacy and resources

The global HIV/co-infection research and advocacy communities, supported by funders, should formalize a network dedicated to advancing needed research with pregnant women. This network should facilitate research with pregnant women 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 pregnant women.



While there are helpful advocacy efforts, tools, and educational resources around research with pregnant women in the HIV/co-infection space, their efforts are dispersed and often based on temporary funding. Funders of HIV and co-infection research and global health programs can strongly increase needed research by providing financial resources for a longer-term advocacy and resource network whose dedicated purpose is to support pathways to research with pregnant women.

3. Enhance training

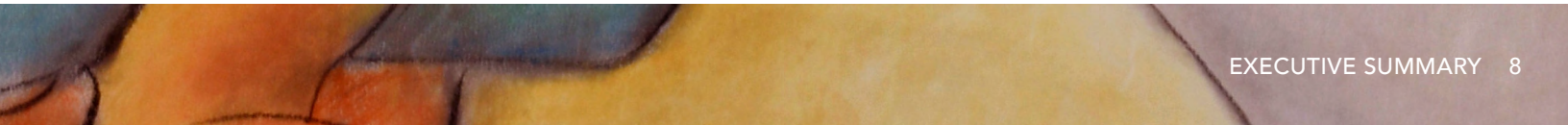
Those involved in the conduct, monitoring, oversight, and community consultation of research in the HIV/co-infection space should be provided training in the ethical and legal issues relevant to research with pregnant women.

Lack of information or misunderstandings about the design and permissibility conditions of research with pregnant women represent a strong barrier to needed research. Those involved in research and its oversight may lack understanding of the regulations, ethical frameworks, and best practices around research with pregnant women, which could offer confidence to pursue and approve research that meets appropriate ethical and regulatory standards. Confusion around regulatory and ethical eligibility criteria, in particular, can keep researchers from contemplating, oversight committees from approving, and community partners from endorsing needed research with pregnant women. Capacity building in this area, which can take advantage of or build on excellent existing modules, is thus essential to enabling needed research.

Supporting inclusion

4. Design for inclusion

Researchers designing trials addressing HIV/co-infections should commit to a goal of integrating pregnant women wherever possible and optimizing opportunities to gather pregnancy-specific data.

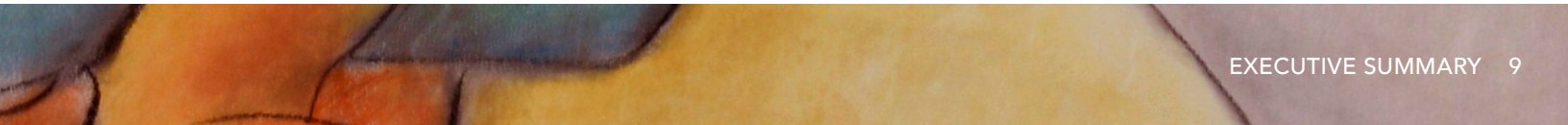


Because pregnant women are such significant, distinctive, and important end-users of preventive and treatment drugs for HIV/co-infections, it is critical that trials make best use of opportunities to gather pregnancy-specific data. As part of the research community's collective responsibility to provide adequate protection and reduce delays in access to needed drugs for pregnant women, researchers designing trials of HIV/co-infection treatments and preventives should proactively seek designs that will allow for the inclusion of pregnant women and optimize opportunities for gathering pregnancy-specific data. Inclusion in trials can create valuable knowledge-gathering opportunities, including opportunities to provide the in-human data that guidelines often look for before recommending use during pregnancy.

5. Review for and facilitate inclusion

Regulatory review sections, research ethics committees, and funders of HIV/co-infection research should require proposed clinical trial 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.

Currently, regulations require protocols to justify the eligibility of pregnant women's enrollment or retention in a study, but no justification is required for excluding them.[36] Regulatory review sections, research ethics committees, and funders of research can be important drivers of cultural change away from the summary exclusion of pregnant women in research by shifting this justificatory burden. They can also encourage and facilitate inclusive designs through specific incentives and supports: funders can incentivize research with pregnant women through preferential funding; regulatory review sections can facilitate matchmaking between independent academic researchers and interested industry partners; and RECs can proactively work with investigators to identify approvable designs.



6. Ensure equitable research on pregnant women's own health

Agenda setters in HIV/co-infection research should commit to equitably promoting the study of pregnant women's 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 woman's health.

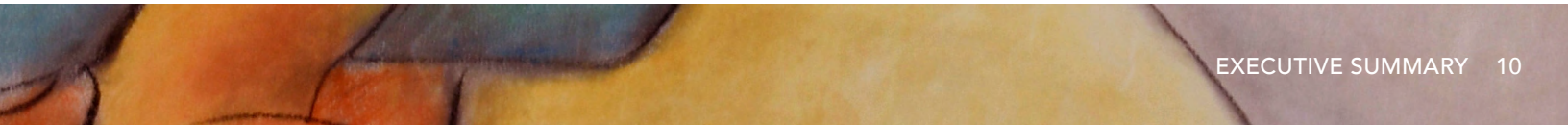
Pregnant women are entitled to have their own health needs taken into account, not just the health needs of the fetus, in decisions of whether and which drugs to use. Without research directed at both maternal and fetal outcomes, it will be impossible for clinical care or public health programs to offer guidance that accounts for the full profile of considerations needed to ethically serve the interests of both pregnant women and the children they bear. This is especially important given the historical patterns in HIV, which in early years attended centrally to the pregnant woman as a vector of HIV transmission rather than an end in herself. Adopting a commitment to equity is thus essential.

Achieving priority research

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.

While pregnant women's access to drugs should not be made contingent on the availability of pregnancy-specific PK data, new drugs should reach market with pregnancy-specific dosing information in hand at the time of licensure, or as soon as possible after regulatory approval. Shifting the timing of available PK data in pregnancy to the time the drug is being reviewed for approval as a routine matter



will help ensure appropriate dosing across drug options upon rollout. This recommendation can be achieved through commitments from the drug industry, encouragement from regulators, and support from funders.

8. Enhance post-approval safety evaluations

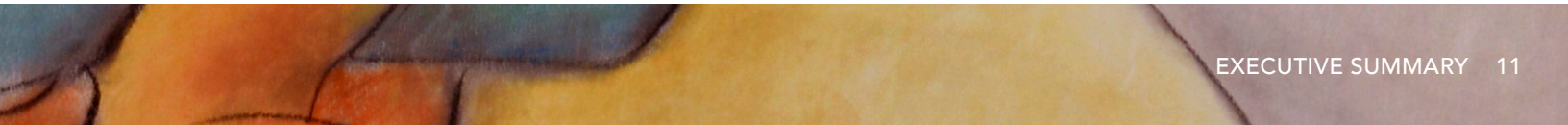
The HIV/co-infection research community should commit to a more robust and regularized structure of post-approval safety evaluations to ensure both adequate pharmacovigilance and pregnant women's timely access to important drugs. This includes expanding prospective registries, conducting timely prospective 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 women accessing important drugs.

Enhancing safety data specific to pregnancy is important to making informed clinical decisions and counteracting reticence in prescribing based on poorly characterized risk. While pregnant women's access to new drugs should not be further burdened with yet greater evidence requirements than practice and guidance developers already impose, the HIV/co-infection community should move toward a standard of practice to expand prospective adverse event data collection, assure the timely, post-approval safety studies of drugs with widespread use in pregnancy, and timely pursuit of safety signals.

9. Address legacy evidence gaps

Currently approved preventives and treatments for HIV/co-infections 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.

Even as we advance more timely and robust evidence gathering for new drugs in pregnant women, currently available therapies should be reviewed for evidence gaps that may significantly affect drug access, equity, or risk in the context of pregnancy. Priority should be given to the most pressing and impactful gaps, which could



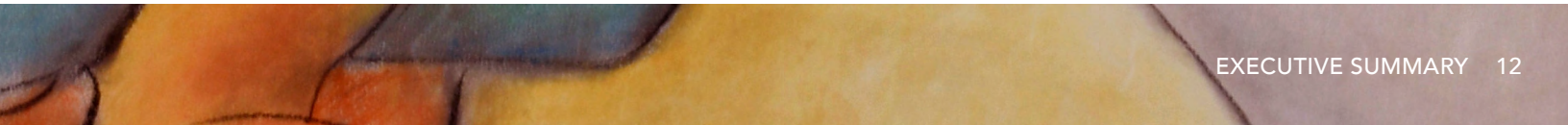
include a range of possible scenarios, such as inadequate evidence about maternal outcomes for drugs deemed safe for the fetus, inadequate fetal safety or maternal outcomes data for drugs that are widely used to good effect outside the context of pregnancy, or information on PK of approved drugs used in pregnancy. Funders of HIV/co-infection research can make a critical difference in supporting needed research with pregnant women by directing funding to this neglected subpopulation, especially in areas where industry's general market incentives are lowest.

Ensuring respect

10. Ensure access to life-saving experimental drugs

Pregnant women should be guaranteed fair access to participate in trials and special access programs for experimental interventions that offer potential life-saving benefits in contexts where no or poor alternatives exist.

Sometimes, experimental drugs are the only option available in high-stakes contexts in which individuals face a life-threatening disease and have no or poor options for treatment or prevention. In such cases, experimental drugs may offer not just a small incremental benefit, but the only or best potential for a lifesaving intervention. The HIV/co-infection community should anticipate the potential for future game-changing drugs and the importance of ensuring fair access to pregnant women during their experimental stage. Pregnancy in itself should not be a reason to exclude a person from access to an intervention that is potentially life-saving, particularly in the absence of good alternative treatments, and especially when pregnant women or their neonates face higher than usual risks from the disease in question. Pregnant women should not be excluded from participating in such trials or programs unless there is demonstrable evidence that the risks outweigh the potential benefits to the women and their children.



11. Respect and support decisional authority

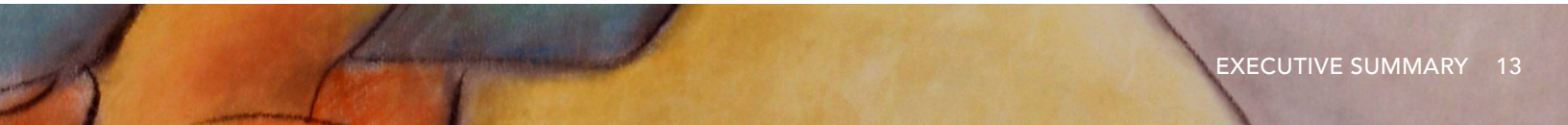
When a pregnant woman of legal standing is eligible to participate in research, her voluntary and informed consent should be sufficient to authorize her participation. Accommodations should be made to facilitate a woman's ability to engage the father, her family, or other personal supports, and to promote their understanding of the benefits and risks of research participation.

Pregnant women of legal age should be at the center of decisions about whether to participate in research. Researchers should also provide meaningful decisional support to prospective participants, including facilitating consultation and shared decision-making with fathers, partners, family members, or other personal support according to the woman's wishes. Strong caution should be used before adding formal paternal consent as a precondition to a pregnant woman's participation in research, as this additional layer of authorization can create barriers to pregnant women's access to research that may be beneficial to themselves or the fetus, and may not take into account the highly contextual specifics of individual relationships.

12. Contextualize risk findings

Those conducting HIV/co-infection research with pregnant women 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 woman and those that would accrue secondarily to her child should her health be benefited.

Clear risk assessment, communication, and translation is important in any research, but research with pregnant women brings special challenges and imperatives. Untoward events such as miscarriage and birth defects regularly occur in pregnancy. However, when such events occur in research contexts, unproven causal associations with the intervention may be presumed. Further, certain biases in risk

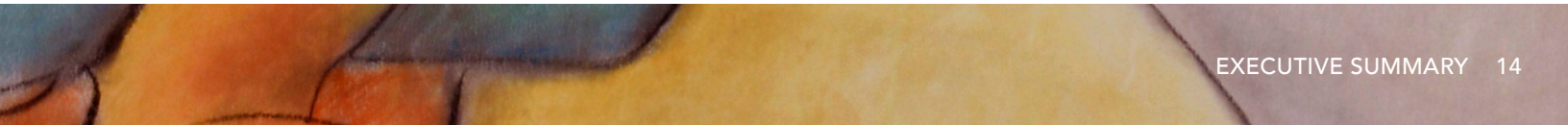


perception have been noted, including the tendency of over-weighting the risks of intervention compared with the risks of not intervening, as well as over-weighting risks to the fetus compared with benefits to the woman. For these reasons, all studies, including observational cohort studies, should develop thoughtful communication strategies before the research begins, and follow key practices for communicating risk.

• • •

The HIV research community has long been an exemplar of finding pathways to address complex and underserved communities. Moreover, the HIV research community has demonstrated for decades, continuing with current vanguard studies, that ethical and impactful research with pregnant women is possible.[37–41] As the global HIV research community continues to work together to end HIV and address its deadly co-infections, it is imperative to ensure equitable attention to a population so centrally affected by these diseases. Pregnant women and the children they bear deserve nothing less.

To read the full report and guidance, see hiv.pregnancyethics.org



References

1. World Health Organization. Prevention of mother-to-child transmission—Estimates by WHO region. 2019. Accessed January 22, 2020.

2. World Health Organization. Mother-to-child transmission of HIV. https://www.who.int/hiv/topics/mtct/about/en/. Accessed November 9, 2019.

3. Wedi COO, Kirtley S, Hopewell S, Corrigan R, Kennedy SH, Hemelaar J. Perinatal outcomes associated with maternal HIV infection: a systematic review and meta-analysis. Lancet HIV. 2016;3(1):e33-48. doi:10.1016/S2352-3018(15)00207-6

4. Evans C, Jones CE, Prendergast AJ. HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. Lancet Infect Dis. 2016;16(6):e92-e107. doi:10.1016/S1473-3099(16)00055-4

5. le Roux SM, Abrams EJ, Donald KA, et al. Growth trajectories of breastfed HIV-exposed uninfected and HIV-unexposed children under conditions of universal maternal antiretroviral therapy: a prospective study. Lancet Child Adolesc Health. 2019;3(4):234-244. doi:10.1016/S2352-4642(19)30007-0

6. le Roux SM, Abrams EJ, Donald KA, et al. Infectious morbidity of breastfed, HIV-exposed uninfected infants under conditions of universal antiretroviral therapy in South Africa: a prospective cohort study. Lancet Child Adolesc Health. 2020;4(3):220-231. doi:10.1016/S2352-4642(19)30375-X

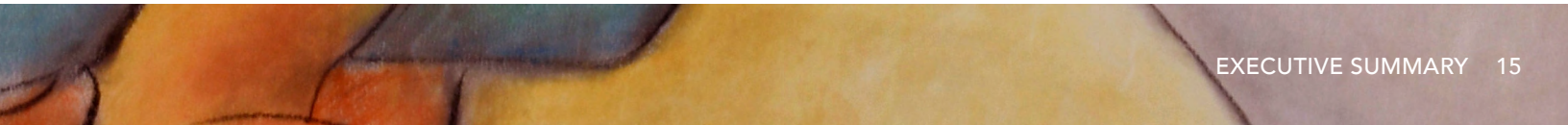
7. Brennan AT, Bonawitz R, Gill CJ, et al. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. AIDS. 2016;30(15):2351-2360. doi:10.1097/QAD.0000000000001211

8. Calvert C, Ronsmans C. HIV and the risk of direct obstetric complications: a systematic review and meta-analysis. PLoS One. 2013;8(10):e74848. doi:10.1371/journal.pone.0074848

9. Lathrop E, Jamieson DJ, Danel I. HIV and maternal mortality. Int J Gynaecol Obstet. 2014;127(2):213-215. doi:10.1016/j.ijgo.2014.05.024

10. Thomson KA, Hughes J, Baeten JM, et al. Increased risk of HIV acquisition among women throughout pregnancy and during the postpartum period: a prospective per-coital-act analysis among women with HIV-infected partners. J Infect Dis. 2018;218(1):16-25. doi:10.1093/infdis/jiy113

11. Vazquez L, Moll AP, Kacin A, Ndlovu NE, Shenoi SV. Perceptions of HIV preexposure prophylaxis among young pregnant women from rural KwaZulu-Natal, South Africa. AIDS Patient Care STDS. 2019;33(5):214-219. doi:10.1089/apc.2018.0242



12. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329(5996):1168-1174. doi:10.1126/science.1193748

13. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399-410. doi:10.1056/NEJMoa1108524

14. Microbicide Trials Network, Sponsored by: Division of AIDS, US National Institute of Allergy and Infectious Diseases US National Institute of Child Health and Human Development, US National Institute of Mental Health, US National Institutes of Health. MTN-003: Phase 2B Safety and Effectiveness Study OfTenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women. 2008.

15. Guffey MB, Richardson B, Husnik M, et al. HPTN 035 phase II/IIb randomised safety and effectiveness study of the vaginal microbicides BufferGel and 0.5% PRO 2000 for the prevention of sexually transmitted infections in women. Sex Transm Infect. 2014;90(5):363-369. doi:10.1136/sextrans-2014-051537

16. Sheffield JS, Siegel D, Mirochnick M, et al. Designing drug trials: considerations for pregnant women. Clin Infect Dis. 2014;59 Suppl 7:S437-44. doi:10.1093/cid/ciu709

17. Westreich D, Rosenberg M, Schwartz S, Swamy G. Representation of women and pregnant women in HIV research: a limited systematic review. PLoS One. 2013;8(8):e73398. doi:10.1371/journal.pone.0073398

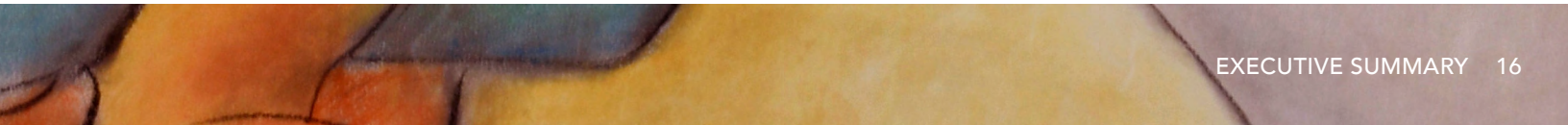
18. Gupta A, Hughes MD, Garcia-Prats AJ, McIntire K, Hesseling AC. Inclusion of key populations in clinical trials of new antituberculosis treatments: current barriers and recommendations for pregnant and lactating women, children, and HIV-infected persons. PLoS Med. 2019;16(8):e1002882. doi:10.1371/journal.pmed.1002882

19. Moore BR, Davis TME. Pharmacotherapy for the prevention of malaria in pregnant women: currently available drugs and challenges. Expert Opin Pharmacother. 2018;19(16):1779-1796. doi:10.1080/14656566.2018.1526923

20. Gupta A, Mathad JS, Abdel-Rahman SM, et al. Toward earlier inclusion of pregnant and postpartum women in tuberculosis drug trials: consensus statements from an international expert panel. Clin Infect Dis. 2016;62(6):761-769. doi:10.1093/cid/civ991

21. Gilbert EM, Darin KM, Scarsi KK, McLaughlin MM. Antiretroviral pharmacokinetics in pregnant women. Pharmacotherapy. 2015;35(9):838-855. doi:10.1002/phar.1626

22. Colbers A, Mirochnick M, Schalkwijk S, Penazzato M, Townsend C, Burger D. Importance of prospective studies in pregnant and breastfeeding women living with human immunodeficiency virus. Clin Infect Dis. 2019;69(7):1254-1258. doi:10.1093/cid/ciz121



23. McIlleron H, Chirehwa MT. Current research toward optimizing dosing of first-line antituberculosis treatment. Expert Rev Anti Infect Ther. 2019;17(1):27-38. doi:10.1080/14787210.2019.1555031

24. Wilby KJ, Ensom MHH. Pharmacokinetics of antimalarials in pregnancy: a systematic review. Clin Pharmacokinet. 2011;50(11):705-723. doi:10.2165/11594550-000000000-00000

25. Schalkwijk S, Colbers A, Mirochnick M. Module 3: Pregnant and Breastfeeding Women. WHO. 2017.

26. Adegbola A, Abutaima R, Olagunju A, et al. Effect of pregnancy on the pharmacokinetic interaction between efavirenz and lumefantrine in HIV-malaria coinfection. Antimicrob Agents Chemother. 2018;62(10). doi:10.1128/AAC.01252-18

27. Bauserman M, Conroy AL, North K, Patterson J, Bose C, Meshnick S. An overview of malaria in pregnancy. Semin Perinatol. 2019;43(5):282-290. doi:10.1053/j.semperi.2019.03.018

28. US Centers for Disease Control. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis, Recommendations - Treating Pregnant Women with Tuberculosis and HIV Co-Infection. https://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/recommendations05.htm. Accessed November 6, 2019.

29. Momper JD, Best BM, Wang J, et al. Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. AIDS. 2018;32(17):2507-2516. doi:10.1097/QAD.0000000000001992

30. Crauwels HM, Osiyemi O, Zorrilla C, Bicer C, Brown K. Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen. HIV Med. 2019;20(5):337-343. doi:10.1111/hiv.12721

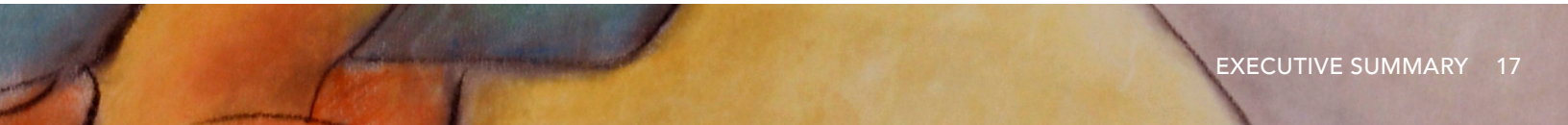
31. Patterson KB, Dumond JB, Prince HA, et al. Protein binding of lopinavir and ritonavir during 4 phases of pregnancy: implications for treatment guidelines. J Acquir Immune Defic Syndr. 2013;63(1):51-58. doi:10.1097/QAI.0b013e31827fd47e

32. Kazma JM, van den Anker J, Allegaert K, Dallmann A, Ahmadzia HK. Anatomical and physiological alterations of pregnancy. J Pharmacokinet Pharmacodyn. February 2020. doi:10.1007/s10928-020-09677-1

33. Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. Clin Infect Dis. 2012;55(11):1532-1549. doi:10.1093/cid/cis732

34. Kovacs SD, Rijken MJ, Stergachis A. Treating severe malaria in pregnancy: a review of the evidence. Drug Saf. 2015;38(2):165-181. doi:10.1007/s40264-014-0261-9

35. Huntington S, Thorne C, Newell M-L, et al. Pregnancy is associated with elevation of liver enzymes in HIV-positive women on antiretroviral therapy. AIDS. 2015;29(7):801-809. doi:10.1097/QAD.0000000000000620



36. Task Force on Research Specific to Pregnant Women and Lactating Women. Report to the Health and Human Services Secretary and Congress. 2018.

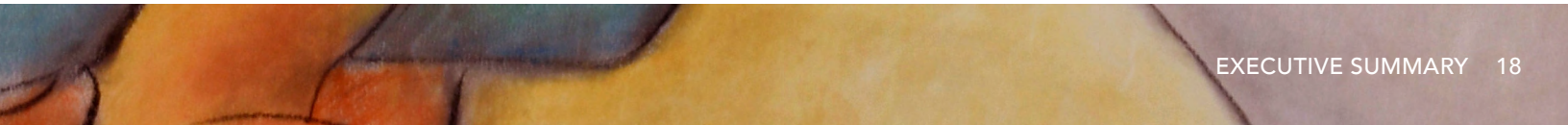
37. Waitt C, Orrell C, Walimbwa S, et al. Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: A randomised trial (DolPHIN-1 study). PLoS Med. 2019;16(9):e1002895. doi:10.1371/journal.pmed.1002895

38. Kintu K, Malaba T, Nakibuka J, et al. RCT of dolutegravir vs. efavirenz-based therapy initiated in late pregnancy: Dolphin-2. CROI Conference. http://www.croiconference.org/sessions/rct-dolutegravir-vs-efavirenz-based-therapy-initiated-late-pregnancy-dolphin-2. Published March 2019. Accessed November 6, 2019.

39. Lockman S. IMPAACT 2010: Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and their Infants. 2016.

40. Fowler MG, Qin M, Fiscus SA, et al. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. N Engl J Med. 2016;375(18):1726-1737. doi:10.1056/NEJMoa1511691

41. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. N Engl J Med. 2019;381(9):827-840. doi:10.1056/NEJMoa1905230



Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies

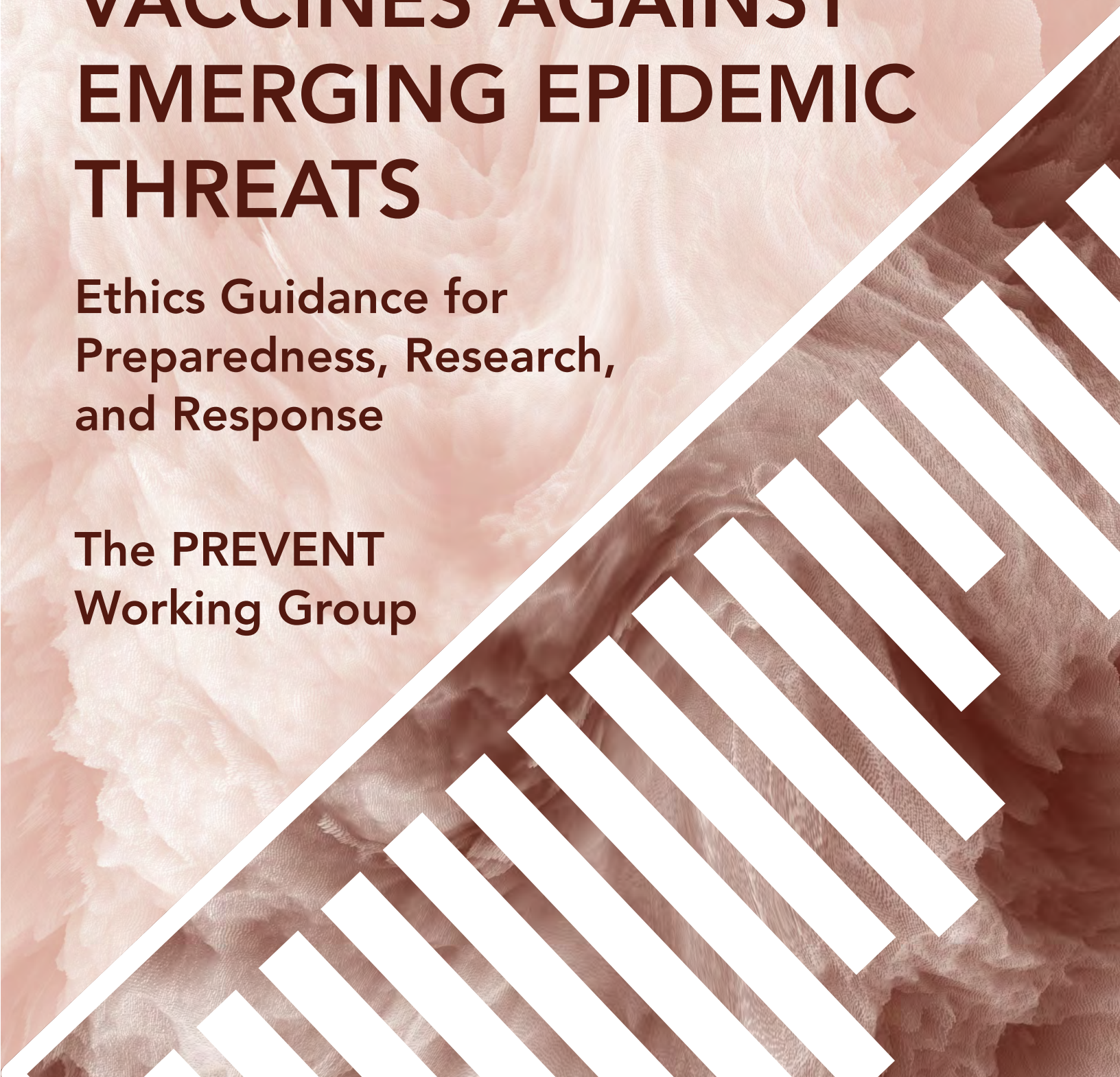
PREVENT

wellcome

PREGNANT WOMEN & VACCINES AGAINST EMERGING EPIDEMIC THREATS

Ethics Guidance for Preparedness, Research, and Response

The PREVENT Working Group



Johns Hopkins Berman Institute of Bioethics
The Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Project

This work is a product of The PREVENT Working Group. PREVENT is a grant-funded project led by faculty at Johns Hopkins University alongside co-investigators at Georgetown University and the University of North Carolina at Chapel Hill, with external contributions from Working Group Members.

The PREVENT Project is funded by the Wellcome Trust (203160/Z/16/Z).

The recommendations, interpretations, and conclusions expressed in this work do not necessarily reflect the views of the institutions with which Working Group members are affiliated.

Suggested citation:

> The PREVENT Working Group. *Pregnant Women & Vaccines Against Emerging Epidemic Threats: Ethics Guidance for Preparedness, Research, and Response*. Baltimore, MD: September 2018.

*Corresponding Author: Carleigh B. Krubiner (ckrubiner@cgdev.org)

Available at: vax.pregnancyethics.org

EXECUTIVE SUMMARY

Recent epidemics, including Zika virus, Lassa Fever, Ebola, and H1N1 influenza, have highlighted the ways in which infectious disease outbreaks can severely—and at times uniquely—affect the health interests of pregnant women and their offspring.[i] For some pathogens, pregnant women are at significantly higher risk of serious disease and death. Infection in pregnancy can also result in pregnancy loss or severe congenital harms. Even if the disease caused by the pathogen is no worse in pregnancy, the harms of infection in pregnant women can potentially affect two lives.

These serious and often disproportionate risks underscore the critical need to proactively consider the interests of pregnant women and their offspring in efforts to combat epidemic threats. This is especially true for vaccines, essential tools in the public health response to infectious diseases. Despite increasing support of maternal immunization strategies and efforts to develop certain vaccines specifically targeted to pregnant women, the vast majority of new vaccine products are rarely designed with pregnant women in mind. Moreover, widespread failure to appropriately include pregnant women in vaccine research means that evidence about safety and efficacy in pregnancy has been limited and late in coming. As a result, in numerous outbreaks and epidemics, pregnant women have been denied opportunities to receive vaccines that would have protected them and their offspring from the ravages of these diseases.

This way of treating pregnant women in vaccine research and deployment is not acceptable. Business as usual can no longer continue.

To ensure that the needs of pregnant women and their offspring are fairly addressed, new approaches to public health preparedness, vaccine research and development (R&D), and vaccine delivery are required. This Guidance provides a roadmap for the ethically responsible, socially just, and respectful inclusion of the interests of pregnant women in the development and deployment of vaccines against emerging pathogens. The Guidance is a product of the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group—a multidisciplinary, international team of 17 experts specializing in bioethics, maternal immunization, maternal-fetal medicine, obstetrics, pediatrics, philosophy, public health, and vaccine research and policy—in consultation with a variety of external experts and stakeholders.

We recognize the recommendations contained in this Guidance will not always be easy to follow. For some, it will require a new way of thinking about pregnant women and vaccines. For many, it will require a commitment of will and of financial resources. Addressing inequities in biomedical research and public health rarely comes cheaply or without hard work. In terms of the lives saved and the suffering averted, the resources and the effort needed to ensure that pregnant women and their offspring are treated fairly will be more than worth it.

i We use the term "women" throughout this document, and while we appreciate that individuals who do not identify as women can still become pregnant, transgender and gender non-conforming individuals face different (though also substantial and problematic) barriers to participating in clinical research and having their health needs met that lie beyond the scope of this work. We use the term "offspring" throughout this report to broadly refer to fetuses as well as any persons born whose interests may be affected by *in utero* exposures to pathogens or vaccine administrations.

VISION

The guidance aims to realize a world in which:

Pregnant women
are not unjustifiably
excluded from participating
in vaccine studies.

Pregnant women and their
offspring benefit from advances in
vaccine technologies and are
not left behind as new vaccine
products are developed.

Pregnant women
have access to safe and effective
vaccines to protect them and their
offspring against emerging
and re-emerging pathogenic
threats.

RECOMMENDATIONS

PUBLIC HEALTH EMERGENCY PREPAREDNESS

RECOMMENDATION 1

Health information systems and infectious disease surveillance systems should be strengthened and integrated to ensure that data relevant to maternal, obstetric, and newborn health outcomes can inform scientific and public health responses to emerging pathogenic threats.

- **DIRECTED TO:** public health authorities; the World Health Organization (WHO) and regional health organizations; developers and users of routine health information and global health security systems, including organizations with a focus on maternal and child health outcomes; organizations developing innovative approaches to data collection and surveillance; funders and sponsors of maternal health studies and global health surveillance

Routine health information systems and infectious disease surveillance systems are both essential to an appropriate and rapid response to emerging pathogenic threats. Collecting baseline data on maternal, obstetric, and newborn health can advance the interests of pregnant women and their offspring by enabling detection of increases in adverse events that may signal the presence of infectious disease threats. These baseline rates are also needed to help interpret whether adverse events surrounding pregnancy have any causal link to vaccination. Infectious disease surveillance systems should routinely include pregnancy status and maternal, obstetric, and newborn outcomes in case reports. These data, when integrated with baseline rates from health information systems, can help determine whether a circulating pathogen causes additional or more severe harms in pregnancy.

RECOMMENDATION 2

Evidence-based strategies to promote confidence about vaccination in pregnancy should be developed and implemented ahead of outbreaks, including stakeholder engagement with health care providers, women, their families, and their communities.

- **DIRECTED TO:** public health authorities; health care providers; professional medical associations; medical and health training programs; community leaders; civil society organizations and vaccine advocacy groups; research institutes; funders and sponsors; the media

For immunization programs to be successful, it is critical that populations have confidence in the benefits of a vaccine and its safety, and in the health benefits of vaccination more broadly. Inadequate confidence in vaccines can be especially pronounced among pregnant women and those who care for them. Evidence about safety in pregnancy is limited because of the historic absence of vaccine trials in pregnant women. Moreover, pregnant women and health care providers are understandably concerned about fetal harm, and they are frequently bombarded with mixed messages about what may or may not be harmful in pregnancy. Working now to better understand and address the various sources and drivers of vaccine confidence among pregnant women and their communities will be critical to ensure appropriate vaccine uptake by pregnant women during outbreaks and epidemics.

RECOMMENDATION 3

Communication plans should be developed for clear, balanced, and contextualized dissemination of vaccine study findings, recommendations for vaccine use in pregnancy, and any pregnancy-specific adverse events.

- **DIRECTED TO:** clinical investigators; scientific journal editors; funders and sponsors; public health authorities; global, regional, and local vaccine advisory groups; professional medical associations; regulatory authorities; civil society organizations and vaccine advocacy groups; the media

Because pregnant women, health providers, and the public often overestimate potential fetal harms associated with medications and biologics, effective communication in vaccine development and delivery is critical. In research studies, the required timely reporting of clinically relevant signals and findings on vaccine safety and efficacy in pregnancy to regulatory authorities is not enough. Effective communication to the public and to clinicians through a variety of channels, including traditional and social media, is essential. In an epidemic response that recommends vaccination in pregnancy, communication plans must be clear about any known risks to pregnant women and their offspring, and why the anticipated benefits of vaccination outweigh these risks. When immunization in pregnancy is not recommended, communication plans should be sensitive to fears and concerns about the pathogenic threat that pregnant women share with the rest of the population, and provide them with information about what alternatives, if any, are available to them. In both research and epidemic responses, one best practice for communicating reports of adverse pregnancy or birth outcomes is to present the findings alongside the best available information about the baseline rates of these adverse events, and to acknowledge that many of them have no known cause.

RECOMMENDATION 4

Research efforts that aim to advance vaccine development by using new technologies to study human immune system function and response should include investigations specific to pregnant women and their offspring.

- **DIRECTED TO:** clinical investigators; basic research scientists; funders

Because pregnancy can alter immune response and because both maternal and fetal immune responses may change over the course of gestation, it is important that these foundational studies examine the distinctive characteristics of maternal and fetal immune systems. Understanding these differences could critically inform the development and identification of new vaccines that are safe and effective in pregnancy.

RECOMMENDATION 5

Mechanisms for incentivizing vaccine development for emerging and re-emerging infections and mitigating existing disincentives should include and address pregnancy-specific concerns of vaccine developers.

- **DIRECTED TO:** policymakers; regulatory authorities; funders and sponsors; vaccine developers; civil society organizations and those who are positioned to influence vaccine research, adoption, and delivery, including WHO, the World Economic Forum, and the Coalition for Epidemic Preparedness Innovations (CEPI)

Vaccine developers and manufacturers face significant market challenges and uncertainties in pursuing products targeting emerging and re-emerging pathogens. These challenges can become even more complicated when vaccine products are studied in and ultimately offered to pregnant women—for whom there may be heightened concerns of legal and financial liability. Current mechanisms in place to encourage development of

beneficial biomedical products and protect developers and manufacturers against liability concerns—as well as new incentive programs being explored for vaccines against epidemic threats—need to be intentionally inclusive of the needs and interests of pregnant women.

RECOMMENDATION 6

To help ensure systematic and enduring change in the treatment of pregnant women in global vaccine policy and practices, the World Health Organization should convene a consultation of relevant stakeholders and experts. The Consultation should identify specific strategies to establish for pregnant women the presumption of inclusion in both vaccine research and deployment, including whether a dedicated, standing expert group is needed.

Throughout this Guidance we make multiple recommendations to help ensure that pregnant women and their offspring can fairly benefit from the protection that vaccines offer against emerging epidemic threats. These recommendations outline specific actions that need to be taken, but institutional change at every level—globally, regionally, and nationally—will be required to operationalize these new approaches and move advisory and decision-making bodies toward the new default of presumptive inclusion of pregnant women. To seed this institutional change and explore specific strategies for the systematic consideration of pregnant women in international policies and practices governing vaccine research and delivery, WHO should convene a multi-day, global Consultation of relevant stakeholders. The Consultation should provide a critical opportunity to discuss and determine the best strategies to systematically integrate consideration of the interests of pregnant women and their offspring throughout all relevant WHO-supported activities, including whether a dedicated, standing group of relevant and diverse experts is needed. The Consultation should also consider ways to support regional and national public health authorities who may wish to establish similar expert groups.

Institutional change at every level will be required to establish a new default of presumptive inclusion of pregnant women.

The Presumptive Inclusion of Pregnant Women

"Presumption of inclusion" does not entail the automatic or absolute inclusion of pregnant women in every vaccine study or every vaccine campaign. Instead, a presumption of inclusion changes the default position. It normalizes the position that pregnant women are to be included in vaccine deployment programs and vaccine R&D. With inclusion of pregnant women as the default position, the burden of proof, both scientific and ethical, falls on those who want to argue for their exclusion. There will certainly be cases where the exclusion of pregnant women from a particular vaccine trial or vaccine campaign will be justified, but starting from a presumption of inclusion helps instantiate and maintain a fundamental shift in the way pregnancy and pregnant women are viewed in the field of vaccines.

VACCINE RESEARCH & DEVELOPMENT

RECOMMENDATION 7

Suitability for use in pregnancy should be a strong consideration in development and investment decisions for vaccines against emerging pathogenic threats.

- **DIRECTED TO:** CEPI, U.S. Biomedical Advanced Research and Development Authority (BARDA), and other funders and sponsors; WHO emergency response teams, R&D Blueprint teams and TPP Working Groups; vaccine developers

If pregnant women, and the offspring they carry, are among those threatened by an emerging pathogen, then suitability for use during pregnancy should be an important vaccine development priority. Organizations investing in the vaccine pipeline against emerging pathogenic threats should try to ensure that, among candidates prioritized for development, at least some use platforms and adjuvants that would make them suitable for use in pregnancy. Early investment in options that are most likely to be acceptable in pregnancy can pave the way for pregnant women and their offspring to realize benefits from vaccine candidates that ultimately prove successful—and help ensure that they, like other population groups, will be protected against emerging infectious diseases. For pathogens that pose significantly greater threats in pregnancy—of fetal harm, maternal harm, or both—funding calls should designate greater investment priority to candidates likely to be suitable for use in pregnancy. When pregnant women or their offspring are at higher risk of harm, it would be particularly unjust for their needs not to be included in vaccine development priorities.

RECOMMENDATION 8

When pathogens pose a risk of severe harm to pregnant women or their offspring and the most promising vaccine candidates are likely to be contraindicated for routine use in pregnancy, investments should be made in alternative vaccine candidates that could be more readily used in pregnancy.

- **DIRECTED TO:** CEPI, BARDA, and other funders; vaccine developers

It is possible that the vaccine candidates that move most rapidly through the R&D pipeline are found to be problematic for use in pregnancy. Unless other vaccines with more favorable profiles for use in pregnancy are then prioritized, it is possible that pregnant women and their offspring will end up without any vaccine protection against the emerging pathogenic threat. This prospect is particularly dire when the target pathogen has more severe consequences in pregnancy. When pregnant women and their offspring suffer disproportionately compared with other population groups from an emerging infectious disease threat, justice calls for the vaccine enterprise to make every reasonable effort to bring to market a safe and effective product that pregnant women can use.

Pregnant women need to be on the agenda when decisions about investment and funding are made.

RECOMMENDATION 9

Non-clinical studies that are a prerequisite for clinical trials in pregnant women, such as developmental toxicology studies, should be initiated early in the clinical development of promising vaccine candidates, before efficacy trials are planned.

- **DIRECTED TO:** CEPI, BARDA, and other funders and sponsors; vaccine developers; national regulatory authorities

Current regulatory guidance often requires that certain non-clinical studies must be completed prior to including pregnant women in clinical trials. Because pregnant women should be able to participate in large-scale efficacy studies conducted during outbreaks whenever the benefits outweigh the risks (see Recommendation 11), any non-clinical studies required prior to clinical evaluation in pregnant women should be conducted as soon as promising vaccine candidates move from phase 1 to phase 2 clinical trials.

RECOMMENDATION 10

Studies to assess immune responses to vaccines in pregnancy should be conducted before or between outbreaks whenever scientifically possible and ethically and legally acceptable.

- **DIRECTED TO:** CEPI, BARDA, and other funders and sponsors; vaccine developers; clinical investigators

Although much of the work to evaluate vaccines in pregnancy will be done during outbreaks and epidemics (see Recommendation 11), there will be some cases in which it will be both beneficial and feasible to generate immunogenicity data in pregnancy before or between outbreaks. Because immune system functioning is altered in pregnancy, it is possible that a vaccine will be less immunogenic or induce atypical immune responses in pregnant women, with potential implications for its effectiveness as well as the dosing and frequency required in pregnancy to generate sufficient protection. Such immunogenicity studies would be particularly valuable if a correlate of protection for the vaccine has already been established. In the absence of an outbreak or epidemic, it may be difficult to demonstrate that studies to assess immune response in pregnant women have a favorable risk-benefit profile. However, there may be instances in which the future exposure to a pathogen among a particular population is likely enough to conclude that the potential benefits of being protected would outweigh the risks associated with a particular candidate vaccine.

RECOMMENDATION 11

Clinical development plans for investigational vaccines against emerging and re-emerging pathogens should include studies designed to evaluate vaccines in pregnancy. Pregnant women should have opportunities to enroll in vaccine studies conducted during outbreaks and epidemics whenever the prospect of benefit outweighs the risks to pregnant women, their offspring, or both.

- **DIRECTED TO:** CEPI, BARDA, and other funders and sponsors; vaccine developers; clinical investigators and trial implementation partners; research ethics committees; national regulatory authorities

This recommendation rests on two claims of justice about the importance of treating pregnant women and their offspring fairly in the conduct of research on vaccines for emerging and re-emerging infections. The first of these justice claims pertains to pregnant women as a class: as a matter of equity, as well as public health, the evidence base for pregnant women should be as good as possible and generated as contemporaneously as possible to the evidence for the general population. The second, independent reason motivated by justice is that pregnant women, as the moral equals of others,

should have fair access to the prospect of direct benefit that may ensue from receiving an experimental vaccine. For both of these reasons, it is critical that vaccine research conducted during outbreaks include appropriate plans for research with pregnant women when there is a reasonable judgment that the prospective benefits of enrollment outweigh the risks.

RECOMMENDATION 12

Vaccine studies that include women of childbearing potential should have plans to systematically collect data on immunogenicity and pregnancy-specific indicators of safety from participants who are unknowingly pregnant at the time of exposure or become pregnant within a relevant window following vaccine administration.

- **DIRECTED TO:** CEPI, BARDA, and other funders and sponsors; vaccine developers; clinical investigators and trial implementation partners; research ethics committees; national regulatory authorities

In trials enrolling women of childbearing potential, including vaccine trials conducted in outbreak contexts, it is predictable that some women not known to be pregnant at the time of enrollment will nevertheless be pregnant at enrollment, or become pregnant in the course of the trial. Historically, data from inadvertent exposures during pregnancy have been a key source of information regarding the safety profiles of vaccines in pregnancy. Having a plan to systematically generate evidence from participants who are unknowingly pregnant at the time of administration also enables capturing data from vaccine exposures earlier in pregnancy than would be likely in trials prospectively enrolling pregnant women. Wherever possible, systematic observational studies that are designed to capture inadvertent exposures to vaccine during pregnancy should also include longitudinal evaluation of safety, immunogenicity, and other relevant outcomes. Data from inadvertent exposures during pregnancy should be collected using standardized methods and case definitions and must be cautiously interpreted, particularly when adverse events occur in early pregnancy, as these very commonly occur unrelated to vaccine exposure.

RECOMMENDATION 13

Women participating in vaccine trials who become aware of a pregnancy during the trial should be guaranteed the opportunity, through a robust re-consent process, to remain in the trial and complete the vaccine schedule when the prospect of direct benefit from completing the schedule can reasonably be judged to outweigh the incremental risks of receiving subsequent doses.

- **DIRECTED TO:** clinical investigators and trial implementation partners; vaccine developers; research ethics committees; national regulatory authorities

In vaccine trials that include prospectively enrolled pregnant women, participants who become pregnant after enrollment should be provided the opportunity to continue to receive vaccine doses after a renewed consent process. In trials that exclude pregnant women from prospective enrollment, determinations about continued dosing should be based on assessment of the potential benefits and harms specific to the circumstances of the pregnant participant, including possible risks associated with receiving an incomplete vaccination series and the risks already incurred from the first vaccination. In both cases, a robust re-consent process will be essential to allowing pregnant women to determine whether they want to receive additional doses. Regardless of whether they choose or are permitted to continue with the vaccine schedule, participants who become pregnant should be provided all study-related benefits and ancillary care to which they would otherwise be entitled.

RECOMMENDATION 14

When a pregnant woman of legal standing to consent is judged eligible to enroll or continue in a vaccine trial, her voluntary and informed consent should be sufficient to authorize her participation.

- **DIRECTED TO:** clinical investigators and trial implementation partners; research ethics committees; national authorities in charge of governance and oversight of human subjects research

As a matter of respect, and as a key aspect of ensuring fair access to investigational vaccines, the consent of pregnant women who are judged eligible to participate in or continue receiving doses in a vaccine trial should be sufficient for participation. Pregnant women are the moral equals of other self-governing adults. Further, requiring the consent of additional actors can present a material barrier to the benefits research may offer to the offspring. At the same time, researchers should support pregnant women who wish to involve partners, family members, and other personal supports in decisions to join or remain in vaccine trials.

RECOMMENDATION 15

Experts in maternal and perinatal health, pediatrics, and research ethics should be involved in decisions about funding; trial design; research ethics oversight; and the generation, analysis, and evaluation of evidence on vaccine use in pregnancy.

- **DIRECTED TO:** funders and sponsors; vaccine developers; clinical investigators; research ethics committees; national health authorities in charge of research governance and regulations; data safety monitoring boards

Pregnant women deserve that decisions affecting them will be made in careful, thoughtful, and evidence-based ways, involving the most informed experts possible. Experts in obstetrics and gynecology, maternal-fetal medicine, pediatrics, and neonatology, especially those who have experience with infectious diseases, immunology, and maternal immunization, have specialized knowledge that is critical to properly identifying and addressing the needs and interests of pregnant women and their offspring in research and development.

RECOMMENDATION 16

Whenever possible, the perspectives of pregnant women should be taken into account in designing and implementing vaccine studies in which pregnant women are enrolled or in which women enrolled may become pregnant.

- **DIRECTED TO:** clinical investigators; vaccine developers; research ethics committees; community advisory boards; funders and sponsors; public health authorities

Community engagement and participatory-based approaches to biomedical research have been increasingly recognized as good practice in the design and conduct of human subjects research. In the context of vaccine studies enrolling pregnant women, soliciting the perspectives of pregnant women from the communities in which the research will be conducted offers a way to demonstrate respect, and can be critical to the success of a study. The perspectives of pregnant women can improve various aspects of study design by, for example, determining what information and outcomes are most important to pregnant women, ascertaining culturally relevant considerations for the consent process, and establishing the appropriate frequency and location of study visits based on the daily demands on women's lives throughout pregnancy and after delivery.

VACCINE DELIVERY DURING THE EPIDEMIC RESPONSE

RECOMMENDATION 17

Pregnant women should be offered vaccines as part of an outbreak or epidemic response. Pregnant women should only be excluded if a review of available evidence by relevant experts concludes that the risks to pregnant women and their offspring from the vaccine are demonstrably greater than the risks of not being vaccinated.

- **DIRECTED TO:** public health authorities; national immunization programs; recommending and advisory bodies, including professional medical associations, SAGE, and other relevant WHO advisory committees; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery in the outbreak response, including UNICEF, MSF, and International Federation of Red Cross

Because pregnant women are the moral equals of others, and because there is nothing about being pregnant that would make them or their offspring less susceptible to the harms of emerging pathogenic threats, the default position of advisory bodies and public health authorities should be that pregnant women are offered vaccines alongside other affected populations during an epidemic response. Any recommendations or decisions not to use vaccines in pregnancy during an outbreak or epidemic requires justification of exclusion based on a reasonable determination that the risks to pregnant women and their offspring from vaccination are demonstrably greater than the likely benefits of being protected from the pathogen. This determination should be made by relevant experts, including those in maternal, perinatal, and pediatric health. ***The absence of evidence and the mere theoretical or even documented risk of fetal harm is generally not sufficient to justify denying pregnant women access to a vaccine in an outbreak or epidemic.*** Even when the risk of fetal harm from the vaccine is significant, if the likelihood and severity of harms from the pathogen are high enough for pregnant women and their offspring, then the benefits of vaccination may still outweigh the risks.

RECOMMENDATION 18

When there is a limited supply of vaccine against a pathogenic threat that disproportionately affects pregnant women, their offspring, or both, or when only one vaccine among several is appropriate for use in pregnancy, then pregnant women should be among the priority groups to be offered the vaccine.

- **DIRECTED TO:** public health authorities; national immunization programs; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; WHO; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross

It is not uncommon in outbreak and epidemic settings for vaccine demand to exceed supply. For some pathogenic threats, pregnant women and their offspring may be among the hardest hit groups; in these cases, as with any other high-risk group, they should be a priority in the allocation of a vaccine that is in short supply. Additionally, even when the threat is no worse for pregnant women than it is for other affected population groups, vaccinating a pregnant woman protects not only the pregnant woman but also her offspring. Particularly for high-consequence pathogens with significant mortality rates, there may be considerable additional benefit in vaccinating pregnant women.

During an epidemic, the default should be to offer vaccines to pregnant women alongside other affected populations.

RECOMMENDATION 19

When vaccines are offered to pregnant women during outbreaks or epidemics, prospective observational studies should be conducted with pregnant women and their offspring to further advance the evidence base for use in pregnancy.

- **DIRECTED TO:** vaccine manufacturers; public health and regulatory authorities; national immunization programs; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross; researchers; funders; groups that oversee research with human subjects, including research ethics committees

Implementing prospective observational studies in pregnant women and their offspring who receive the vaccine as part of the outbreak or epidemic response provides an important opportunity to narrow the evidence gap between pregnant women and other population groups. If such studies are not conducted, decision-makers in future outbreaks and epidemics will be faced with the same evidence gap as current decision makers—an unacceptable outcome from both an equity and a public health perspective. Moreover, safety data obtained from evaluating a vaccine derived using a novel platform in pregnant women may inform future decision-making regarding the suitability of that platform for development of vaccines against other pathogens.

RECOMMENDATION 20

When vaccines are offered to pregnant women during outbreaks and epidemics, the consent of the pregnant woman should be sufficient to authorize administration whenever the pregnant woman is of legal standing to consent to medical care.

- **DIRECTED TO:** public health authorities; national immunization programs; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross; clinicians and obstetricians; pregnant women and communities

As a matter of respect, and as a key aspect of ensuring fair access to vaccines during an outbreak or epidemic, when vaccines are offered to pregnant women, their consent should be sufficient to authorize administration. Women should be presumed to have authority for decisions about their own medical care. Women are no different from men in this respect, and pregnant women are no different than women who are not pregnant. All adults, regardless of gender or pregnancy status, have rights of self-determination over decisions that affect their bodies and their health. Pregnant women who wish to engage or consult with their partners or other family or friends in making their decisions about vaccination should be supported in doing so.

Ensuring that pregnant women have vaccines to protect them and their offspring will require generation of evidence from pregnant women.

RECOMMENDATION 21

When evidence supports a determination that the risk of serious maternal or fetal harm from the vaccine outweighs the vaccine's benefits, pregnant women should be a priority group for access to alternative preventative or treatment measures.

- **DIRECTED TO:** public health authorities; teams overseeing the epidemic response, such as Public Health Emergency Operations Centers and incident management teams; organizations involved in vaccine delivery as part of the outbreak response, including UNICEF, MSF, and International Federation of Red Cross; providers

Despite the best possible research and development efforts, the available vaccine for a given outbreak or epidemic may have sufficiently severe pregnancy-specific risks, even compared with the risks posed by the pathogen, that it is not made available to pregnant women. The moral objective remains, however, of giving pregnant women and their offspring as close to an equal chance of avoiding the harms of infection as the rest of the population. If they cannot be protected by immunization, then pregnant women, along with any other population group that cannot receive the vaccine, should be given preferential access to alternative preventive interventions and treatments.

RECOMMENDATION 22

When vaccines against emerging pathogens are not recommended for use in pregnancy, inadvertent vaccine exposures during pregnancy should be anticipated and mechanisms put in place for the collection and analysis of data from pregnant women and their offspring on relevant indicators and outcomes.

- **DIRECTED TO:** public health and regulatory authorities; vaccine manufacturers; national immunization programs; funders and sponsors

Even when pregnant women are intentionally excluded from the vaccine response effort, it is reasonable to expect that some of the women who are vaccinated will be unknowingly pregnant at the time of vaccine administration, or will become pregnant within a relevant window of its administration. Collecting data about outcomes in these women and their offspring in the midst of an active outbreak or epidemic will be difficult and costly, but there are two sets of ethical and public health reasons why it is critically important to do so. First, collecting data from unintentional exposures to vaccine in pregnancy during an outbreak or epidemic affords an important opportunity to gather evidence about novel vaccine technologies and thus to help ensure that pregnant women are not left behind as vaccine technology advances. Second, research and public health communities have a responsibility to pursue evidence about the likelihood and nature of any associated risks pregnant women and their offspring face from these unintended exposures to inform personal and clinical decision-making.

MEMBERS OF THE PREVENT WORKING GROUP

Ruth Faden Principal Investigator Johns Hopkins Berman Institute of Bioethics	**Carleigh Krubiner** Co-Principal Investigator Johns Hopkins Berman Institute of Bioethics	**Ruth Karron** Co-Principal Investigator Johns Hopkins Bloomberg School of Public Health
Margaret Little Co-Investigator Georgetown University Kennedy Institute of Ethics	**Anne Lyerly** Co-Investigator University of North Carolina Center for Bioethics	
Jon Abramson Wake Forest University School of Medicine	**Richard Beigi** Magee-Womens Hospital of University of Pittsburgh Medical Center	
Alejandro Cravioto Universidad Nacional Autónoma de México Faculty of Medicine	**Anna Durbin** Johns Hopkins Bloomberg School of Public Health	
Bruce Gellin Sabin Vaccine Institute	**Swati Gupta** International AIDS Vaccine Initiative (IAVI)	
David C. Kaslow PATH Essential Medicines	**Sonali Kochhar** Global Healthcare Consulting	
Florencia Luna FLACSO-Argentina Bioethics Program & CONICET	**Carla Saenz** Pan American Health Organization Regional Program on Bioethics	
Jeanne Sheffield Johns Hopkins University School of Medicine	**Paulina Tindana** Navrongo Health Research Centre	

Pregnancy Research Ethics
for Vaccines, Epidemics,
and New Technologies
PREVENT

wellcome

UNIVERSITY OF BIRMINGHAM

Birmingham Health Partners
Collaboration. Innovation. Application.

Healthy Mum, Healthy Baby, Healthy Future

The Case for UK Leadership in the Development of Safe, Effective and Accessible Medicines for Use in Pregnancy

—

May 2022

Foreword

Baroness Manningham-Buller

When I was asked to become joint chair of the Commission that has produced this report, I am ashamed to say that I wasn't aware that there was an acute problem. Despite being at Wellcome for twelve years and Imperial College for six, I had no idea that research into conception and pregnancy was largely neglected, and that virtually no drugs had been developed and trialled for pregnant women in the many decades since thalidomide. This leaves women at the mercy both of general diseases, the diseases of pregnancy and drugs which are usually unlicensed. The evidence taken by the Commission in its inquiry convinces us that this urgently needs to change. We suggest how.

Baroness Manningham-Buller
LG, DCB, FMedSci

Professor Peter Brocklehurst

This policy commission report represents a clear and timely platform to improve the care we provide pregnant and breastfeeding women, by increasing the availability of safe, effective and accessible medicines for their use.

During the work of the Commission, we heard from pregnancy and baby charities, as well as experts from across a broad range of sectors. All of them, without exception, highlighted the profound lack of research activity in pregnancy – with 'research' covering the full spectrum of academic, clinical and industrial endeavour – and all expressed the need to do something to improve this terrible situation. Such consensus would not have been possible even 10 years ago, and it is a testament to all the individuals who have been championing this neglected area for so many years that we now have an opportunity to act.

And what is achievable, if all this report's recommendations were to be implemented in full? The stories of HIV and the Covid vaccine are two examples of what concerted and substantial investment in research can achieve. HIV infection, at least in affluent parts of the world, has become a manageable long-term condition with a wide range of medications available, a situation which was unimaginable 30 years ago. And several Covid vaccines were produced, tested, and then rolled-out within a year of the Covid pandemic starting. Imagine what could happen to conditions such as preterm birth or pre-eclampsia, conditions which have led to the deaths of millions of babies and many thousands of women within the UK and worldwide over the past decades, if we had a similar response and sense of urgency about developing new medicines to manage them.

We have an opportunity to make a real difference – let us not squander it.

Professor Peter Brocklehurst
MBChB, MSc, FRCOG, FFPHm, FMedSci
Professor of Women's Health
Director of Research and Development, Birmingham Clinical Trials Unit

Contents

Note on terminology: While this report will refer to 'pregnancy', this term is used broadly to encompass pregnancy and breastfeeding. We use the terms 'woman' and 'mother' throughout the report, but the recommendations will also apply to people who do not identify as women and who are pregnant or have given birth. The term 'medicines' includes vaccines.

Note on geographical coverage: Whilst this report makes policy recommendations for the UK, there are no specific recommendations for policy in Northern Ireland, which is subject to EU regulatory oversight.

Disclaimer: This report is the product of a multi-stakeholder inquiry convened by the University of Birmingham and Birmingham Health Partners. The Commissioners have agreed its conclusions and recommendations. Individual points within the text do not necessarily represent the views of individual Commissioners. Nothing in this report can be taken as representing the views of the Commissioners' employers.

Co-Chairs

Baroness Manningham-Buller
LG, DCB, FMedSci
House of Lords
Co-President, Chatham House

Professor Peter Brocklehurst
MBChB, MSc, FRCOG, FFPH, FMedSci
Professor of Women's Health, University of Birmingham
Director of Research and Development, Birmingham Clinical Trials Unit

Commissioners

Dr Allyah Abbas-Hanif
Chair of the Policy and Communications Group, Faculty of Pharmaceutical Medicine, Royal College of Physicians

Professor Anna David
Director of the Institute for Women's Health, Professor of Obstetrics and Maternal Fetal Medicine, University College London, National Institute for Health and Care Research, University College London Hospitals Biomedical Research Centre

Dr Christine Ekechi
Co-Chair of the Race Equality Taskforce, Royal College of Obstetricians and Gynaecologists, Consultant Obstetrician & Gynaecologist, Imperial College Healthcare NHS Trust

Marcus Green
Chief Executive, Action on Pre-Eclampsia (UK)

Dr A. Metin Gülmezoglu
Executive Director, Concept Foundation, Geneva

Mark Hilton
Life Sciences and Healthcare Partner, Bird & Bird

Steve Hoare
Quality, Regulatory Science & Safety Policy Director, The Association of the British Pharmaceutical Industry (ABPI)

Policy Commission Management

Sundeep Kaur Bhogal
Strategic Projects Development Officer (Policy Commission Manager), University of Birmingham

Michelle Read
Strategic Projects Development Partner (Life Sciences), University of Birmingham

Dr Eliot Marston
Head of Strategic Projects and Partnerships (Life Sciences), University of Birmingham

Editor

Shaoni Bhattacharya

Contact

pregnancypolicycommission@contacts.bham.ac.uk

Executive summary

The ongoing revolution in medicines and vaccines for longstanding and emerging health challenges has completely failed pregnant women.

Pregnant women and babies throughout the world continue to get sick and die from largely preventable or treatable causes. While the scale may be smaller, this is no less true in developed countries such as the UK. Despite this, the way in which medicines are developed currently risks preventing pregnant women from accessing the benefits of safe and effective medicines.

Recently, the exclusion of pregnant women from Covid vaccine trials has led to needless deaths amongst pregnant women and babies, tragically highlighting the issue. Failure is not simply a commercial issue – it is something which all parts of society must take accountability for and work together to solve. The Commission recognises that government expenditure is restricted as a consequence of world events but the cost of inaction is billions of pounds to the UK economy every year, causing untold physical and psychological effects.

The UK must take the opportunity to position itself at the global forefront of medicines development for use in pregnancy and breastfeeding, using the people, infrastructure and opportunities at its disposal.

This Policy Commission interviewed senior figures from pregnancy and baby charities, the NHS, universities, industry, and government, to help it set out a clear agenda for what needs to be done to improve the lives of millions of people, not just for women while they are pregnant, but for the health of future generations.

The interviews highlighted a number of reasons why medicines for pregnancy have not been developed and made a range of suggestions for how these could be overcome. This work will affect – and therefore must involve – a wide range of stakeholders at every stage. The Commission provides a blueprint for action and will provide ongoing support to implementing the recommendations set out in this report.

The UK Government's 'Vision for the Women's Health Strategy for England' identifies an urgent need to address severe health inequalities with respect to the access to safe and effective medicines for pregnant women, with maternal health identified as a key priority. The Commission hopes this report will be a helpful contribution, as government looks to develop and implement its strategy.

RECOMMENDATIONS

1. Deliver effective advocacy for medicines in pregnancy through a coalition of pregnancy and baby charities, working together with the public, researchers from academia and industry as well as Government to create a shared vision for safe medicines evaluation and development in pregnancy. This will allow for clear and consistent messages to the public and clinicians.

2. Pregnant women should be offered the opportunity to take part in all clinical trials of medicines that could be used in pregnancy, unless there are specific safety concerns.

3. Prioritise updates for existing medicines with the potential to be used in pregnancy, with regulators and industry working towards pregnancy-specific information on safety, dosing and effectiveness. Resources should be put in place to maintain this activity, particularly for generic medicines.

4. De-risk insurance processes for early and late phase clinical trials of new and existing medicines for use in pregnancy, using lessons and successes from other challenges.

5. Incentivise industry to develop pregnancy-specific medicines, utilising cross-stakeholder working to ensure that the UK is in a globally-competitive – and globally-collaborative – position to drive drug development for pregnancy-specific conditions.

6. Establish a UK-wide national network of research centres encouraging major public and private investment and collaboration in pregnancy research expertise and infrastructure. This will ensure sustainable drug development from discovery science through to pre-clinical screening tools and clinical evaluation.

7. Improve use of routine clinical care maternity data to help assess the safety and effectiveness of new and existing medicines used in pregnancy. Establish a designated maternity 'Health Data Research Hub' through Health Data Research UK with a focus on medicines evaluation in pregnancy.

8. Appoint a UK Steering Committee aligned to the Government's Women's Health Strategy to deliver the above recommendations, with oversight of implementation, ensuring milestones are set and monitored.

Introduction:
Why medicines in pregnancy matter

Most pregnant women will have a healthy pregnancy and give birth to healthy babies. An increasing number of women, however, will either have one or more health conditions before they become pregnant which require on-going treatment, or they may develop complications of pregnancy which require treatment. The care of these women is severely hampered by a lack of suitable medicines, that we definitively know to be safe and effective for use in pregnancy or during breastfeeding. As a consequence, women and babies worldwide continue to become sick and die during or immediately after pregnancy. Despite this, over the last 40 years, only two new medicines have been approved for use in pregnancy.

Each day globally
800 women die
7,000 newborns die
5,500 babies are stillborn

'Maternal health is a driver of human health and population health – without investment, the population will suffer. Population health drives economic stability and the health of a nation.'

Professor Neena Modi, Imperial College London and President of the British Medical Association

Around the world, every day, over 800 women and nearly 7,000 newborns die, while around 5,500 babies are stillborn. Almost all of these deaths are preventable. Pregnancy complications such as pre-eclampsia, prematurity, haemorrhage, infection and birth asphyxia account for the majority of these deaths.

While pregnancy in the UK is generally considered safe, women and babies are still dying needlessly as a direct result of preventable pregnancy complications: every year some 5,000 babies in the UK are either stillborn or die shortly after birth, and approximately 70 mothers die due to pregnancy-specific conditions. Others may have pre-existing and potentially life-threatening health conditions such as epilepsy, diabetes or depression, that are made more challenging to manage while pregnant.

Why is health during pregnancy particularly important?

Health during pregnancy has ramifications far beyond the outcomes of the pregnancy. Ill health during this period affects partners, wider family and society both in the short- and long-term. Childhood death and disability as a consequence of pregnancy complications have enormous, reverberating effects on people's lives and society as a whole. A stillbirth is not a 'one-off event', but can affect a family's mental wellbeing for life, with consequent social and economic costs. Preterm birth costs the economy £2.9 billion in a single year, according to a 2009 estimate of pre-term births in England and Wales. This includes the long-term costs of disabilities affecting 28% of the roughly 60,000 premature births in the UK each year.

What is more, pregnancy is a unique window during which the health and wellbeing of future generations is laid down. Our time in the womb and how we grow and develop before birth affects the risks of a range of diseases in adulthood, including diabetes and heart disease, as well as our general quality of health.

Improving population health can only be a gain in terms of individual and societal wellbeing; a healthy workforce underpins national wellbeing and prosperity, but that health begins during fetal life.

Medicines in pregnancy

Three out of four women take some form of medication during pregnancy. As society changes and more women become mothers at older ages, pregnancy may also become more medically complex. Pregnant women may have one or more underlying health conditions that require continuing treatment.

Women who require medication can have difficult choices to make when they become pregnant. Some medications are known to be unsafe to take during pregnancy, but suddenly stopping a medicine may result in even greater harm (see Epilepsy in pregnancy). This 'knowledge gap' as a result of inadequate scientific research and information is a huge problem, pushing the responsibility – and risk – of decision-making, in the absence of information, onto individual clinicians and women. Crucially, the root of medical inequality for pregnant women and their unborn children may lie within the wider context of gender bias in society. Many witnesses stressed that structural sexism may be a leading factor for the dearth of research and medicines in this area.

'We know that every day in the UK, 14 babies are either stillborn or die in the neonatal period… In some cases, medicines would not have saved the baby's life, but in many cases it might have done – and that's why it's such an important issue.'

Clea Harmer, Chair of the Pregnancy and Baby Charities Network

Pregnant women and their babies are denied the benefits of modern medicine enjoyed by the wider population, with potentially devastating results. The neglect of maternal medicines also hits those hardest who are already experiencing inequality in other areas of society. Black women are four times more likely to die from complications during pregnancy than white women; Asian women twice as likely. Older mothers, those from economically deprived groups, and mixed-ethnicity women are also more likely to die during or soon after pregnancy. In response, the Government has established a Maternity Disparities Taskforce to 'level-up' maternity care and tackle poor outcomes for women from ethnic minority communities and those living in deprived areas.

There is a real opportunity to address severe inequality with respect to access to safe and effective medicines in pregnancy, well-aligned with the current UK government focus on addressing health inequalities through the Women's Health Strategy.

The need to address this issue is beginning to be recognised around the world. The Concept Foundation, supported by the Bill & Melinda Gates Foundation have established the 'Accelerating Innovation for Mothers (AIM)' project. Designed to speed up maternal health research & development through global partnerships, the project aims to drive innovation of new medicines and technologies for pregnancy-specific conditions. Removing the stigma surrounding the inclusion of pregnant women in medicines research is central to the project.

Furthermore, the pharmaceutical industry have acknowledged their role in researching and developing new medicines in pregnancy. For example, the EU Innovative Medicines Initiative, ConcePTION, brings together over 60 partner organisations, including 16 pharmaceutical companies, to build a collaborative environment capable of providing evidence-based information on the safety of medications during pregnancy and create the first Europe-wide breast milk biobank for research purposes.

Epilepsy in pregnancy

Sudden unexpected death from epilepsy during pregnancy or in the following year has doubled in recent years in the UK, as shown by a 2020 MBRRACE report, which reviews all deaths of pregnant women and babies.

Women with epilepsy face a 'pregnancy lottery' with an impossible choice: do they take their epilepsy medication, several of which are known to increase the risk of major congenital malformations, and risk severe, long-term physical and neurodevelopmental harm to their babies? Or do they stop taking epilepsy medicines during their pregnancy and risk severe seizures, which also has consequences for their babies?

The use of epilepsy medicine in pregnancy has a difficult history. For decades, doctors prescribed sodium valproate during pregnancy, though since 1974 it has carried a safety warning that tests in animals had shown it could cause birth defects. Thousands of babies were subsequently born with physical and neurodevelopmental disabilities.

Patient-led advocacy, media and political attention eventually led to an almost complete ban of valproate in women of childbearing age, unless a pregnancy prevention plan is in place. However, a 2021 report by the Medicines and Healthcare Products Regulatory Agency (MHRA) Commission on Human Medicines revealed that a number of other anti-seizure medications taken in pregnancy could also cause harm to the unborn child.

'The clinical trials agenda has a major role to play in the Government's 'Levelling Up' programme.'

Rt Hon Sir Iain Duncan Smith MP, Rt Hon Theresa Villiers MP and George Freeman MP in Taskforce on Innovation, Growth and Regulatory Reform independent report, May 2021

The Commission

The 2021 report by the University of Birmingham and Birmingham Health Partners, 'Safe and Effective Medicines for Use in Pregnancy: A Call to Action' highlighted the absence of research and information on the safety of medicines in pregnancy. It also drew attention to the urgent health needs of this neglected group both nationally and internationally, and the potential for saving and improving millions of lives globally. The findings and recommendations presented here are the culmination of evidence gathered by a Policy Commission, set up in direct response to this earlier review.

Scope of the Commission

Convened by the University of Birmingham and Birmingham Health Partners, the Commission focused primarily on the UK, canvassing knowledge and opinions from key parties including patient groups, the pharmaceutical industry, scientists, clinicians, NHS leaders, regulators and insurers. It aimed to explore the scale of the problems that are preventing the evaluation and development of safe medicines for use in pregnancy and collected recommendations for how these could be overcome.

Aim

The Commission's overarching aim was to suggest solutions that, if enacted, could save the lives of women and babies, and improve the health of future generations. The UK is currently well placed to not only tackle critical inequalities at home, but to spearhead a global revolution for mothers and their babies, leveraging its National Health Service and independent regulatory environment.

Specific objectives:

1. To identify why there has been so little investment in evaluating the safety and effectiveness of medicines for pregnant women.
2. To identify specific barriers for patients, practitioners, policymakers, industry, and litigation experts in developing research in this field of medicine.
3. To provide solutions for overcoming the barriers identified, recognising the value all stakeholders can contribute and gain.
4. To drive tangible action positioning the UK as a leader in developing and testing safe, effective and accessible medicines for use in pregnancy.

Process of evidence gathering

Expert witnesses were asked to present evidence on the specific aims and objectives of the commission in relation to three main areas of unmet need:

- How we can improve the safety and effectiveness of existing medicines currently used in pregnancy.
- How new medicines developed for conditions in adults, which could be used in pregnant women, should be evaluated for use in pregnancy.
- How new medicine development for pregnancy-specific conditions for example, pre-term birth or pre-eclampsia could be facilitated.

See Appendices for a full list of Commissioners and Witnesses.

Creating a flourishing UK environment for change: opportunities, challenges and solutions

1. Clear and consistent messaging on medicines in pregnancy

The popular slogan 'Nothing about us without us' sums up one of the major planks of change: engaging with the public and patient voices – in this case, women and their families – in effective advocacy.

Historically, despite making up more than half of the population, women have been left out of key decisions on their health by a traditionally paternalistic system. The exclusion of all women, and then pregnant women, from clinical trials after the thalidomide tragedy stems from the medical maxim 'first do no harm'. Ironically, this move to protect pregnant women may have done the opposite, denying women and babies numerous advances in modern medicines.

Awareness is key, and lack of it may be one of the reasons why vociferous pressure has not come from pregnancy and baby charities on the issue of neglect in medicines for pregnancy.

Those women directly affected in pregnancy may become aware of the paucity of information and research only when they conceive, for example, because they have a condition like epilepsy, or because they develop a complication such as pre-eclampsia.

Women actively seek information on research in pregnancy, and evidence suggests they want to be involved in research, particularly if there is already a risk to their unborn baby's health. Although pregnancy may be a short window of time, its effects are lifelong and generational, as witnesses pointed out.

A number of charities including Action on Pre-Eclampsia, the Epilepsy Society and the National Childbirth Trust handle enquiries from concerned pregnant women and their families via dedicated helplines. But these charities are small compared with patient charities in some other areas, such as Cancer Research UK or the British Heart Foundation, which show vocal and effective advocacy across a single unifying health context.

The evidence heard by the Commission suggests a strong imperative for one unified voice from pregnancy and baby charities on the issue of the evaluation and development of medicines for use in pregnancy. Encouraging smaller parent and baby charities to come together might provide more effective and powerful lobbying. There may also be lessons to learn on unified advocacy from other areas.

It is possible that through increased awareness of the issues with the use of medicines in pregnancy, a woman's assumption that a medicine used in pregnancy has been thoroughly tested may be challenged. This could result in them deciding not to take the medicine at all, resulting in even greater harm to them and their baby. An important part of raising awareness will therefore be to ensure that women know that in order to have a healthy baby, they need to be healthy in pregnancy. This may mean taking medicines which may not have been thoroughly tested but where the likely benefits outweigh the possible harms.

> ***'A healthy baby needs a healthy mother to have a healthy start. It is not fair or right and it is very short sighted to exclude pregnant and breastfeeding women from clinical trials.'***
>
> **Professor Catherine Nelson-Piercy, Consultant Obstetric Physician at Guy's and St Thomas' NHS Foundation Trust**

Risk is a hard concept to convey, but, as one witness explained to the Commission, 'difficult and complex' are not reasons 'to look away'.

In addition to a lack of awareness that there is a problem with our existing knowledge about the effectiveness and safety of many medicines which are widely used in pregnancy, we heard repeatedly that the information we do have is poorly presented to clinicians and women. Currently, there are many different sources of information on medicines in pregnancy – and these may give different messages, may be unverified or be superseded by more recent research evidence. This makes it difficult for women to make an informed decision, and for healthcare professionals to give up-to-date, consistent information. Unified, coherent, and trusted sources of information about medicines currently used in pregnancy for both pregnant women and healthcare professionals are essential, but currently lacking.

Reliance on and influence of social media for medical information, and increasing polarisation of views may need to be taken into account in advocacy and any future communications strategy. A witness from the pregnancy and baby charity sector highlighted personal threats to their junior staff during promotions of their flu vaccine campaign to pregnant women during the Covid pandemic.

The growing reluctance among younger pregnant women to take any kind of medicines was also noted by clinicians. Setting up an overarching body to improve the way women and healthcare professionals receive information would help, as well as better training for midwives, doctors and pharmacists on medicines in pregnancy. The MHRA recently set up the Safer Medicines in Pregnancy and Breastfeeding Consortium to bring stakeholders together to improve the health information that women receive.

Together, evidence heard by the Commission points to fragmented, incoherent advocacy and information on medicines in pregnancy within the UK, causing severe detriment both to individual women and the wider case for change.

'Unexpectedly, pregnant people are remarkably willing to participate in drug trials…the willingness to consume something resulting in a better outcome for babies is something people embrace very, very positively.'

Jane Brewin, Chief Executive of Tommy's Charity

Recommendation 1

Deliver effective advocacy for medicines in pregnancy through a coalition of pregnancy and baby charities, working together with the public, researchers from academia and industry as well as Government to create a shared vision for safe medicines evaluation and development in pregnancy. This will allow for clear and consistent messages to the public and clinicians.

Learning from the End Violence Against Women (EVAW) Coalition

Established in 2005, EVAW brought together a coalition of 124 specialist women's charities (UK based and international), academics, activists and NGOs to deliver a unified voice to demand action from the UK government and international bodies to tackle violence against women and girls (VAWG).

In response to EVAW's effective advocacy and lobbying, the public profile of VAWG grew larger and louder and the government stepped up its response by announcing its Ending Violence Against Women and Girls Strategy (2016-2020) and the commitment of £80 million in funding to support frontline work such as refuges, national helplines and rape crises centres. Cross-society collaboration was integral to this strategy and required a cross-government approach which included the Home Office, the Department for Education, Government Equalities Office and the Foreign, Commonwealth and Development Office. Dedicated teams and resources were set up across government departments to drive the strategy.

In 2021, the government announced its continued commitment to tackling VAWG through a refreshed strategy, passed the Domestic Abuse Act and introduced mandatory training and statutory guidance for frontline professionals. Through EVAW's coherent voice, the "visibility and urgency" of VAWG in the public mind led to policymakers making prevention a key strategy. The UN Women's Prevention Framework, the UK's Violence Against Women and Girls Strategy and London's 'VAWG' strategy show that prevention policy is now a priority at the local, domestic and global level.

Uniting charities, health providers, academics, and policymakers, EVAW's strategy provided a unified approach, resulting in cross-sector collaboration, a clear VAWG strategy, dedicated resources across government, and legislative change. The same commitment must be applied to advocate for women and their unborn babies put at risk of death and disability by the lack of medicines in pregnancy.

2. Inclusion of pregnant women in clinical trials

Developing, testing and bringing to market medicines for pregnancy is seen as inherently risky by regulators, industry, academia and the insurers that underwrite clinical trials, due to the lack of fundamental biology, safety knowledge and advice. This is perpetuated by the legacy of thalidomide, and other medicines in the past that were shown to have adverse effects in unborn children. In the case of the medicine diethylstilbestrol (DES), which was given to women at risk of early miscarriage, the effects were generational. It was linked in the 1960s to vaginal and cervical cancers in daughters exposed to DES while they were in the womb, and subsequently to pubertal, menstrual and pregnancy complications in their children.

Thalidomide was never tested in humans – tests in chickens did not reveal any birth defect problems. Today's environment for testing new medicines is very different from that in the 1950/60s.

Industry and regulators are generally considered to be conservative in their approach. And while caution may be considered a virtue in this area, over-caution has led to unintended and grave consequences as it means that pregnant women are left without safe, effective and accessible medicines.

While lessons learned from thalidomide prompted the birth of modern pharmacovigilance (monitoring for safety) and have undoubtedly prevented further tragedies, there is a concern that by being too precautionary, society may be unburdening its responsibility to assess risk unfairly onto individual women and healthcare professionals. The Commission heard the same message many times from different sectors: that deciding on a medicine's risk in pregnancy is too often left to the individual woman to bear.

Concerns about regulatory and ethical approval may hinder research. However, the idea that clinical trials in pregnancy won't receive approval is a myth, said one witness from the MHRA, who stressed that approvals are made on a case-by-case basis.

The consequences of a lack of clear expectations around inclusion, as well as confused messaging on medicines in pregnancy can be disastrous. The rollout of vaccination against Covid in pregnant women is a case-in-point (see The Calamitous Case of Covid Messaging), where exclusion of pregnant women from clinical trials coupled with a lack of cohesive public messaging has had dire consequences.

> ***'After thalidomide and DES, the approach to risk management wasn't proportionate. A lot of […] that is based on the idea that thalidomide had been tested in pregnancy – but it had not. They were managing the wrong risk. But like a bump in the carpet if you push it [the risk] down somewhere, it comes up elsewhere.'***
>
> **Professor Richard Ashcroft, Deputy Dean and Professor of Bioethics, City Law School**

The Commission heard a strong case for introducing licensing requirements for all new medicines that would make testing for use in pregnancy compulsory in most cases. This type of 'Maternal Investigation Plan' (MIP) would draw on the experiences of the 'Paediatric Investigation Plan' (PIP) brought in by the European Union in 2007.

Under this regulation, companies applying for licences for new medicines must present a plan to study the medicine in children (unless inappropriate for this age group). In return, those with a successful plan receive a six-month patent extension. This scheme greatly improved the product pipeline for children's medicines, creating some 260 new medicines or indications for children since its launch. The proportion of clinical trials in children rose by over 50% with the new PIP regulations.

A similar MIP approach should be seriously considered. The Commission noted, however, that some drawbacks to PIPs were also highlighted. Some experts questioned how beneficial PIPs have been in reality, sometimes making adult drugs 'go through the mill' when they had no appropriate use in children. In other cases, PIPs had had unanticipated consequences leading to medicines being withdrawn. One witness said: 'There's nothing worse than hearing from a paediatrician that a key cancer medicine has gone.' One approach might be to pilot MIPs for a short period to gauge their effectiveness in light of this information.

In addition, a MIP structure should challenge the practice that women are automatically removed from trials if they become pregnant during the trial. A review to assess the safety of ongoing participation should be undertaken rather than automatic removal.

Introducing some licencing requirements for new medicines to be considered for use in pregnancy would require significant cross-sector working between regulators, clinicians, researchers, industry and pregnant women themselves – but such an environment could open up a new market for novel therapies.

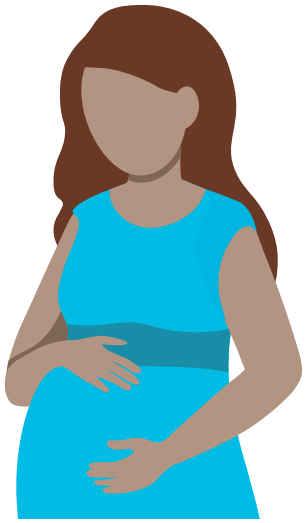
Together, the Commission heard a clear need for regulators, as well as other relevant health research bodies, to make explicit the need for pregnant women to be included in trials. In this context, regulators should be viewed very much as 'enablers' rather than 'barriers', and as proactive partners in the innovation process.

'Excluding pregnant women from the Covid vaccine trials has resulted in pregnant women dying needlessly.'

Professor Peter Brocklehurst, University of Birmingham, on behalf of the Commission

'You cannot justify developing a treatment in a way that excludes 50% of the people who might benefit from it. That is unethical. It is unjust.'

Professor Richard Ashcroft, Deputy Dean and Professor of Bioethics, City Law School



Recommendation 2

Pregnant women should be offered the opportunity to take part in all clinical trials of medicines that could be used in pregnancy, unless there are specific safety concerns.

The Calamitous Case of Covid Messaging

While the incredibly rapid development and rollout of vaccines for the Covid pandemic has demonstrated just what can be achieved when governments, funders, regulators, industry and universities pull together in a crisis, one group of the public has been hugely underserved. Changing and confused communications on vaccination in pregnant women has had tragic and fatal consequences.

Pregnant women were excluded from all of the early Covid vaccine trials, so that when vaccination was initially rolled out, pregnant women were not called forward because there was uncertainty about whether the vaccines were effective in pregnancy and whether they were safe.

The public messaging changed once real-world data became available, and pregnant women were advised to get vaccinated (from December 2020). Unfortunately, by then, the message had become confused, with many pregnant women and health professionals believing the vaccine was unsafe in pregnancy.

As a result, Covid wards and intensive care units filled up with unvaccinated pregnant women. A Health England report in October 2021 showed that one in five of the most critically ill Covid patients in hospital were unvaccinated pregnant women.

The RECOVERY trial was set up to identify treatments for all ill patients with Covid but did not initially consider including pregnant women until a month after it was set up in 2020, after strong lobbying efforts. Nevertheless, many health professionals remained reluctant to give the treatments that this trial has shown to be effective to pregnant women, due to a fear of treatment in pregnancy among practitioners.

1 in 5

of the most critically ill Covid patients in hospital were unvaccinated pregnant women.

3. Up-to-date pregnancy information for existing medicines

The commission heard that existing medicines information – the known, current evidence about individual medicines in relation to pregnancy – may in some instances not be fully up to date with the latest evidence and is usually extremely cautious. By updating information available for identified, appropriate medicines, at least more accurate safety information would be available to patients and healthcare practitioners. Significant progress on this front has been made recently in the US, which the MHRA has been closely monitoring.

We can also make better use of the data we already have – or could potentially have. For example, pre-licensing data on medicines could be sought from drug developers. We often have decades of post-marketing data on many medicines that are used by pregnant women or given "off-label" by doctors – however the medicine's Summary of Product Characteristics (the reference information for health care professionals on how to use the medicines safely and effectively) may not reflect all currently available evidence, particularly for older "off-patent" medicines. Healthcare professionals and pharmacists in the UK commonly rely on the British National Formulary (BNF) as a reference guide to prescribing. But their information may be outdated because it is based on the Summary of Product Characteristics – and this, the Commission was told is 'very cautionary'.

Work between global regulators, together with The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), could provide a significant and timely step-change in available information, enabling more effective decision-making by both clinical professionals and the public.

> ***'We need one body - the BNF [the British National Formulary], the MHRA, the ABPI [Association of the British Pharmaceutical Industry] are all pulling in different directions.'***
>
> **Professor Catherine Nelson-Piercy, Consultant Obstetric Physician at Guy's and St Thomas' NHS Foundation Trust**

Recommendation 3

Prioritise updates for existing medicines with the potential to be used in pregnancy, with regulators and industry working towards pregnancy-specific information on safety, dosing and effectiveness. Resources should be put in place to maintain this activity, particularly for generic medicines.

4. Reducing R&D risks in pregnancy

The fear of litigation is a major concern for those developing medicines. In the UK, the compensation settlement for a baby damaged while in utero has been as high as £37 million. This could rise to a staggering US$110 in the US, where juries are involved in awarding compensation.

A hugely important element in de-risking clinical research, especially given the concerns over litigation, is the area of insurance. Industry and academic researchers currently struggle to find insurance for clinical trials involving pregnant participants, and likewise insurers grapple to assess the risks of these studies given so few are conducted and so few have resulted in any litigation (see Overcoming the insurance 'chicken-and-egg' situation).

Insurers rely heavily on the existing experience of clinical trials in making their assessments of risk, and with so few trials conducted in pregnancy, this is lacking. A combination of these factors means their premiums may be disproportionate to the compensation limits they can offer.

However, with more data and a better assessment of risks, premium costs may be reduced and insuring trials in pregnancy could be seen as less of a gamble. There is precedence in this scenario. Clinical trials of children's medicines were once seen as 'incredibly risky', but since the advent of Paediatric Investigation Plans (PIPs) and other initiatives such as the Medicines for Children Research Network, the number of clinical trials of medicines in children has increased substantially, meaning that insurers no longer view them with such concern.

While there is willingness from insurers to address these issues, they cannot do so without input from government and possibly regulators and the research community. Co-insurance with government, and collaboration between insurers, was suggested as a solution. There is an example for this working effectively as in the case of insurance against terrorism in the UK. Here, the UK government agrees to pick up the excess on a claim by the commercial sector if it is too large to be covered by the insurer under a scheme called 'Pool Re'.

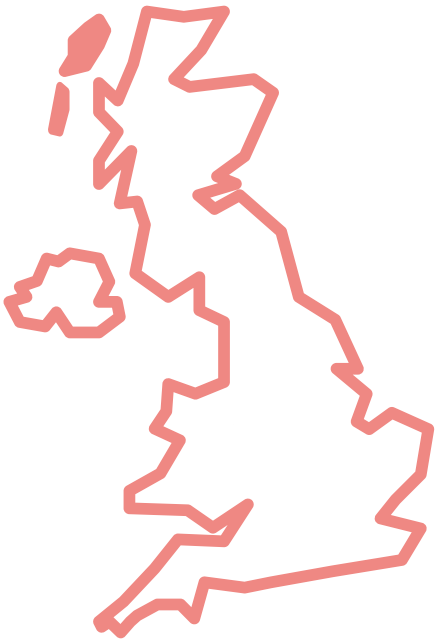
A similar agreement was made by the government and Lloyds of London regarding business interruption insurance during the Covid pandemic. A system akin to Pool Re would be a workable solution for insuring clinical trials of medicines which include pregnant women.

Insurers noted that this would probably only be needed for the short-term as an increase in clinical trials activity would provide more data to be able to confidently assess risk. Short-term investment by the government might also lead to high returns, enabling the UK to become a global hub for pregnancy research, backed by the insurance industry. The UK is already well placed to tackle this, as Lloyds has a global network with licences already in place across many territories. The human and real financial cost, through litigation and long-term costs associated with issues such as pre-term birth, should also factor into decisions on investment.

Together, the Commission was convinced of the significant opportunities to mitigate perceived risk and accelerate innovation through effective collaboration between government, insurers and researchers. And the good news is that with an initial boost, this area could grow becoming self-sustaining within a few years. The Commission recognises that initial investment will be costly but strongly urges the Government to factor in the cost of doing nothing.

'Far more people die from failure in this area than from terrorism. If we can arrange insurance for terrorism we should be able to produce a similar scheme for pregnant women.'

Baroness Manningham-Buller, House of Lords, Co-President of Chatham House, Co-Chair of the Commission



In the UK

the compensation settlement for a baby damaged while in utero has been as high as

£37 million

Overcoming the insurance 'chicken-and-egg' situation
Insurance is vital in order for clinical trials to be run. To underwrite or insure clinical trials – or indeed anything – insurers and their actuaries need real-world data to calculate risk, particularly how many claims are made by clinical trial participants, and what is the value of the settlements. But how do you accurately calculate risk if there is no data, or very little?

There are extremely few pregnancy intervention studies. Even at the University of Oxford – where 3,311 clinical studies are currently being led – only 2% of those were able to involve pregnancy (mainly surveys or observational in nature).

The few studies also means that pregnancy is not seen as a profitable area for insurers. Rather, the potential costs of claims are enormous because the standard form of clinical trials insurance in the UK is on a 'no-fault basis'. In other words, the burden of proof is not on the trial participant.

According to insurers, it is difficult to assign responsibility for potential birth defect effects, given the relatively high frequency of birth defects in the general population, which is approximately 1 in every 47 births in the UK.

'Pregnancy forms that potential perfect storm where you have high claim severity, and you have this latency between the intervention and the potential congenital abnormality arising, which means that you may have large numbers of participants exposed before you see the side effects.'

Ben Ward, Insurance Underwriter, Newline group

Recommendation 4

De-risk insurance processes for early and late phase clinical trials of new and existing medicines for use in pregnancy, using lessons and successes from other challenges.

5. Stimulating the market

Bringing any new medicine to market is a long process requiring significant investment, with only around one in ten medicines entering clinical trials ever making it to market. Under the classic pharmaceutical industry business model, areas such as medicines for use in pregnancy are often unattractive because of high perceived risks and excessive costs, complex studies and onerous regulatory hurdles. Perceived risks and low financial rewards for treatments during a relatively short-term physiological change – i.e. nine months – can make investment in pregnancy unattractive. However, some 210 million women become pregnant each year, which is a significant population with unmet need.

For established medicines used for non-pregnancy conditions, there are no incentives for testing in, or repurposing for pregnancy, with concerns about new risks arising from their use in pregnancy acting as a deterrent. Additionally, concerns about stigma and reputational risk are high in case complications in a clinical trial in pregnancy arise.

Alongside interventions which mitigate risk, there is a need to explore and implement economic incentives, such as the extension of a medicine's licensing patent. We could encourage approaches such as 'parallel trials', whereby clinical trials are run at the same time including both the general population and pregnant women, avoiding delay to a medicine's availability to the general population without depriving women of potential benefits in specific studies related to pregnancy. Many lessons can be learned from children's medicines and development of therapeutics for rare, or 'orphan', diseases.

Together, the Commission heard compelling evidence that mitigation of risk also required effective tools and approaches to stimulate innovation in this field, leveraging good practice whilst ensuring effectiveness in this specific context.

The Commission heard evidence of the difficulties in designing and conducting trials of medicines for pregnancy specific conditions due to the existence of different medical definitions of conditions, diverse standards of care for control groups, and different outcomes for studies. As medicines trials are often international, this is true across countries and as well as within countries such as the UK.

The lack of uniformity presents many practical difficulties for industry and academic researchers conducting trials in pregnancy. Where study participants may need to be recruited in the labour ward, obtaining fully informed consent in stressful situations may be challenging. The need for long-term follow-up of mothers and infants can also present difficulties.

Better collaboration between international regulators is also needed for the harmonisation of guidelines and to align the regulatory requirements, especially as trials in pregnancy may involve multiple sites across many countries to recruit a sufficiently large patient cohort to make trials results meaningful.

The Commission was convinced of the urgent need for work to standardise practice, processes and pathways for clinical trials and regulatory approvals in pregnancy at both a national and global level, and that setting standards for pregnancy medicine evaluation represented a real opportunity for UK leadership.

There does seem to be a growing desire and movement to tackle some of these issues among regulators including the UK's MHRA, EMA and the US Food and Drugs Administration.

Newfound regulatory independence promises the possibility of streamlined medicines development. In particular, the MHRA has developed a new fast-track process called the Innovative Licensing and Access Pathway (ILAP), and it believes that medicines for pregnancy, for example for pre-eclampsia, would be a good fit for this.

Industry could be further incentivised by early and efficient access to study participants; through the creation of new market opportunities which are "de-risked" through shared approaches to affordability; and working with the Commercial Medicines Unit within the NHS to agree joint-working with regulators, the NHS and NICE to incentivise the development of medicines and therapies in this area. The UK has the potential to collaborate with regulators and health bodies across the world on appropriate incentives, opening up new markets and opportunities for industry.

Recommendation 5

Incentivise industry to develop pregnancy-specific medicines, utilising cross-stakeholder working to ensure that the UK is in a globally-competitive – and globally collaborative – position to drive drug development for pregnancy-specific conditions.

6. Increasing investment in pregnancy research

Reproduction and childbirth is a 'Cinderella' area of research. It receives neither the funding, attention, nor status that other areas of science and health research garner. Though this area directly affects up to 51% of the population – in truth the entire population, since we are all a product of reproduction – only 2.1% of health research funding in the UK is spent on reproductive health and childbirth.

The UK spends about £51 million a year on pregnancy research, a small fraction of which is relevant to medicines use in pregnancy. For every £1 spent on pregnancy care in the NHS, only 1p is spent on research. For comparison, pregnancy-related litigation costs to the NHS in 2018-19 were £2.5 billion, making up approximately 49% of the total cost of clinical negligence claims.

Pregnancy-related litigation costs to the NHS in 2018-19 were

£2.5 billion

making up approximately 49% of the total cost of clinical negligence claims.

This paucity of investment – and subsequent paucity of pregnancy R&D – has serious knock-on effects. One witness noted that the UK remains 'at a 1990s level for progress in this field', where other areas of health science have flourished. This deficit runs through every stage from basic biology to pre-clinical medicines screening, and translation into novel therapies and other interventions which could save lives and relieve suffering for many mothers and babies.

Despite remarkable scientific advances in our understanding of human health and disease in other areas, we know little in comparison about basic human reproductive biology – the early embryo; how medicines affect the workings of the placenta; how medicines cross the placenta from mother to child; the handling of medicines by the fetus; and much of the basic physiology of pregnancy is still poorly understood. Improved understanding of discovery science in reproductive health and embryology is vital. Many of the issues in pregnancy are laid down at the earliest stages – in the first 12 weeks of gestation - so knowing the science of this early stage may be particularly crucial.

Understanding these basics better would help at an earlier stage in the process of designing and developing medicines for use in pregnancy. For example, if researchers could show that a new medicine does not cross the placenta at all, this would provide some reassurance for testing that specific drug in clinical trials with pregnant women.

Better pre-clinical tests would lead to a more secure and safe knowledge base before medicines go into clinical trials with pregnant women. This would mean potentially, that medicines likely to be harmful in pregnancy, would be screened out early. Good *in vitro, in vivo* and *in silico* models are needed to screen drug candidates and test the potential effects of medicines given in pregnancy, before the human clinical trial stage.

However, our lack of basic research knowledge and the unique nature of human pregnancy have been barriers.

There are no good animal models to test medicine candidates in pregnancy. Those commonly used have very different placental systems from humans, and do not naturally develop the pregnancy complication pre-eclampsia, for example.

Recent advances bring some hope to the field. A human placental stem cell line was successfully developed by Japanese researchers in 2018. And technological improvements in areas such as 'virtual' clinical studies, better computer modelling, microfluidics and organoids (bioengineered mini organs in the lab) means that we may see effective 'placenta-on-a-chip' models in the next three to five years. The UK could pioneer these technologies, and in turn accelerate pregnancy medicines research faster - provided research investment was prioritised.

The Commission also heard from different sectors that the low status and funding of reproductive science creates difficulties in attracting and retaining researchers. Too often, young scientists are lost to higher-profile and better-resourced areas such as cancer. This is also a challenge on the clinical side of research and care – there are fewer than 10 obstetric physicians in the entire UK, mostly based in London and Oxford.

Together, the Commission was convinced of the need for a clear national strategy related to pregnancy research, to address funding issues across the field: from discovery and translational science to clinical trials and evaluations; and to make the sector more attractive to recruit and retain talented researchers. There was also a compelling rationale to develop better and more efficient pre-clinical screening tools and reproductive toxicology models. Providing clear focal points of public and private investment as 'hubs' for a coherent UK community, well-linked with wider global funders and innovators, will be crucial to accelerating progress.

'We basically do not understand enough about the physiology of normal pregnancy and certainly about pregnancy complications, in order to know what we should be targeting.'

Professor Graham Burton, University of Cambridge

Recommendation 6

Establish a UK-wide national network of research centres encouraging major public and private investment and collaboration in pregnancy research expertise and infrastructure. This will ensure sustainable drug development from discovery science through to pre-clinical screening tools and clinical evaluation.

7. Joining up maternity care records

Health research in the UK benefits from the NHS' longitudinal health records. However, many health registries do not link up medical data, so information on the effects of medicines cannot be analysed easily. If health records were made accessible through one system, the UK could offer huge potential for following-up the long-term health effects of medicines post-marketing. Better data capture generally would also be helpful, including data on miscarriages, maternal and baby outcomes and electronic prescribing during pregnancy.

A joined-up health data network could build on existing infrastructure across the country. The independent, non-profit organisation Health Data Research UK (HDR UK) already joins up health data science, working with public and private partners, across 31 locations nationwide.

A number of 'Health Data Research Hubs', funded by the Government under the Industrial Strategy Challenge Fund are designated centres of excellence with the expertise to maximise innovations developed from health data across a number of specific contexts, such as eye health, acute care, cancer and respiratory disease. The HDR UK model presents an opportunity to establish a new research hub with a specific focus on using routine clinical maternity data to assess existing and new medicines in pregnancy.

The Commission was convinced of the need to ensure that this aspect of the UK's health sector is supported through appropriate coordination and investment to become truly 'innovation-ready' for pregnancy medicines research.

Recommendation 7

Improve use of routine clinical care maternity data to help assess the safety and effectiveness of new and existing medicines used in pregnancy. Establish a designated maternity 'Health Data Research Hub' through Health Data Research UK with a focus on medicines evaluation in pregnancy.

8. Oversight and delivery

The Commission heard compelling evidence why each of the recommendations highlighted here was vital, both individually but also as part of a mutually-reinforcing approach to creating a position for the UK to drive this vital area forward. However, the individual delivery mechanisms, timescales, necessary stakeholders and markers of success for each of these differs drastically.

A long-term implementation plan is therefore needed to drive forward and oversee developments in this area. Ideally, a Government-appointed group (along the lines of a 'National Steering Committee') representing stakeholders from the public, industry, clinical, academic and regulatory spheres would have the resources and executive power to effect meaningful change.

Implementation needs to align with the Government's recently published Women's Health priorities to ensure a holistic UK approach to women's health across the life course.

The Commission was convinced that women with experience of pregnancy complications should be central to the establishment and delivery of this group.

This group should be formally tasked with driving forward the implementation of the recommendations of this report; monitoring progress against agreed targets; and also developing links internationally to ensure that the UK's leadership delivers true global benefits.

Recommendation 8

Appoint a UK Steering Committee aligned to the Government's Women's Health Strategy to deliver the above recommendations, with oversight of implementation, ensuring milestones are set and monitored.

Conclusions

There is an urgent need for action to address the underserved area of medicines use in pregnancy. Without it, women and babies will continue to die when they could be saved. They will continue to experience long-term health effects, disability and distress, which might be avoided. It is no longer ethical to deny pregnant women and their unborn babies access to safe, modern medicines that the rest of the population enjoys.

We strongly urge that the wide array of stakeholders identified here across the public, scientific, clinical, industry, regulatory and governmental sectors, come together to address the recommendations of this Commission. That together they advocate for change, respond to research and funding issues, and, where necessary, work to change official guidance or law to enable progress in this much neglected area.

As well as the individual costs, investment into safe and effective medicines in pregnancy could save tremendous societal and economic costs: not least because the health of a mother affects the health of her baby, and the health of her baby's babies. Health in pregnancy reverberates down the generations. By boosting generational health, we can boost population health, and thereby the country's overall health, wellbeing and prosperity.

The UK is well placed to become a global pioneer of maternal health research innovation. We have the health infrastructure of our NHS, with its birth-to-death records. Our medicines regulator is able to fast-track drug development and make changes to streamline the process, as well as working globally with Europe, the US and other regions. We are already a global hub for insurance – and we can support and build on this to add to our potential in becoming a leader in clinical studies for medicines in pregnancy.

Now is the time to act – but we will need leadership and investment. With a long-term, cross sector implementation plan we can bring the area of safe, effective and accessible medicines for use in pregnancy into the 21st century. We can save lives, save money, and boost the wellbeing of mothers and babies in the UK and across the world.

‘My risk of having heart disease depends partly on my lifestyle now but also on the quality of the egg from which I grew. And the quality of that egg was determined when my mother was in utero herself. And she was born in 1922 - so that’s 100 years ago.’

Professor Graham Burton, University of Cambridge

Appendices

Appendix 1: Commission Work Programme

Scoping Phase Activities

- Developing the idea for the Policy Commission with University of Birmingham and Birmingham Health Partners.
- Literature review of research and data in the public domain.
- Production and dissemination of 'Safe and Effective Medicines for Use in Pregnancy: A Call to Action' report.
- Appointing the commissioners.
- Commissioners' initial roundtable to agree the terms of reference and decide which expert witnesses to approach for evidence.

Evidence Sessions

Six evidence stakeholder focused sessions were held, followed by a commission summary meeting to agree recommendations.

- Session 1 – Patient Groups, 21st September 2021, Royal College of Physicians, London
- Session 2 – Industry, 22nd September 2021, Royal College of Physicians, London
- Session 3 – Researchers, 19th October 2021, Royal College of Physicians, London
- Session 4 – Practitioners, 20th October 2021, Royal College of Physicians, London
- Session 5 – Litigation and Regulatory Experts, 16th November, The Academy of Medical Sciences, London
- Session 6 – MHRA & Insurance, 17th November, The Academy of Medical Sciences, London

Review and Writing Phase

Activities included:

- Reviewing oral and written evidence submitted to the commission.
- Commissioners' meeting to finalise the content and format of the report.
- Finalising the findings and recommendations of the commission.

2. Commissioners' biographies

Baroness Manningham-Buller, LG, DCB, FMedSci
House of Lords
Co-President, Chatham House

Eliza Manningham-Buller was Chair of Wellcome Trust from 2015 to April 2021, having served as a Governor since 2008. In 2015, Eliza became the Co-President of Chatham House, Royal Institute of International Affairs. She served on the Council of Imperial College from 2009 and was Chair of Council from 2011 to 2015.

She was appointed an independent, crossbench peer in the House of Lords in 2008, has been a member of the Privileges and Conduct Committee and the Joint Committee on the National Security Strategy, and is currently a member of the Science and Technology Committee.

Previously, Eliza had a career with MI5 for more than 30 years, including a posting to the British Embassy in Washington. She served as Director General from 2002 to 2007 and before that was Deputy Director General, with responsibility for operations.

Eliza was educated at Benenden School and Lady Margaret Hall, Oxford. She taught English for three years before joining MI5 in 1974.

Professor Peter Brocklehurst MBChB, MSc, FRCOG, FFPH, FMedSci, Professor of Women's Health, Director of Research and Development, Birmingham Clinical Trials Unit

Peter Brocklehurst is Professor of Women's Health, and Director of Research and Development at the Birmingham Clinical Trials Unit, at the University of Birmingham. Peter trained as an Obstetrician and Gynaecologist and is honorary consultant in Public Health. His expertise is in randomised controlled trials and observational epidemiology.

Previously Peter was Director of the Institute for Women's Health at UCL (2011-2016) where he was Professor of Women's Health, and before that Director of the National Perinatal Epidemiology Unit at the University of Oxford (2002-2011) where he was Professor of Perinatal Epidemiology. He has Chaired or been a member of several funding panels (including the DH Policy Research Programme Commissioning Board; NIHR HTA Commissioning Board; Wellbeing of Women Research Advisory Group; MRC Methodology Research Programme panel). He currently Chairs the UKCRC Pregnancy Research Review Group. He is a Fellow of the Academy of Medical Sciences, and emeritus NIHR Senior Investigator.

Dr Allyah Abbas-Hanif, Chair of the Policy and Communications Group, Faculty of Pharmaceutical Medicine, Royal College of Physicians

Dr Allyah Abbas-Hanif is a consultant in pharmaceutical medicine and a specialist doctor in cardiology. She is Head of Clinical Development at MirZyme Therapeutics, a pregnancy specific biotech. Her academic role of Honorary Senior Clinical Lecturer at Imperial College London allows her to expand policy and research to improve drug development processes for underserved groups. She trained at the University of Birmingham and Yale University.

Allyah is the Chair of the Policy and Communications Group at the Faculty of Pharmaceutical Medicine, Royal College of Physicians. She co-chairs the Paediatric and Women's Health Group at the Faculty of Pharmaceutical Medicine and also co-chairs the Maternal Health Project Group at the Association of the British Pharmaceutical Industry. She sits on Expert Groups focusing on Covid drug development and clinical trial innovation.

Allyah supports several philanthropic projects and is a trustee of the Better Community Business Network. She has led cardiology and emergency medical relief projects for displaced people for international NGOs including the Syrian American Medical Society.

Professor Anna David, Director of the Institute for Women's Health, University College London, Honorary Consultant, Obstetrics and Maternal Fetal Medicine, UCL Hospital, National Institute for Health and Care Research, University College London Hospitals Biomedical Research Centre

Anna is Director of the Elizabeth Garrett Anderson Institute for Women's Health at University College London in London and an Honorary Consultant in Obstetrics and Maternal Fetal Medicine at UCL Hospital. Clinically, she specializes in fetal medicine, severe congenital disease, fetal growth restriction and prevention of preterm birth. Her research team is developing novel prenatal therapies using stem cells and gene therapy. She coordinated the introduction of fetal surgery for spina bifida to the UK in 2018 and co-leads the UCL Centre for Prenatal Therapy.

Anna leads a European Commission FP7 funded consortium 'EVERREST' translating an adenovirus vector maternal growth factor gene therapy for severe fetal growth restriction into the clinic. This 6-year program explored the bioethics of gene therapy in pregnancy, conducted preclinical efficacy and reproductive toxicology studies and developed a first-in-woman clinical trial protocol. Anna also leads UCL as a partner in a European Commission Horizon 2020 funded consortium 'BOOSTB4', that has regulatory and ethical approval to perform the first clinical trial of in utero stem cell transplantation for osteogenesis imperfecta, a severe congenital skeletal dysplasia. She led a Delphi consensus process that generated MFAET, the first system to define and grade maternal and fetal adverse events for clinical trials in pregnancy.

Dr Christine Ekechi, Consultant Obstetrician & Gynaecologist, Queen Charlotte's & Chelsea Hospital, Imperial College Healthcare NHS Trust, Women's Health Educator and Advocate

Dr Ekechi is the Co-Chair of the Race Equality Taskforce at the Royal College of Obstetricians & Gynaecologists and also their spokesperson for racial equality. Her interest is in the gender and racial disparities continually present within the health system today. In addition, Dr Ekechi is the RCOG Clinical Champion for The Women's Network. Dr Ekechi sits as a Member on the Maternity Working Group for the NHS Race and Health Observatory. She also sits on the board as a Trustee for gynaecology cancer charity, The Eve Appeal, and is their Medical Ambassador.

Dr Ekechi is equally focussed on maternity safety and serves as a member of the Multi-Professional Advisory Panel for Baby Lifeline – a UK charity focused on the supportive care of pregnant women and newborn babies. She holds a Masters in Reproductive Health Research from the London School of Hygiene and Tropical Medicine and her previous public health experience includes working with the UN, UNICEF, and national governments in the UK, Nigeria, Senegal, Malawi and Kenya. Using this extensive experience, Dr Ekechi is particularly interested in the social drivers that underpin inequity in individual health outcomes, health knowledge and education, and healthcare delivery.

Dr Ekechi curates and delivers women's health education seminars for corporate companies, charities and interested groups, empowering all women to better manage their health. Dr Ekechi uses her various platforms to discuss all subjects in women's health whilst also calling for greater awareness from women, clinicians and other agencies in improving women's health outcomes.

Dr Ekechi is the lead for early pregnancy ultrasound training at the renowned early pregnancy unit at Queen Charlotte's Hospital and regularly teaches and writes in this field. She also practices at The Portland Hospital, the largest private women's and children's hospital in the UK. Dr Christine Ekechi is the Founder and Director of Early Pregnancy Plus, an innovative holistic early pregnancy care service in central London.

Marcus Green, Chief Executive, Action on Pre-Eclampsia (UK)

Marcus is the part time CEO of APEC, a role he's held since June 2016. He's led the development of the research programme where he's placed a strong emphasis on patient voices. He has also been involved in international developments with the charity including APEC International and APEC Ghana.

Marcus's career started in working for a political party where he worked on local, national and European polls as well as election observing in Albania, campaigning in Malawi and lecturing in Eastern Europe as part of the Westminster Foundation for Democracy.

After this Marcus started his career in charities where his first director role was with a charity for the visually impaired before becoming CEO of a hospice. In the 4.5 years he was there, he oversaw the building of a new hospice, a doubling of turnover, and a tripling of patients.

Marcus then set up his own Management Consultancy specialising in supporting leadership teams, boards and CEOs. Marcus's interest in pre-eclampsia came after his wife suffered with it, 13 years ago. Outside of work, Marcus was the Cathedral Photographer for the best-selling *Britain's Pilgrim Places* is on the Council of The Friends of Gloucester Cathedral, is studying for an MBA, writing another book, and chairs a computer software development company.

Dr A. Metin Gülmezoglu, Executive Director, Concept Foundation

Dr A. Metin Gülmezoglu is an Obstetrician Gynaecologist who has worked in Turkey, South Africa, and the United Kingdom and is currently working in Geneva, Switzerland. Metin is the Executive Director of Concept Foundation, a nonprofit non-governmental organisation working on improving access to sexual and reproductive health medicines and technologies in low- and middle-income countries worldwide.

Prior to joining Concept Foundation, Metin worked at the World Health Organization, as the Coordinator for Maternal and Perinatal Health and Abortion from 2013 until mid-2019. Since the mid-1990s, Metin has worked as a sexual and reproductive health researcher within the global health environment. Metin's own research focuses on major causes of maternal death.

He has coordinated large, multicenter, multicountry randomised controlled trials during his time at the WHO and led a highly successful public private partnership between the WHO, Merck for Mothers, and Ferring Pharmaceuticals, evaluating the effectiveness of heat stable carbetocin. In addition to his thematic research interests, Metin has always had an interest in research methodology, good research practice and mentoring young researchers, especially those from low- and middle-income countries.

Metin has published more than 300 articles and book chapters and given numerous presentations in global, regional and national conferences and meetings. Metin is an honorary fellow of the Royal College of Obstetricians and Gynaecologists in the UK and honorary member of The Society for Maternal Fetal Medicine in the USA.

Mark Hilton, Intellectual Property Group Partner, Bird & Bird Co-head of International Life Sciences and Healthcare Group

Mark is a partner in Bird & Bird's leading international intellectual property group, based in London. As one of the team's pre-eminent litigators, he has particular experience advising on complex multi-jurisdictional IP disputes. Mark is also co-head of the international Life Sciences and Healthcare group and specialises in patent litigation and Life Sciences regulatory advice in the area of pharmaceuticals, biosimilars, biotechnology and medical devices.

In the course of over 20 years of experience of patent litigation, Mark has been involved in devising successful litigation strategies and co-ordinating complex multi-jurisdictional disputes for clients, which often include the interplay of patent and regulatory protections. He is keen to advance the use of technology to improve the delivery of these services to clients and has developed various IT solutions to improve information exchange and make significant improvements to productivity. In particular, Mark has led a project to develop an online patent litigation management tool that allows clients immediate access to the status of all of their litigation, efficient communication of instructions and budget control, while at the same time reducing the overall cost of the litigation.

Mark has a BSc in Chemistry and a PhD in Organic Chemistry, which he obtained while working in the industry before undertaking training with Bird & Bird. He has written and spoken on a range of IP topics, is an associate of the Chartered Institute of Patent Attorneys (CIPA) and a member of the Law Society of Ireland.

Steve Hoare, Quality, Regulatory Science & Safety Policy Director, The Association of the British Pharmaceutical Industry (ABPI)

An analytical chemist by training, Steve Hoare had a career leading quality functions within the pharmaceutical industry. His experience covers the full lifecycle of medicines from early drug discovery through to manufacture and supply.

In his current role, Steve leads policy development in Regulatory Science for the Association of the British Pharmaceutical Industry and is the ABPI regulatory lead for their Maternal Health Project Group, which comprises industry, academia, clinicians, regulators, and patients. The remit for this Project Group is to improve the number of medicines/therapies available to prescribe during pregnancy, through reducing barriers to inclusion of pregnant women in clinical trials, and to address data gaps in both research and post-marketing of medicines.

Appendix 3: The Witnesses

Jane Brewin
CEO, Tommy's

Eleni Tsigas
CEO, Preeclampsia Foundation

Clea Harmer
Chair, Pregnancy and Baby Charities Network

Sarah McMullen
Director of Impact and Engagement, NCT

Dr Pauline Williams
Senior Vice President, Head of Global Health R&D, GlaxoSmithKline Medicines Research Centre

Dr Mirjam Mol-Arts
Executive Vice-President, Chief Medical and Science Officer, Ferring Pharmaceuticals

Gisela Abbam
Senior Director, Government Affairs, PerkinElmer Inc, Chair of British Science Association and Member of the Advisory Board, Everywoman Ltd.

Dr Flic Gabbay
President, Faculty of Pharmaceutical Medicine and CEO Transcript

Prof Amin Rostami-Hodjegan
Director of the Centre for Applied Pharmacokinetic Research (CAPKR). Senior Vice President of R&D and Chief Scientific Officer, Certara

Professor Mark Turner
Professor of Neonatology and Research Delivery, University of Liverpool

Professor Jane Norman
Dean, Faculty of Health Sciences, University of Bristol

Professor Graham J Burton
Mary Marshall and Arthur Walton Professor Emeritus of the Physiology of Reproduction, University of Cambridge

Professor Steve Cunningham
Professor of Paediatric Respiratory Medicine, University of Edinburgh and Chair of the MHRA Paediatric Medicines Expert Advisory Group

Professor Neena Modi
President of the British Medical Association, Professor of Neonatal Medicine, Imperial College London, and Trustee of Their World

Dr Matthew Jolly
National Clinical Director for the Maternity Review and Women's Health, NHS England

Professor Catherine Nelson-Piercy
Professor of Obstetric Medicine and Consultant Obstetric Physician, Guy's and St Thomas' NHS Foundation Trust

Gill Walton
Chief Executive, Royal College of Midwives

Professor Richard Ashcroft
Deputy Dean and Professor of Bioethics, City Law School

Professor Corinne de Vries
Head of Science and Innovation Support, Human Medicines Research & Development Support Division, European Medicines Agency

Dr Sabine Straus
Chair, Pharmacovigilance Risk Assessment Committee (PRAC), European Medicines Agency

Professor Dame Lesley Regan DBE MD DSc FRCOG
Head, Department of Obstetrics & Gynaecology and Chair of Wellbeing of Women

Dame June Raine DBE
Chief Executive, MHRA

Dr Janet Nooney
Expert Scientific Assessor, MHRA

Rob Hannaford
Insurance Underwriter, Newline Group

Ben Ward
Insurance Underwriter, Newline Group

Gary Priest
Risk and Insurance (Research) Lead, University of Oxford

Nathan Draper
Policy and Public Affairs Manager, the Epilepsy Society

Appendix 4: References

Berezow A. Clinical Trial Success Rates By Phase And Therapeutic Area. American Council on Science and Health. June 2020 **https://www.acsh.org/news/2020/06/11/clinical-trial-success-rates-phase-and-therapeutic-area-14845**

Bhattacharya S. on behalf of Birmingham Health Partners Centre for Regulatory Science and Innovation, Safe and Effective Medicines for Use in Pregnancy: A Call to Action, January 2021

Chappell LC, David AL. 2016. 'Improving the Pipeline for Developing and Testing Pharmacological Treatments in Pregnancy.' *PLOS Medicine 13 (11): e1002161* **https://doi.org/10.1371/journal.pmed.1002161**

Cooksey, D. A review of UK health research funding. December 2006 **https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/228984/0118404881.pdf**

Eichler HG, Abadie E, Baker M, Rasi G. Fifty years after thalidomide; what role for drug regulators? Br J Clin Pharmacol 2012; 74: 731–3.

End Violence Against Women. Our members. [Accessed 30/3/22] **https://www.endviolenceagainstwomen.org.uk/about/our-members/**

Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. Contemp Clin Trials Commun. 2018 Sep; 11: 156–164. Published online 2018 Aug 7. doi: 10.1016/j.conctc.2018.08.001

Gov.UK. 'Call to end violence against women and girls'. 25 November 2010. **https://www.gov.uk/government/publications/call-to-end-violence-against-women-and-girls [Accessed 30/3/22]**

Gov.UK. 'Covid-19 vaccination: a guide on pregnancy and breastfeeding'. **https://www.gov.uk/government/publications/Covid-19-vaccination-women-of-childbearing-age-currently-pregnant-planning-a-pregnancy-or-breastfeeding/covid-19-vaccination-a-guide-for-women-of-childbearing-age-pregnant-planning-a-pregnancy-or-breastfeeding [Accessed 20/1/22]**

Gov.UK. 'Innovative Licensing and Access Pathway'. **https://www.gov.uk/guidance/innovative-licensing-and-access-pathway [Accessed 25/1/22]**

Gov.UK. 'Safer Medicines in Pregnancy and Breastfeeding Consortium'. **https://www.gov.uk/government/publications/safer-medicines-in-pregnancy-and-breastfeeding-consortium [Accessed 28/1/22]**

Gov.UK. 'Strategy to end violence against women and girls: 2016 to 2020'. 8 March 2016. **https://www.gov.uk/government/publications/strategy-to-end-violence-against-women-and-girls-2016-to-2020 [Accessed 30/3/22]**

Gov.UK. 'Tackling violence against women and girls'. 21 July 2021. **https://www.gov.uk/government/publications/tackling-violence-against-women-and-girls-strategy [Accessed 30/3/22]**

Gov.UK. 'Taskforce on Innovation, Growth and Regulatory Reform independent report'. 16 June 2021 **https://www.gov.uk/government/publications/taskforce-on-innovation-growth-and-regulatory-reform-independent-report [Accessed 25/1/22]**

Health Data Research UK. 'Who Are We?' **https://www.hdruk.ac.uk/about-us/ [Accessed 20/1/22]**

Herring C, McManus A, Weeks A. 2010. 'Off-Label Prescribing during Pregnancy in the UK: An Analysis of 18,000 Prescriptions in Liverpool Women's Hospital.' *International Journal of Pharmacy Practice* 18 (4): 226–29. **https://onlinelibrary.wiley.com/doi/abs/10.1211/ijpp.18.04.0007**

Hoover RN. et al. *'Adverse health outcomes in women exposed in utero to diethylstilbestrol.'* N. Engl. J. Med. 365(14), 1304–1314, **https://doi.org/10.1056/NEJMoa1013961** (2011). Jakes AD, Watt-Coote I, Coleman M, Nelson-Piercy C. 2016. 'Obstetric medical care and training in the United Kingdom.' Obstetric Medicine 10 (1): 40–42.

Lintern S. 'Family wins £37m in one of the largest maternity negligence claims in NHS history'. The Independent. July 2020. **https://www.independent.co.uk/news/health/maternity-safety-nhs-negligence-guys-thomas-a9357501.html**

Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. 2009. 'The Cost of Preterm Birth Throughout Childhood in England and Wales.' Pediatrics 123 (2): e312–27. **https://doi.org/10.1542/peds.2008-1827**

MBBRACE-UK. 'Saving Lives, Improving Mothers' Care: Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2016-18'. December 2020. **https://www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/maternal-report-2020/MBRRACE-UK_Maternal_Report_Dec_2020_v10_ONLINE_VERSION_1404.pdf**

Medley N, Vogel JP, Care A, Alfirevic Z. 'Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews.' Cochrane Database Syst. Rev. 2018;11:CD012505 Published online 2018 Nov 14. doi: 10.1002/14651858.CD012505.pub2

NHS England. 'NHS encourages pregnant women to get Covid-19 vaccine'. 11 October 2021. **https://www.england.nhs.uk/2021/10/nhs-encourages-pregnant-women-to-get-covid-19-vaccine/ [Accessed 20/1/22]**

Pool Re. **https://www.poolre.co.uk/about/ [Accessed 25/1/22]** and **https://www.poolre.co.uk/cover/ [Accessed 6/3/22]**

Public Health England. 'National Congenital Anomaly and Rare Disease Registration Service: Congenital anomaly statistics 2018'. August 2020. **https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1008030/NCARDRS_Congenital_anomaly_statistics_report_2018.pdf**

RAND Europe. 'Pregnancy Research Review: Policy Report'. 2020
RECOVERY. 'Randomised Evaluation of COVID-19 Therapy (RECOVERY) for Pregnant and Breastfeeding Women'. **https://www.recoverytrial.net/files/recovery-in-pregnant-women-for-hcp-v15-1-2021-12-22.pdf/@@download [Accessed 20/1/22]**

Royal College of Obstetricians & Gynaecologists. 'COVID-19 vaccines, pregnancy and breastfeeding' guidance. **https://www.rcog.org.uk/en/guidelines-research-services/coronavirus-covid-19-pregnancy-and-womens-health/covid-19-vaccines-and-pregnancy/covid-19-vaccines-pregnancy-and-breastfeeding/ [Accessed 20/1/22]**

SANDS. Sands and Tommy's joint policy unit. **https://www.sands.org.uk/joint-policy-unit**

United Nations Inter-Agency Group for Child Mortality Estimation, Report 2021. Levels and trends in child mortality 2021

UNIVERSITY OF BIRMINGHAM
Edgbaston, Birmingham,
B15 2TT, United Kingdom
www.birmingham.ac.uk

Designed and printed by
UNIVERSITY OF BIRMINGHAM | creativemedia

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

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

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

TABLE OF CONTENTS

Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations about how and when to include pregnant women in drug development clinical trials for drugs and biological products based on the Food and Drug Administration's (FDA's or Agency's) current thinking on this subject.[2] Specifically, this guidance supports an informed and balanced approach to gathering data on the use of drugs and biological products during pregnancy through judicious inclusion of pregnant women in clinical trials and careful attention to potential fetal risk. This draft guidance is intended to serve as a focus for continued discussions among various entities such as the Agency, pharmaceutical manufacturers, the academic community, institutional review boards (IRBs), and others who are involved with the conduct of clinical trials in pregnant women.[3]

This guidance discusses the scientific and ethical issues that should be addressed when considering the inclusion of pregnant women in drug development clinical trials. From a scientific and ethical standpoint, the population of pregnant women is complex based on the interdependency of maternal and fetal well-being, and the need to take into consideration the risks and benefits of a drug to both woman and fetus (American College of Obstetricians and Gynecologists 2015). The scientific and ethical issues discussed in this guidance apply both to clinical trials that enroll pregnant subjects and to clinical trials that allow enrolled subjects who become pregnant to remain in the trial.

[1] This guidance has been prepared by the Division of Pediatric and Maternal Health in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research and the Office of Good Clinical Practice, Office of Special Medical Programs, in the Office of the Commissioner at the Food and Drug Administration.

[2] Throughout this guidance, the term *drug* means drug and biological products regulated by CDER or CBER.

[3] In addition to consulting guidances, sponsors are encouraged to contact the appropriate review division to discuss specific issues that arise during drug development.

Some of the information provided in this guidance applies to drugs indicated to treat pregnancy-specific conditions (e.g., preterm labor, pre-eclampsia), but the larger focus is on drugs indicated for conditions that occur commonly among females of reproductive potential. Women in this group may require treatment for chronic disease or acute medical problems, and may become pregnant multiple times during the reproductive phase of their lives.

This guidance does not discuss general clinical trial design issues or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials*, *E10 Choice of Control Group and Related Issues in Clinical Trials*,[4] and the draft ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials*.[5] The draft guidance for industry *Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling*[6] and certain disease-specific and drug class-specific guidances may provide additional considerations for studying pregnant women during drug development.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In the interests of promoting maternal/fetal health and informed prescribing decisions during pregnancy, this guidance addresses the challenges of including pregnant women in drug development research. There are more than 60 million women in the United States between the ages of 15 and 44 years, and almost 4 million births per year (U.S. National Vital Statistics Reports). Like women who are not pregnant, some pregnant women need to use drugs to manage chronic disease conditions or treat acute medical problems. To the extent there is labeling information for pregnant women, it is usually based on nonclinical data with or without limited human safety data. The frequent lack of information based on clinical data often leaves the health care provider (HCP) and the patient reluctant to treat the underlying condition, which in some cases may result in more harm to the woman and the fetus than if she had been treated. In addition, pregnant women often use medically necessary drugs without a clear scientific understanding of the risks and benefits to themselves or their developing fetuses (Lyerly et al. 2008).

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs or Biologics guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

[5] When final, this guidance will represent the FDA's current thinking on this topic.

[6] When final, this guidance will represent the FDA's current thinking on this topic.

Currently, information about drug use in pregnancy generally is collected in the postmarketing setting, using data from observational studies such as pregnancy exposure registries and other cohort studies, case control studies, and surveillance methods. Historically, there have been barriers to obtaining data from pregnant women in clinical trials in an effort to protect them and their fetuses from research-related risks. However, in certain situations, it may be helpful to collect data in pregnant women in the setting of a clinical trial (Goldkind et al. 2010). For example, it may be useful to compare the safety and efficacy of a drug that has been considered the standard of care for pregnant women with a newer treatment (Jones et al. 2010). In other situations, a woman's health and the well-being of her fetus may benefit from clinical trial participation. For example, a pregnant woman may need access to experimental therapies in a clinical trial setting because there are no approved treatment options available. Sometimes a drug treatment offered only through a clinical trial will hold out the prospect of direct benefit to the pregnant woman and/or her fetus beyond otherwise available therapies. For example, some clinical trials for drugs that treat human immunodeficiency virus (HIV), tuberculosis, and malaria enroll pregnant women (or provide that patients who become pregnant can continue enrollment) based on ethical principles and clinical need.

There are multiple reasons for considering the inclusion of pregnant women in clinical trials, including the following:

- Women need safe and effective treatment during pregnancy
- Failure to establish the dose/dosing regimen, safety, and efficacy of treatments during pregnancy may compromise the health of women and their fetuses
- In some settings, enrollment of pregnant women in clinical trials may offer the possibility of direct benefit to the woman and/or fetus that is unavailable outside the research setting
- Development of accessible treatment options for the pregnant population is a significant public health issue

Extensive physiological changes associated with pregnancy may alter drug pharmacokinetics and pharmacodynamics, which directly affects the safety and efficacy of a drug administered to a pregnant woman through alterations in drug absorption, distribution, metabolism, and excretion.[7] Pregnancy-related changes in various organ systems (e.g., gastrointestinal, cardiovascular, and renal) also may alter drug pharmacokinetics and pharmacodynamics. For example, a 30 to 40 percent increase in glomerular filtration rate results in much higher rates of clearance for some drugs during pregnancy (Mattison and Zajicek 2006); therefore, prescribing often occurs in the absence of knowledge regarding the dose required to achieve the desired therapeutic effect (Andrew et al. 2007).

[7] See the draft guidance for industry *Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling.*

Filling the knowledge gaps regarding safe and effective use of drugs in pregnant women is a critical public health need, but one that raises complex issues.

III. ETHICAL CONSIDERATIONS

The inclusion of pregnant women in clinical trials is guided by human subject protection regulations and involves complex risk-benefit assessments that vary depending on the seriousness of the disease, the availability of other treatments, the trial design, and whether the proposed investigation will occur in the premarketing or postmarketing setting. Because of the complex ethical issues involved in designing clinical trials that include pregnant women, sponsors should consider including an ethicist in planning their drug development programs. Moreover, sponsors should consider meeting with the appropriate FDA review division early in the development phase to discuss when and how to include pregnant women in the drug development plan. These discussions should involve FDA experts in bioethics and maternal health.

A. FDA Regulations That Govern Research in Pregnant Women

FDA-regulated clinical trials in pregnant women must conform to all applicable FDA regulations, including those related to human subject protections (21 CFR part 56, Institutional Review Boards, and 21 CFR part 50, subpart B, Informed Consent of Human Subjects). In addition, if the trial is supported or conducted by the Department of Health and Human Services (HHS), then 45 CFR part 46 may also apply, which would include subpart B, Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.[8] The FDA regulations do not contain a section similar to 45 CFR part 46, subpart B; however, the FDA recommends that these requirements be satisfied for FDA-regulated clinical research. Subpart B requires that trials supported or conducted by HHS meet all of the following 10 conditions:

1. Where scientifically appropriate, nonclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal[9] and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

3. Any risk is the least possible for achieving the objectives of the research;

[8] See 45 CFR 46.204.

[9] See section III.B., Research-Related Risks, for discussion of minimal risk.

4. The pregnant woman's consent is obtained in accord with the informed consent provisions of 45 CFR part 46, subpart A;

5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of 45 CFR part 46, subpart A, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;

6. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

7. For children as defined in § 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of 45 CFR part 46, subpart D;

8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

10. Individuals engaged in the research will have no part in determining the viability of a neonate.

IRBs are required to possess the professional competence necessary to review the specific research activities that they oversee (21 CFR 56.107(a)). IRBs must include persons who are knowledgeable in areas about the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice (21 CFR 56.107(a)). Therefore, if an IRB regularly reviews research involving pregnant women, the IRB must consider including one or more individuals who are knowledgeable about and experienced in working with such subjects (21 CFR 56.107(a)). When an IRB considers whether to approve a protocol involving pregnant women, it should consider only those risks and benefits (direct to the subjects, or generalizable knowledge) that may result from the research itself (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research) (21 CFR 56.111(a)(2)). Additionally, IRBs are required to determine that additional safeguards are included in the trial to protect the rights and welfare of subjects who are pregnant (21 CFR 56.111(b)).

Additional issues are raised by pregnant minors. Depending on state law, a pregnant minor may be considered emancipated by virtue of her pregnancy, a mature minor, or still a child (see the definition of children under 21 CFR 50.3(o)). IRBs should be familiar with applicable law of the jurisdiction in which a trial will be conducted. In the event that a clinical trial regulated by the FDA allows the enrollment of pregnant minors, or a minor becomes pregnant while enrolled in a clinical trial, and the pregnant minor meets the definition of a child under applicable state law, the IRB would have to comply with the applicable requirements of 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations.

B. Research-Related Risks

Research-related risks may meet the regulatory definition for *minimal risk* or may involve greater than minimal risk. FDA regulations define minimal risk as follows (21 CFR 50.3(k)):

> "*Minimal risk* means that 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."

Research-related risks are the risks specifically associated with the trial interventions or procedures. If a woman is assigned to receive a drug while enrolled in a clinical trial (i.e., the assignment of the drug is determined by the protocol), then the risks associated with the drug would be considered research-related.

In contrast, risks are not research-related when they are independent of the study and not associated with a trial intervention or protocol requirements. In other words, when a study collects data about drug treatment during pregnancy but the drug was prescribed before study enrollment by the patient's HCP, then the risks associated with the drug use are not research-related risks (Sheffield et al. 2014). For example, in a study in which the investigator plans to assess the pharmacokinetics of a particular selective serotonin reuptake inhibitor (SSRI) during pregnancy, the investigator enrolls pregnant women with a history of major depression who are currently managed on this drug. In this study the SSRI does not create research-related risk, because the patients are already using the SSRI (as previously prescribed by their HCPs) to manage their medical conditions. The only risks of the study are those associated with study-specific procedures (e.g., blood sample collection), and potential loss of confidentiality or privacy.

In this situation, the research-related risk to the fetus is minimal, and the purpose of the research is the development of important biomedical knowledge, which cannot be obtained by any other means. Some dedicated pharmacokinetic (PK) studies conducted with pregnant women (such as the previous SSRI example) can offer direct benefit to subjects if the data are used during the trial to adjust the dosing for individual subjects when clinically appropriate. The informed consent process should include discussion of expectations about whether trial data will be monitored and evaluated in a way that can potentially benefit the subject during the trial.

There may be circumstances in which a clinical trial can potentially expose a fetus to greater than minimal risk. Pregnant women can be enrolled in clinical trials that involve greater than minimal risk to the fetuses if the trials offer the potential for direct clinical benefit to the enrolled pregnant women and/or their fetuses. For example, this benefit may result from access to: (1) a needed but otherwise unavailable therapy (e.g., a new antituberculosis drug for multidrug resistant disease); or (2) a drug or biologic that reduces the risk for acquiring a serious health condition (e.g., a vaginal microbicide that reduces transmission of HIV and herpes simplex virus).

C. General Guidelines for Including Pregnant Women in Clinical Trials

This section provides general guidelines and considerations for including pregnant women in clinical trials. However, every drug development situation is unique, and individualized approaches to clinical trial design may be required to facilitate inclusion of pregnant women in specific drug development plans.

The FDA considers it ethically justifiable to include pregnant women with a disease or medical condition requiring treatment in clinical trials under the following circumstances:

<u>In the postmarketing setting (i.e., FDA-approved drugs)</u>

- Adequate nonclinical studies (including studies on pregnant animals) have been completed[10]

  and

- There is an established safety database in nonpregnant women from clinical trials or preliminary safety data from the medical literature and/or other sources regarding use in pregnant women

  and one of the following:

- Efficacy cannot be extrapolated

  and/or

- Safety cannot be assessed by other study methods

<u>In the premarketing setting (i.e., investigational drugs)</u>

- Adequate nonclinical studies (including studies on pregnant animals) have been completed

  and

- The clinical trial holds out the prospect of direct benefit to the pregnant woman and/or fetus that is not otherwise available outside the research setting or cannot be obtained by any other means (e.g., the pregnant woman may not have responded to other approved treatments or there may not be any treatment options)

The above conditions would also apply to a drug that is being developed to treat a pregnancy-specific condition.

[10] The phrase *adequate nonclinical studies* refers to recommendations for the design and conduct of reproductive toxicology and other nonclinical studies described in the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *S5(R2) Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility*.

Women who become pregnant while enrolled in a clinical trial

When a pregnancy has been identified during a clinical trial, unblinding should occur so that counseling may be offered based on whether the fetus has been exposed to the investigational drug, placebo, or control. The risks and benefits of continuing versus stopping investigational treatment can be reviewed with the pregnant woman. Pregnant women who choose to continue in the clinical trial should undergo a second informed consent process that reflects these additional risk-benefit considerations.

If fetal exposure has already occurred, a woman who becomes pregnant while enrolled in a clinical trial should be allowed to continue on the investigational drug if the potential benefits of continued treatment for the woman outweigh the risks of ongoing fetal exposure to the investigational drug, of discontinuing maternal therapy, and/or of exposing the fetus to additional drugs if placed on an alternative therapy. Regardless of whether the woman continues in the trial, it is important to collect and report the pregnancy outcome.

IV. OTHER CONSIDERATIONS

Including pregnant women in a trial involves careful risk-benefit assessments. All trials must be designed to minimize risk as much as possible while preserving the ability to achieve the objectives of the research (21 CFR 56.111). Some general considerations for sponsors and investigators include:

- Obtaining adequate reproductive and developmental toxicology data in relevant nonclinical models
- Identifying the trial population that will derive the most benefit while trying to minimize risk
- Considering the gestational timing of exposure to the investigational drug in relation to fetal development
- Choosing appropriate control populations

Sponsors should also consider the issues discussed in the following sections when designing a clinical trial that will include pregnant women.

A. Disease Type and Availability of Therapeutic Options in the Pregnant Population

Sponsors should take into account the incidence of the disease, the severity of the disease (e.g., whether or not it is life-threatening), and the availability of other therapeutic options and their risks. Pregnant patients with no other viable therapeutic options (e.g., drug resistance, drug

intolerance, contraindication, drug allergy) to treat a serious or life-threatening disease or condition may be appropriate candidates to enroll in a clinical trial.

B. Timing of Enrollment

The most appropriate time to include pregnant women in clinical trials during drug development may differ. Nonclinical reproductive and developmental toxicology studies generally should be completed before enrolling pregnant women in clinical trials.[11] In general, phase 1 and phase 2 clinical trials in a nonpregnant population that include females of reproductive potential should be completed before sponsors enroll pregnant women in later phase clinical trials. Sponsors should consider whether any of the following situations apply in determining when to enroll pregnant women in the drug development process.

- *If there are limited safety data or other approved (i.e., safe and effective) treatments are available*: In this situation, it may be more appropriate to complete phase 3 clinical trials in a nonpregnant population before enrolling pregnant women and exposing them to the investigational drug

- *If there are limited therapeutic options*: In these situations, the risk-benefit considerations may favor enrollment of pregnant women in earlier phase trials

- *If there are safety data for a drug that has been studied previously for other indications or populations*: In these situations, the risk-benefit considerations may favor enrollment of pregnant women in earlier phase trials

C. Pharmacokinetic Data

Because of the extensive physiological changes associated with pregnancy, PK parameters may change, sometimes enough to justify changes in dose or dosing regimen. For drug development programs where there are plans to enroll pregnant women in a phase 3 clinical trial, PK data in pregnant women should be collected during the phase 2 clinical trials to guide appropriate dosing in phase 3. In situations where pregnant women are enrolled in phase 3 clinical trials for a marketed drug, PK data should be collected as part of the trial.

In appropriate situations, nonpregnant women who become pregnant while on the investigational drug and consent to remain on the drug can also consent to PK assessments at steady state to collect data on correct dosing during pregnancy. Modeling and simulation have been increasingly used to support the design of clinical PK studies (Xia et al. 2013; Ke et al. 2013). For PK studies including pregnant patients, physiological changes during and after pregnancy that are critical for drug absorption and disposition may need to be considered in the model.

For additional information on PK modeling, study design considerations, and PK studies in pregnant women, refer to the draft guidance for industry *Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling*.

[11] See ICH M3(R2).

D. Safety Data Collection and Monitoring

When pregnant women are enrolled in a clinical trial, data collection elements should include, at a minimum: gestational age at enrollment; gestational timing and duration of drug exposure; and pregnancy outcomes including adverse maternal, fetal, and neonatal events. Enrolled pregnant patients should also receive obstetrical care that meets the recognized standards of care. Infants born to mothers who were exposed to the investigational drug should have follow-up safety information collected. Systemic drug exposure to the fetus/newborn can be evaluated by collecting cord blood or neonatal levels of drug and/or metabolites, depending on the timing of exposure to the drug and its half-life.

Clinical trials that enroll pregnant women should include investigators or consultants who have expertise in obstetrics and/or maternal/fetal medicine, depending on the underlying conditions treated by the investigational drug.

All clinical trials require monitoring (21 CFR 312.50 and 312.56), and no single approach to monitoring is appropriate or necessary for every clinical trial.[12] Clinical trials that involve pregnant women should include a data monitoring plan that includes members with relevant specialty and perinatal expertise to permit ongoing recognition and evaluation of safety concerns that arise during the course of the trial. This facilitates appropriate, expert assessment of adverse event reports.

E. Stopping a Clinical Trial That Enrolls Pregnant Women

There may be situations where it would be appropriate to stop a randomized, controlled clinical trial that is enrolling pregnant women. Examples include the following:

- An appropriately planned interim analysis demonstrates superior efficacy of the control or active comparator arm.

- There are documented serious maternal or fetal adverse events that can be reasonably attributed to drug exposure and are deemed to exceed the potential benefits of drug treatment. This determination should include consideration of alternative effective treatments and the risks of the underlying condition.

[12] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* and the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring*.

REFERENCES

American College of Obstetricians and Gynecologists, 2015, Ethical Considerations for Including Women as Research Participants, Committee Opinion No. 646, November.

Andrew, MA, TR Easterling, DB Carr, D Shen, ML Buchanan, T Rutherford, R Bennett, P Vicini, and MF Hebert, 2007, Amoxicillin Pharmacokinetics in Pregnant Women: Modeling and Simulations of Dosage Strategies, Clin Pharm and Therapeutics, 81(4):547–556.

Goldkind, S, L Sahin, and B Gallauresi, 2010, Enrolling Pregnant Women in Research — Lessons From the H1N1 Influenza Pandemic, N Engl J Med, Jun 17, 362(24):2241–2243.

Jones, H, K Kaltenbach, S Heil, S Stine, M Coyle, A Arria, K O'Grady, P Selby, P Martin, and G Fischer, 2010, Neonatal Abstinence Syndrome After Methadone or Buprenorphine Exposure, N Engl J Med, Dec 9, 363(24):2320–2331.

Ke, AB, SC Nallani, P Zhao, A Rostami-Hodjegan, and J Unadkat, 2013, Expansion of a PBPK Model to Predict Disposition in Pregnant Women of Drugs Cleared Via Multiple CYP Enzymes, Including CYP2B6, CYP2C9, and CYP2C19, BJCP, 77:3:554–570.

Lyerly, AD, MO Little, and R Faden, 2008, The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research, Int J Feminist Approaches to Bioethics, Fall, 1(2):5–22.

Mattison, D and A Zajicek, 2006, Gaps in Knowledge in Treating Pregnant Women, Gend Med, Sep, 3(3):169–82.

Sheffield, JS, D Siegel, M Mirochnick, RP Heine, C Nguyen, K Bergman, RM Savic, J Long, KE Dooley, and M Nesin, 2014, Designing Drug Trials: Considerations for Pregnant Women, Clinical Infectious Diseases, 59(S7):S437–S444.

U.S. National Vital Statistics Reports Rapid Release, 2017, Births: Provisional Data for 2016, Report No. 002, June.

Xia, B, T Heimbach, R Gollen, C Nanavati, and H He, 2013, A Simplified PBPK Modeling Approach for Prediction of Pharmacokinetics of Four Primarily Renally Excreted and CYP3A Metabolized Compounds During Pregnancy, AAPSJ, 15(4):1012–1024.

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

Clinical Lactation Studies: Considerations for Study Design

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

TABLE OF CONTENTS

Clinical Lactation Studies: Considerations for Study Design Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for sponsors conducting clinical lactation studies. The Food and Drug Administration (FDA or Agency) has required lactation studies under section 505(o)(3) of the Food, Drug, and Cosmetic Act (FD&C Act) under some circumstances and is considering additional circumstances in which lactation studies may be required. In addition, sponsors in some circumstances may elect to conduct lactation studies absent a requirement or request from the Agency.

This guidance reflects FDA's current recommendations regarding pre- or post-marketing lactation studies by drug sponsors.[2] This guidance provides information to facilitate the conduct of lactation studies. Such studies can inform breastfeeding with drug use recommendations included in the *Lactation* subsection of labeling.

The recommendations in this guidance reflect discussions from the 2007 Pediatric Advisory Committee meeting[3] and the 2016 Lactation Workshop,[4] which considered how data from clinical lactation studies can inform the safety of a drug when used during lactation.[5] This draft guidance replaces the draft guidance for industry *Clinical Lactation Studies — Study Design, Data Analysis, and Recommendations for Labeling*, which published in February 2005.

[1] This guidance has been prepared by the Division of Pediatrics and Maternal Health in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] See https://wayback.archive-it.org/7993/20170403222238/https://www.fda.gov/ohrms/dockets/ac/oc07.htm#pac.

[4] See https://www.fda.gov/Drugs/NewsEvents/ucm486761.htm.

[5] Wang J, Johnson T, Sahin L, et al., 2017, Evaluation of the Safety of Drugs and Biological Products Used During Lactation: Workshop Summary, Clinical Pharmacol Ther, 101(6):736–744.

This guidance does not address specific lactation labeling recommendations. These topics are addressed in 21 CFR 201.57(c)(9)(ii) and the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2014).[6]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Despite significant efforts to improve the quantity and quality of information in labeling for drug use during lactation, there remains a paucity of human data. Therefore, lactating women and their health care providers often must make decisions about drug treatment and continuation of breastfeeding during therapy without quality human data in labeling. For that decision to be evidence based, lactating women and health care providers would need information including, at a minimum, the amount of drug in human milk, the effect of the drug on milk production, and an understanding of the risks posed by the drug on the breastfed infant based on expected levels of exposure and adverse drug event data.

Data from clinical lactation studies, along with other relevant data (e.g., drug physicochemical characteristics, mechanism of drug entry into breast milk, data from nonclinical studies, important infant factors) can be analyzed to evaluate the safety of a drug when used during lactation. The data can also be used to develop recommendations to minimize infant exposure, when appropriate.

III. CONSIDERATIONS FOR CLINICAL LACTATION STUDIES

A. Considerations for Conduct of a Clinical Lactation Study

FDA has required lactation studies under section 505(o)(3) of FD&C Act under some circumstances and is considering additional circumstances in which lactation studies may be required. In addition, sponsors in some circumstances may elect to conduct lactation studies absent a requirement or request from the Agency.

FDA encourages sponsors to consider conducting a clinical lactation study whenever such study would be appropriate, even if the study is not being required by the Agency. The following are situations when a sponsor may wish to consider whether conducting a clinical lactation study would be appropriate:

[6] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

- A drug under review for approval is expected to be used by women of reproductive age

- After approval, use of a drug in lactating women becomes evident (e.g., via reports in the medical literature or lay press)

- A new indication is being sought for an approved drug and there is evidence of use or anticipated use of the drug by lactating women

- Marketed medications that are commonly used by women of reproductive age (e.g., antidepressants, antihypertensives, anti-infectives, diabetic and pain medications)

These and other factors should be considered on a case-by-case basis.

B. Ethical Considerations

FDA-regulated clinical trials, including lactation studies, must conform to all applicable FDA regulations, including those related to human subject protections (21 CFR part 56, Institutional Review Boards, and 21 CFR part 50, Protection of Human Subjects (including subpart D, Additional Safeguards for Children in Clinical Investigations)). Sponsors should consider the following ethical considerations with respect to three populations of lactating women who may potentially participate in clinical lactation studies:[7]

1. Lactating women who are prescribed the drug, which is the subject of the lactation study, as part of standard clinical care

    - If a lactating woman was prescribed and is continuing to take a medically necessary drug, it is not necessary to stop the drug for the purposes of enrollment in a research setting. It would be ethically acceptable to enroll women who have already made a decision to take a medically necessary drug while breastfeeding and allow them to continue breastfeeding while taking the drug. The drug exposure, specifically, to the infant would be considered a clinical risk. Any risks associated with the research would still need to be described.

2. Women in a research setting who are administered an investigational drug

    - In a research setting, where a woman who is currently breastfeeding starts an investigational drug for a disorder or condition, breastfeeding must be discontinued for the duration of the study because the risks of the exposure to the drug in the breastfeeding infant may outweigh the benefits. The potential drug exposure of a breastfeeding infant must be considered a research risk (and offers no clinical benefit to the infant).

7 Wang J, Johnson T, Sahin L, et al., 2017, Evaluation of the Safety of Drugs and Biological Products Used During Lactation: Workshop Summary, Clin Pharmacol Ther, 101(6):736–744.

- It is acceptable to enroll breastfeeding women who are participating in a clinical trial of an investigational drug in clinical lactation studies if the breastfeeding woman agrees to temporarily pump and discard milk to avoid exposing an infant to the investigational drug. The length of time that the milk will need to be discarded should be specified in the protocol and will vary depending on factors such as the half-life of the drug.

3. Women who are healthy volunteers and are administered the investigational drug for the purpose of clinical research

- In a research setting where a healthy woman who is currently breastfeeding volunteers for a clinical lactation study, breastfeeding must be discontinued for the duration of the study so that an infant is not exposed to the investigational drug.

C. Study Design Considerations

In considering the appropriate type of clinical lactation study to conduct, the sponsor should consider strategies that minimize the burden of data collection on the mother while obtaining adequate data. The study should avoid disruption of the breastfeeding routine and support return to breastfeeding if breastfeeding must be temporarily discontinued. Additionally, use of remote clinical study sites may provide access to a patient population that may not otherwise be willing or able to participate. Home health care nursing visits can be particularly important to successful recruitment and conduct of lactation studies of drugs with longer half-lives, when many visits occur over a period of several weeks.

1. General Study Designs

Sponsors should consider the following types of study designs for clinical lactation studies:

- Lactating woman (milk-only) study

  – A milk-only study can be used to detect the presence of a drug in breast milk, quantify or estimate the total amount of a drug transferred into breast milk (when plasma concentrations are known), and evaluate the effects of a drug on milk production (when milk production in lactating women not taking the drug is known). If the concentration of a drug in breast milk is found to be clinically relevant, this finding could lead to further studies.

  – In general, FDA recommends milk-only studies unless there is a reason to conduct another type of clinical lactation study.

- Lactating woman (milk and plasma) study

  – Milk and plasma collection in lactating women can provide pharmacokinetic (PK) data on a drug in a lactating woman, the amount of drug transferred into breast milk, and the effects of a drug on milk production. In certain situations, the PK data of the

drug may be unknown in lactating women such that obtaining such data would provide additional information in the amount of drug transferred into breast milk (e.g., when there is a concern for accumulation of a drug in breast milk).

- Mother-infant pair study

  – Mother-infant pair studies that include assessment of drug concentrations in infants can provide information on absorption of drugs in infants through breast milk and safety assessments in infants enrolled in these studies. A sponsor should consider this design if information is already available about the extent of drug transfer into breast milk including evidence that the drug accumulates in breast milk and if the drug is likely to be absorbed by the breastfed infant.

2. Other Study Design Considerations

In addition to the type of study design, sponsors should also consider the following study design issues:

- Single-dose design

  – For drugs that are given acutely (e.g., single-dose drug, drugs that do not accumulate with chronic dosing), a single-dose study may be sufficient.

- Longitudinal design

  – For drugs that are administered chronically or given for several treatment cycles, a sponsor may consider a longitudinal study design. Under such a design, samples are obtained from each lactating woman at different time points (e.g., at 2–3 months and then again at 5–6 months).

- Multiple-arm design

  – For drugs that are given acutely (e.g., single dose or short course of therapy), a multiple-arm study can be used to compare different lactating patients at different postpartum times. Under such a study, samples are obtained from different lactating women at different time points (e.g., at 2–3 months, 5–6 months).

3. Study Subject Considerations

The following maternal and infant factors can affect the results of a clinical lactation study. These factors should be collected in all lactation studies.

- Maternal factors

- Maternal weight, age, gestational age at delivery, stage of lactation, length of time postpartum, smoking, alcohol intake, concomitant drugs, ethnicity, race, and existing medical conditions should be collected and reported for each study subject.

- The study should specify subjects who exclusively breastfeed versus those who supplement with infant formula. Although FDA recommends that studies include only women who exclusively breastfeed, including women who are supplementing with infant formula provides *real life* data and may allow for easy collection of pumped milk that would otherwise be discarded. However, studies should report the extent of use of infant formula.

- Infant factors (for infants enrolled in mother-infant pair studies)

  - Age, weight, history of prematurity, drugs, existing medical conditions, ethnicity, and race should be collected and reported for each infant enrolled in a mother-infant pair study.

4. Sample Size Considerations

Sponsors should consider the following for sample sizes in clinical lactation studies:

- Sample size considerations include PK variability for the drug being studied, the study design (i.e., single dose versus multiple dose), and the variability in lactation physiology.

- A sponsor should consider the inter- and intra-subject variability for both mother and breastfed infant, depending on the design and primary objective of the study. For example, an increase to the sample size may be warranted if there is evidence of high inter- or intra-subject variability.

D. Milk Sampling Methods

For milk sampling during clinical lactation studies, sponsors should consider the following:

- Type of milk collected

  - The study design should specify the type of milk to be collected. For example, differences in composition of foremilk versus hindmilk should be accounted for with some drugs because transfer of drugs may be affected by the composition of the milk (e.g., foremilk contains more water and less fat which may affect the transfer of lipophilic drugs).

  - Sampling should ideally take place after the development of mature milk (after approximately 10 days postpartum). Colostrum or transitional milk collection may not reflect drug transfer in mature milk because drug transfer may be transiently increased because of a more porous mammary epithelium. However, sampling of colostrum or transitional milk may be important under certain circumstances. For

example, if concern exists about exposure of the drug in the immediate neonatal period, colostrum samples may be needed.

- The specific timing of the milk sample relative to both the dose and days postpartum should routinely be collected.

- Milk sampling method

  - In general, FDA recommends the collection of the entire milk volume from both breasts over 24 hours. Sampling should occur when drug exposure is at steady state during chronic maternal dosing. For drugs with dosing intervals of more than 24 hours, consideration should be made to collect milk over the entire dosing interval or to collect 24-hour samples during the expected time to peak plasma concentration. The sampling schedule should take into consideration a drug's known PK parameters and be adjusted for drugs with longer dosing intervals, balancing the need for adequate data collection with feasibility.

  - After the milk is collected, the necessary aliquots for assay should be saved using proper storage methods. The remainder of the milk collected can be refed to the infant under certain circumstances (see section III. B., Ethical Considerations). If the milk is allowed to be refed to the infant, the amount taken for assay should not deprive the infant of his or her nutritionally required volume.

  - FDA recommends the use of an electric pump rather than hand expression because electric pumps are more efficient in milk extraction. However, *hospital grade* pumps are not necessary; modern personal electric pumps utilize the same technology and are less costly.

E. Measurement of Infant Milk Intake

Sponsors should consider the following for measuring infant milk intake during clinical lactation studies:

- While a 150 mL/kg/day estimated milk intake is a reasonable assumption to estimate daily infant dosage, greater volumes do occur in early infancy and often correlate to the time of most reported infant adverse drug events. Additional consideration should be given to estimates of infant risk based on a 200 mL/kg/day milk intake in early infancy.

- Measurement of milk volume and weighing infants before and after feeding are methods that provide milk volume data for use in calculating infant exposure.

F. Pharmacokinetic Analysis

Analytical methods should be adequately validated, including both blood and breast milk, to address the accuracy, precision, selectivity, sensitivity, reproducibility, and stability of the parent drug and active metabolites of pharmacological importance.[8]

- Milk pharmacokinetics
  - The area under the milk concentration-time curve (AUC) should be calculated.
  - Average concentration should be based on AUC derived from collections at multiple time points, not just concentrations obtained at one sampling time.
  - Total milk concentration data should be used to estimate PK parameters of the parent drug and metabolites.
  - Peak and trough milk concentrations, as well as time to reach peak milk concentration, should be reported.
- Plasma pharmacokinetics (for milk and plasma study)
  - In general, plasma PK parameter estimates can include the following:
    - Area under the plasma concentration curve
    - Peak plasma concentration
    - Time to peak plasma concentration
    - Plasma clearance or apparent oral clearance
    - Apparent volume of distribution
    - Terminal half-life
  - PK parameters should be expressed in terms of total and unbound concentrations. For drugs and metabolites with a relatively low extent of plasma protein binding, FDA recommends that sponsors describe and analyze the pharmacokinetics in terms of total concentrations.
  - FDA also recommends noncompartmental and/or compartmental modeling approaches to parameter estimation.

G. Estimation of Infant Dosage

Sponsors should consider the following for calculating or estimating infant dosage:

[8] See the guidance for industry *Bioanalytical Method Validation* (May 2018).

- The daily infant dosage (total drug present in milk and consumed by the infant per day) should be calculated or estimated. Sponsors should consider the following to calculate daily infant dosage:

  Daily Infant Dosage (mg/day) = Σ (total drug concentration in each milk collection multiplied by the expressed milk volume in each milk collection)

  or

  Estimated Daily Infant Dosage (mg/kg/day) = M/P multiplied by the average maternal plasma concentration multiplied by 150 mL/kg/day

  M/P is the milk-plasma ratio. The calculation of M/P should be based on AUC and on multiple time points over 24 hours and not just a single point in time. Sponsors should consider an estimate of infant risk based on a 200 mL/kg/day infant milk intake in early infancy.

- The relative infant dose (the percent of the weight-adjusted maternal dosage consumed in breast milk over 24 hours) should be calculated. Sponsors should consider the following for relative infant dose:

  Relative Infant Dose = Infant Dosage (mg/kg/day)/Maternal Dosage (mg/kg/day) multiplied by 100

- If the drug has an approved indication for use in pediatric patients younger than 1 year of age, the estimated daily infant dosage should be compared to the approved dose. Calculation of the percentage of estimated daily infant dosage to the approved dose can provide an estimate of the risk to the infant.

- Infant pharmacokinetics (for a mother-infant pair study) should be considered. If infant drug concentration data are not collected, the average infant drug concentration ($C_{ss,ave}$) can be estimated by using the following formula:

  $C_{ss,ave}$ *= F multiplied by infant dosage/CL*

  F is the bioavailability, and CL is the drug clearance in the infant, if these data are known for the pediatric population.

H. Infant Safety Data Collection

An important component of clinical lactation studies is the collection of safety information in the breastfed infant. Follow-up examination or testing of the infant to evaluate for adverse drug events may be considered depending on the specific risk profile of the drug. Adverse drug event data can also be collected about the infant from mothers through surveys conducted electronically, by phone, or through maternal diaries.

I. Data on Effect of Drug on Milk Production

The clinical lactation studies described in this guidance are not formally designed to assess the effect of a drug on milk production. However, a sponsor should consider assessments about the effect of the drug on milk production in clinical lactation studies. For example, clinical lactation studies may include reports from enrolled women of any effects on milk production and, when feasible, a comparison of milk production before (or after discontinuation of) treatment to milk production during treatment.