

SYMPOSIUM:
GENDER, HEALTH & THE CONSTITUTION

REFORMING CLINICAL TRIAL PREGNANCY EXCLUSIONS

Jennifer D. Oliva*

INTRODUCTION

Pregnant women and fetuses are not expressly excluded from drug and biologics clinical trials by statute or regulation in the United States.¹ Instead, their exclusion from research is the product of several factors, including the lack of incentives for drug and biologics sponsors to conduct such studies and long-standing concerns about liability risk and fetal health.² In addition, the federal Department of Health and Human Services (HHS) and Food and Drug Administration (FDA) have issued regulations, guidance, and policies that, in practice and interpretation, motivate the exclusion of pregnant people and fetuses from participation in the overwhelming majority of clinical trials.³

The ongoing exclusion of pregnant people from drug and biologic clinical trials is paternalistic, unjust, and counterproductive because the failure to include pregnant people in experimental trials can enhance risks to maternal and fetal health. Bioethicists, legal scholars, and other researchers have pleaded for reform in this context for decades on various grounds.⁴ For example, some scholars contend that the exclusion of pregnant people from research trials unfairly shifts the risk-benefit calculus of engaging in drug and biologics treatment during pregnancy from the federal government to pregnant people and their providers.⁵ Others have pointed out that such exclusion violates basic bioethics

*Professor of Law and Val Nolan Faculty Fellow, Indiana University Maurer School of Law; Research Scholar, Addiction & Public Policy, O'Neill Institute for National and Global Health Law, Georgetown University Law Center; Senior Scholar, UCSF/UC Law Consortium on Law, Science & Health Policy, University of California College of the Law, San Francisco.

1. Richard M. Weinmeyer, *Pregnant Pause: The Exclusion of Pregnant Women from Clinical Research As Sex Discrimination*, 20 CARDOZO J.L. & GENDER 599, 609 (2014).

2. See, e.g., Devin D. Smith et al., *Exclusion of Pregnant Women from Clinical Trials during the Coronavirus Disease 2019 Pandemic: A Review of International Registries*, 37 AM. J. PERINATOL. 792, 793 (2020).

3. See, e.g., U.S. Food & Drug Admin., Div. of Pediatric and Maternal Health – Clinical Trials in Pregnant Women, <https://www.fda.gov/drugs/development-resources/division-pediatric-and-maternal-health-clinical-trials-pregnant-women> (explaining that, “[i]n general, pregnant women are excluded from drug development clinical trials”).

4. See, e.g., Indira S. E. van der Zande et al., *Vulnerability of Pregnant Women in Clinical Research*, 43 J. MED. ETHICS 657, 657 (2017) (explaining that “[f]air inclusion of pregnant women in clinical research has been widely promoted over the last decades, due to the pressing need to produce evidence-based knowledge concerning medications that are prescribed to women during pregnancy for both obstetric and non-obstetric illnesses”).

5. See, e.g., Anne Drapkin Lyerly, *Should Pregnant Women be Included in Clinical Trials?*, ASS’N AM. MED. COLLS. NEWS (July 24, 2018), <https://www.aamc.org/news/should-pregnant-women-be-included-clinical-trials>.

principles, including autonomy and beneficence.⁶ A related argument is that the exclusion of pregnant people from clinical trials is a central reflection of the federal government's longstanding policies that prioritize fetal health over maternal well-being.⁷

This essay proceeds in four Parts. Part I provides a brief overview concerning pregnancy drug use in United States. Part II describes the genesis and evolution of the HHS and FDA regulations and policies that generally operate, as interpreted by researchers, to exclude pregnant people from clinical trials. Part III argues that the implementation of legal reforms that ensure the inclusion of pregnant people in clinical trials is imperative given (1) the lessons learned from the COVID-19 emergency clinical trials, (2) the likelihood of enhanced pregnancy drug use surveillance and policing post-*Dobbs*, and (3) the potential implications of the challenge to the FDA's approval of mifepristone currently pending before the United States Supreme Court. Part IV concludes this essay by proposing three categories of reforms: regulatory reforms to the current clinical trials participation rules that pertain to pregnant people, statutory mandates and incentives aimed at enhancing the inclusion of pregnant people in clinical trials, and legal reforms that may mitigate research liability concerns.

I. DRUG USE DURING PREGNANCY

The first reason to confront the challenges of including pregnant women in research is a simple one: women need effective treatment during pregnancy.⁸ There are more than 5 million pregnancies⁹ and approximately 3.6 million births in the United States each year.¹⁰ Pregnant people often require drug and biologic therapeutics to manage chronic

6. Jenna Becker, *Excluding Pregnant People from Clinical Trials Reduces Patient Safety and Autonomy*, HARVARD BILL OF HEALTH (Apr. 16, 2021), <https://blog.petrieflom.law.harvard.edu/2021/04/16/pregnant-clinical-trials-safety-autonomy/>.

7. See Greer Donley, *Encouraging Maternal Sacrifice: How Regulations Governing the Consumption of Pharmaceuticals During Pregnancy Prioritize Fetal Safety Over Maternal Health and Autonomy*, 39 N.Y.U. REV. L. & SOC. CHANGE 45 (2015).

8. Anne Drapkin Lyerly, Margaret Olivia Little & Ruth Faden, *The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research*, 1 INT'L FEM APPROACHES BIOETH. 5, 6 (2008).

9. Ctrs. for Disease Control & Prevention, *U.S. Pregnancy Rates Drug During the Last Decade*, CDC.GOV (Apr. 12, 2023), https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2023/20230412.htmhttps://www.cdc.gov/nchs/pressroom/nchs_press_releases/2023/20230412.htm.

10. U.S. Census Bureau, *Births Now Outpacing Deaths in Over Half the States*, CENSUS.GOV (Dec. 19, 2023), <https://www.census.gov/library/stories/2023/12/state-population-estimates.html>.

diseases or treat acute medical problems.¹¹ As one group of feminist bioethicists aptly put it, “pregnancy is not a prophylaxis against medical illness.”¹²

Some pregnant people have pre-existing conditions ranging from common metabolic disorders, like Type 2 diabetes, to behavioral health conditions, like depression or attention-deficit/hyperactivity disorder (ADHD), to autoimmune diseases, like rheumatoid arthritis and lupus.¹³ Others develop or are diagnosed with serious health care conditions, like cancer, that are unrelated to their pregnancy.¹⁴ Yet another group develops pregnancy-specific, compromising health conditions that “range from difficult (extreme nausea and vomiting) to disabling (sciatic nerve compression) to life threatening for the [pregnant person] or [the] fetus (preeclampsia).”¹⁵ In addition, considerable first trimester medication use is simply unintended because nearly half of all pregnancies in the United States are unplanned.¹⁶

Although reliable metrics are elusive, estimates indicate that the percentage of people who take either prescribed or over-the-counter medications while pregnant may exceed 90% in the United States.¹⁷ In addition, approximately 50% of pregnant people use four or more drugs

11. See, e.g., Euni Lee et al., *National Patterns of Medication Use During Pregnancy*, 15 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 537, 537-38 (2006) (“Many pregnant people require medications to manage previously diagnosed acute or chronic conditions such as asthma and hypertension or to treat pregnancy-induced conditions.”).

12. Lyerly et al., *supra* note 8, at 6.

13. Weinmeyer, *supra* note 1, at 600 (explaining that, “[w]hether it is hypertension, gestational diabetes, or the exacerbation of a preexisting condition, many women need medical interventions beyond those linked directly to their pregnancy and the fetus”).

14. *Id.*

15. Lyerly et al., *supra* note 8, at 6.

16. Guttmacher Instit., *Unintended Pregnancy in the United States*, <https://www.guttmacher.org/fact-sheet/unintended-pregnancy-united-states> (last accessed Jan. 27, 2024) (pointing out that, “[i]n 2011, nearly half (45%, or 2.8 million) of the 6.1 million pregnancies in the United States were unintended”); Claire Cain Miller, *More U.S. Women are Avoiding Unwanted or Mistimed Pregnancies*, N.Y. TIMES (May 3, 2023), <https://www.nytimes.com/2023/05/03/upshot/pregnancy-birth-timing-preference.html> (noting that “[t]he United States has long had one of the highest rates of unintended pregnancy in the industrialized world” and “46 percent of pregnancies are now unintended”).

17. Rieke van der Graaf et al., *Fair Inclusion of Pregnant Women in Clinical Trials: An Integrated Scientific and Ethical Approach*, 19 TRIALS 1, 2 (2018); see also Jill Jin, *Safety of Medications Used During Pregnancy*, 328 JAMA 486, 486 (Aug. 2, 2022), <https://jamanetwork.com/journals/jama/fullarticle/2794762> (positing that “[n]early all pregnant individuals in the US take at least 1 over-the-counter or prescription medication during pregnancy”);Carolynn Dude & Denise J. Jamieson, *Assessment of the Safety of Common Medications Used During Pregnancy*, 326 JAMA INSIGHTS 2421, 2421 (2021) (pointing to a 2018 study in which “97.1% [of the pregnant people surveyed] reported taking at least 1 medication during their pregnancy”).

while gestating.¹⁸ Medications commonly prescribed and administered during pregnancy include, but are certainly not limited to, analgesics, antibiotics, and anti-nausea, asthma, and gastrointestinal therapeutics.¹⁹ Due, at least in part, to the restrictive federal rules that exclude pregnant people from most clinical trials, more than 90% of clinically-approved drugs on the American market lack any human safety data regarding pregnancy consumption.²⁰ As a result, the overwhelming majority of drugs that are consumed by pregnant people are prescribed or administered without adequate risk-benefit and dosing information.²¹

The prevalent use of medications during pregnancy that have never been tested in pregnant people is troubling. Post-market surveillance data proves that pregnancy has dramatic impacts on the absorption, distribution, metabolism, and excretion of drugs (pharmacokinetics) that implicate maternal health.²² Examples abound and include a pregnant woman undergoing chemotherapy who metabolized and excreted the drug “so quickly and thoroughly that it never approached a therapeutic range, despite the fact that she and her fetus were exposed to [the drug’s] toxicities.”²³ Drugs that treat other conditions in pregnant people have been found to have similar effects, that is, their indicated doses produced undesirable side effects but no therapeutic benefits.²⁴

Medications that have only been tested in non-pregnant adults can also have unknown and catastrophic impacts on fetuses when used by pregnant people. Drugs are capable of passing from the pregnant person’s

18. Martina Ayad & Maged M. Constantine, *Epidemiology of Medication Use in Pregnancy*, 39 SEMIN. PERINATOL. 508, 509 (2015).

19. Jin, *supra* note 17, at 486; Dude & Jamieson, *supra* note 17, at 2421; David M. Hass et al., *Prescription and Other Medication Use in Pregnancy*, 131 OBSTET. GYNECOL. 789, 794 (2018).

20. Zhaoxia Ren, Andrew A. Bremer & Aaron C. Pawlyk, *Drug Development Research in Pregnant and Lactating Women*, 225 AM. J. OF OBSTET. & GYNECOL. 33, 33 (2021) (explaining that “the majority of medications prescribed to pregnant and lactating women are used “off-label” because more than 90% of clinically-approved medications do not have appropriate drug labeling information for pregnant and lactating women”); Amina White, *Accelerating the Paradigm Shift Toward Inclusion of Pregnant Women in Drug Research: Ethical and Regulatory Considerations*, 39 SEMINARS IN PERINATOLOGY 537, 537 (2015).

21. Ren, *supra* note 20, at 33; White, *supra* note 20, at 537.

22. See Maisa Feghali, Raman Venkataramanan & Steve Caritis, *Pharmacokinetics of Drugs in Pregnancy*, 39 SEMINARS IN PERINATOLOGY 512, 512 (2015); Maged M. Constantine, *Physiologic and Pharmacokinetic Changes in Pregnancy*, 5 FRONT. PHARMACOL. 1, 1-4 (2014); Donald Mattison & Anne Zajicek, *Gaps in Knowledge in Treating Pregnant Women*, 3 GEND. MED. 169, 169 (2006).

23. Lyerly et al., *supra* note 8, at 3.

24. *Id.*; see also Kate Greenwood, *The Mysteries of Pregnancy: The Role of Law in Solving the Problem of Unknown but Knowable Maternal-Fetal Medication Risk*, 79 U. CIN. L. REV. 267, 269-70 (2010).

blood to the fetus through the placenta and, therefore, have the potential to cause teratogenic harm.²⁵ A broad category of concern to fetal health, for example, are prescription anti-depressants, which have been linked to a number of health conditions in neonates, including pulmonary hypertension and heart conduction problems.²⁶ Other classic examples of drugs that were discovered as teratogens post-approval are thalidomide and diethylstilbestrol (DES).²⁷ As discussed in more detail in the following section, the thalidomide and DES tragedies instigated the enactment of FDA guidance in the late 1970s that explicitly excluded women of reproductive age and pregnant people from clinical trial participation.

II. FEDERAL REGULATION OF PREGNANT PEOPLE IN CLINICAL TRIALS

Our profound ignorance about what drugs to use and when to use [them during pregnancy] has a number of negative repercussions.²⁸

Pharmaceutical manufacturers are required to vault through a grueling, time-consuming, resource-intensive, and costly process in order to secure FDA approval to market a new drug or biologic in the United States.²⁹ The federal Food, Drug, and Cosmetic Act (FDCA) prohibits manufacturers from delivering those products into interstate commerce until they have been approved as safe and effective for their intended use(s) by the FDA.³⁰ The FDCA further demands that manufacturers prove the safety and efficacy of new drug and biologic products through

25. Cleveland Clinic, *Teratogens*, <https://my.clevelandclinic.org/health/articles/24325-teratogens> (last visited Jan. 27, 2024) (explaining that “[a] teratogen is a substance that interferes with normal fetal development and causes congenital disabilities”); Gabriela Pereira et al., *Self-Medication Among Pregnant Women: Prevalence and Associated Factors*, 12 FRONT. PHARMACOL. 1, 2 (2021) (“According to the gestational age at the exposure time and the dose administered, the use of a teratogenic agent during pregnancy can result in varying outcomes, such as fetal death, morphologic malformations, or physiological abnormalities.”); see also Marleen M.H.J. van Gelder et al., *Teratogenic Mechanisms of Medical Drugs*, 16 HUM. REPROD. UPDATE 378, 379 (2010).

26. Tim F. Oberland et al., *Effects of Timing and Duration of Gestational Exposure to Serotonin Reuptake Inhibitor Antidepressants: Population-Based Study*, 192 BRIT. J. PSYCH. 338, 341-42 (2008).

27. Françoise Baylis & Angela Ballantyne, *Missed Trials: Future Opportunities*, in CLINICAL RESEARCH INVOLVING PREGNANT WOMEN 2 (Baylis & Ballantyne eds., 2016).

28. Greenwood, *supra* note 24, at 271.

29. See, e.g., Aylin Sertkaya et al., *Key Cost Drivers of Pharmaceutical Clinical Trials in the United States*, 13 CLINICAL TRIALS 117, 118 (2016) (estimating that its costs between \$1.3-\$1.7 billion to develop an approved drug in the United States).

30. 21 U.S.C. § 355 (d); 21 C.F.R. § 314.50(d)(5)(v) (2020); 21 C.F.R. § 314.126 (2020).

a series of rigorous clinical trials.³¹ Those trials begin with *in vitro* (laboratory) and *in vivo* (animal) research aimed at understanding how the experimental drug works and its toxicity.³² If that preliminary non-human research proves promising, the drug is then tested in successive, controlled human subjects clinical trials to determine its metabolic properties, safety, and efficacy.³³

Once the FDA approves a drug or biologic for any single intended use, it is perfectly legal for authorized providers to prescribe that drug or biologic for any other use, constrained only by the state laws that regulate prescribing practice and the tort liability system.³⁴ Consequently, new drug manufacturers “have a powerful incentive to do the investigation necessary to demonstrate to the satisfaction of the FDA that an experimental drug is safe and effective for one intended use” and *only* one intended use.³⁵ Drug and biologic manufacturers prefer the cheapest and fastest route to market that preserves the longest possible period of market exclusivity for new products.³⁶ Unfortunately, excepting drugs that are specifically indicated for pregnancy-exclusive conditions, that route never includes seeking an approved pregnancy indication or conducting additional expensive and time-consuming trials sufficient for the product to include important pregnancy use information.³⁷

31. 21 U.S.C. § 355(d); 21 C.F.R. § 312.23(a)(8) (2020) (explaining that the investigative new drug (IND) plan should include “information about pharmacology and toxicological studies of the drug involving laboratory animals”); *see also* CTR. FOR DRUG EVALUATION & RSCH., U.S. DEP’T OF HEALTH & HUM. SERVS., GUIDANCE FOR INDUSTRY, INVESTIGATORS, AND REVIEWERS: EXPLORATORY IND STUDIES 2-3 (2006), <https://www.fda.gov/files/Guidance-to-Industry-and-Reviewers—Exploratory-IND-Studies-%28PDF%29.pdf> (expressing that an IND must include information on “any risks anticipated based on the results of pharmacologic and toxicological data collected during studies of the drug in animals” before the commencement of human studies).

32. Food & Drug Admin., *Development & Approval Process Drugs*, <https://www.fda.gov/drugs/development-approval-process-drugs> (last accessed Jan. 27, 2024) (“Before a drug can be tested in people, the drug company or sponsor performs laboratory and animal tests to discover how the drug works and whether it’s likely to be safe and work well in humans. Next, a series of tests in people is begun to determine whether the drug is safe when used to treat a disease and whether it provides a real health benefit.”).

33. *Id.*

34. David A. Simon, *Off-Label Innovation*, 56 GA. L. REV. 701, 719-20 (2022).

35. Greenwood, *supra* note 24, at 283.

36. Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL’Y L. & ETHICS 717, 720-26, 731-32 (2005).

37. Greenwood, *supra* note 24, at 283 (explaining that manufacturers “also have an incentive to do no more than necessary to secure approval, because delays in approval can lessen, and certainly forestall, the period of time during which they can sell their drug subject to patent-protected market exclusivity”).

Among other reasons, this is because the applicable federal rules (1) make it considerably easier for drug manufacturers to obtain an approved use by conducting clinical trials with non-pregnant people than to do so with pregnant people and (2) neither require nor incentivize drug manufacturers to conduct experimental drug trials in pregnant human subjects. It is important, therefore, to provide a quick overview of the applicable federal rules and their limitations in this context.

HHS first promulgated its general regulations governing human subjects research, which are colloquially called the “Common Rule,” in 1991.³⁸ As currently amended, those rules require covered human subjects research to be approved by an Institutional Review Board (IRB) to ensure the ethical treatment of research participants.³⁹ The Common Rule, which is codified at 45 C.F.R. Subpart A, then enumerates seven criteria by which an IRB should evaluate human subjects research proposals.⁴⁰ Those criteria require such research to (1) minimize risks to human subjects; (2) ensure that the risks to subjects are reasonable in relation to their anticipated benefits; (3) ensure that subject selection is equitable; (4) provide informed consent to subjects; (5) properly document informed consent; (6) monitor the data collected to ensure subject safety, where appropriate; and (7) protect the privacy of subjects.⁴¹ Subpart A also makes it clear that an IRB must reject a research proposal that fails to satisfy all of these criteria.⁴²

In addition to the criteria enumerated in Subpart A, human subjects research involving pregnant people and fetuses covered by HHS regulations must comply with the stringent additional requirements enumerated in 45 C.F.R. Subpart B, titled “Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.”⁴³ Those additional criteria permit clinical research on pregnant people and fetuses only where, among other things, (1) the research proposal includes preclinical research on pregnant animals and clinical studies on non-pregnant women⁴⁴ and (2) the risk to the fetus is caused solely by research that holds the prospect of a direct benefit to the pregnant person or the fetus or, where there is no such benefit, the risk to the fetus is not greater than minimal and the research’s purpose is important to biomedical

38. 45 C.F.R. Subpart A.

39. 45 C.F.R. § 46.103.

40. 45 C.F.R. § 46.111.

41. 45 C.F.R. § 46.111(a)(1)-(7).

42. 45 C.F.R. § 46.111(a).

43. 45 C.F.R. Subpart B.

44. 45 C.F.R. § 46.204(a).

knowledge and cannot be obtained by any other means.⁴⁵ These two provisions instigate the exclusion of pregnant people from the overwhelming majority of clinical trials in the United States.

As is evident, the first Subpart B criteria highlighted above requires experimental drug sponsors to conduct two, cost-prohibitive clinical trials prior to initiating any research on pregnant human subjects: one in pregnant animals and a second in non-pregnant women. The FDA, however, neither conditions drug approval on this additional research nor financially incentivizes drug sponsors—through mechanisms like fee waivers, priority review, or expanded market exclusivity—to engage in this timely and costly additional work. As Professor Greer Donley has explained, “[b]ecause there is no regulatory requirement to generate information on drug safety in pregnancy, and drug companies are not forced to compete according to this measurement, there is no financial incentive for drug companies to spend the money investing in this research.”⁴⁶

Demonstrating the rule’s prioritization of fetal risk over maternal well-being, the second Subpart B criteria applies a risk-benefit standard to fetuses that well exceeds the Subpart A standard applicable to human subjects, including pregnant human subjects. As explained above, the general Subpart A rule provides that a human subjects research proposal is ethical so long as the risks are reasonable in relation to the anticipated benefits.⁴⁷ Under Subpart B, by contrast, fetal research is unethical and unlawful unless (1) the fetal risk holds out a direct benefit for the pregnant person or the fetus or (2) the risk to the fetus is no greater than minimal and there is no other means of obtaining important biomedical research.⁴⁸ Due to liability and ethics concerns around fetal protection, IRBs tend to narrowly interpret the “minimal risk” rule that applies to research that lacks a direct benefit to the fetus to exclude pregnant people and fetuses from the majority of drug and biologic clinical trials.⁴⁹

Subpart B also includes a novel and autonomy-depriving informed consent provision that requires *both* maternal and paternal consent when the direct benefit of the research is solely applicable to the fetus unless

45. 45 C.F.R. § 46.204(b).

46. Donley, *supra* note 7, at 53-54.

47. 45 C.F.R. § 46.111(a)(2).

48. 45 C.F.R. § 46.204(b).

49. See, e.g., Robert J. Levine, *IRB Perspectives on Inclusion of Pregnant Women in Clinical Research* in OFF. OF RES. ON WOMEN’S HEALTH, ENROLLING PREGNANT WOMEN: ISSUES IN CLINICAL RESEARCH 37, 39, 41-42 (2010), <https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH-EPW-Report-2010.pdf>; Weinmeyer, *supra* note 1, at 613.

“the father” is unavailable.⁵⁰ Due to this onerous and paternalistic informed consent regulation, it is less burdensome to conduct experimental drug trials on human children than on fetuses in the United States.⁵¹ As one group of scholars explained, “[t]his requirement fails to acknowledge that the interests of a pregnant person and their fetus are intertwined strands in contrast to research conducted in pediatric settings, where the consent of one parent is sufficient to authorize research with a prospect of direct benefit to a child.”⁵²

Although the FDA has not formally adopted Subpart B,⁵³ the agency has a long history of aggressively discouraging the inclusion of pregnant people in clinical trials. The FDA adopted a draconian prohibition on research in pregnant people in response to the dual mid-twentieth century pregnancy-related tragedies involving thalidomide and diethylstilbestrol (DES).⁵⁴ Thalidomide was approved for use in several European countries as a sedative in the mid-1950s, but it was widely prescribed to pregnant women to treat morning sickness.⁵⁵ By the early 1960s, the use of thalidomide during pregnancy was associated with various congenital disabilities, including phocomelia (severe limb malformation).⁵⁶ The United States was largely spared the thalidomide tragedy because the drug had not been approved for market largely due to the efforts of FDA scientist Dr. Frances Kelsey.⁵⁷

50. 45 C.F.R. § 46.204(e) (explaining that, “[i]f 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 . . . 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”).

51. 45 C.F.R. § 46.408(b).

52. Catherine A. Sewell et al., *Scientific, Ethical, and Legal Considerations for the Inclusion of Pregnant People in Clinical Trials*, 227 AM. J. OBSTET. & GYNECOL. 805, 808 (2022).

53. Clinical trials conducted or supported by HHS on new drugs seeking FDA approval, however, remain subject to Subpart B rules. Food & Drug Admin., *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* 4 (Apr. 2018), <https://www.fda.gov/media/112195/download> (explaining that, “if the trial is supported or conducted by [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”).

54. Lucy Langston, *Better Safe Than Sorry: Risk, Stigma, and Research During Pregnancy in CLINICAL RESEARCH INVOLVING PREGNANT WOMEN* 33-36 (Francoise Baylis & Angela Ballantyne, eds. 2016); Punam Sachdeva, *Drug Use in Pregnancy: A Point to Ponder!*, 79 INDIAN J. PHARM. SCI. 1, 1 (2009).

55. James H. Kim & Anthony R. Scialli, *Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease*, 122 TOXICOLOGICAL SCI. 1, 1 (Apr. 2011).

56. *Id.*

57. Miranda R. Waggoner & Anne Drapkin Lyerly, *Clinical Trials in Pregnancy and the “Shadows of Thalidomide”: Revisiting the Legacy of Frances Kelsey*, 119 CONTEMP. CLIN. TRIALS 1, 2 (2022).

DES did not face the same regulatory fate. The FDA approved DES, which is a synthetic form of estrogen, to prevent miscarriage in 1947.⁵⁸ The drug was widely prescribed in the United States and it was not until the early 1970s that researchers discovered that DES was associated with the development of clear cell adenocarcinoma in women who had experienced prenatal exposure to the drug.⁵⁹ The FDA published a bulletin in November 1971 explaining that DES was contraindicated for pregnancy and linked to adenocarcinoma in female offspring.⁶⁰

In response to the thalidomide and DES disasters, the FDA issued a guideline in 1977 titled “General Considerations for the Clinical Evaluation of Drugs.”⁶¹ Concerned that, like thalidomide and DES, any number of approved new drugs had the potential to cause fetal harm, the FDA guideline expressly excluded reproductive-aged people from Phase I and early Phase II clinical trials.⁶² The FDA’s adoption of that policy was paradoxical insofar as it was motivated by the lessons of thalidomide and DES because the thalidomide and DES sagas stemmed from *the absence of robust pre-market research* concerning those drugs’ impacts on pregnant people and fetuses.

Dr. Frances Kelsey, in fact, went to great lengths to emphasize this point to the public throughout her career.⁶³ As she noted in a 1963 speech in New York, the effects of thalidomide “should have been recognized in a well-controlled clinical study involving comparatively few patients during early pregnancy” but “no such studies preceded the drug’s introduction on the market.”⁶⁴ In sum and, as incredible as it sounds, the FDA decided to exclude pregnant people and fetuses from clinical drug trials in response to fetal harm that resulted from their post-market

58. Langston, *supra* note 54, at 35.

59. Nat’l Cancer Instit., *Diethylstilbestrol (DES) Exposure and Cancer*, <https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/des-fact-sheet> (last accessed Feb. 2, 2024).

60. Food & Drug Admin., *Diethylstilbestrol Contraindicated in Pregnancy*, 116 CAL. MED. 85-86 (1972), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1518220/pdf/califmed00122-0115.pdf>.

61. Food & Drug Admin., *General Considerations for the Clinical Evaluation of Drugs* (1977), <https://babel.hathitrust.org/cgi/pt?id=umn.31951003051226s&view=1up&seq=1>.

62. *Id.* at 6, 7, 10.

63. Waggoner & Lyerly, *supra* note 57, at 4 (explaining that “Kelsey’s speeches magnified the need to learn more about teratogenic effects, improve basic research, and expand surveillance of drugs in pregnancy”).

64. *Id.*

exposure to drugs specifically because those drugs had never been tested in pregnant people and fetuses in pre-approval clinical research trials.⁶⁵

Various federal agencies began to soften their position regarding the participation of pregnant people in clinical trials in the 1990s.⁶⁶ More recently, the FDA issued draft guidance that characterizes the inclusion of pregnant people in drug and biologic clinical trials as a “critical public health need.”⁶⁷ That 2018 guidance, however, continues to advance numerous obstacles to inclusion, including, but not limited to, its express recommendation that the onerous, vague, and often narrowly-interpreted HHS Subpart B requirements that pertain to studies including pregnant people and fetuses “be satisfied for FDA-regulated clinical research.”⁶⁸

Consequently, and notwithstanding the FDA’s notable shift toward inclusion, pregnant people continued to be excluded from the vast majority of drug and biologics clinical trials. Researchers published a study in November 2022 that examined the inclusion of pregnant and breastfeeding people in non-obstetric clinical research in the United States.⁶⁹ That study identified 1333 randomized controlled trials that took place between January 1, 2017 and December 31, 2019 that could have included pregnant people.⁷⁰ It found that pregnant people were eligible for just 13 or 1% of those trials.⁷¹ A separate study published in 2013 that investigated Phase IV clinical trials yielded similar results, concluding that “only 1% of industry-sponsored studies were designed specifically for pregnant [people] and 95% of studies of conditions that can affect pregnant [people] excluded pregnant [people] from participation.”⁷²

The study published in 2022 further explained that, “among [the clinical trials] that explicitly excluded [pregnant people], the rationale for exclusion was rarely documented.”⁷³ This is because, whereas the

65. See, e.g., Monique McKiever et al., *Challenges in Conduction Clinical Research Studies in Pregnant Women*, 47 J. PHARMACOKINET. PHARMACODYN. 287, 291 (2020) (explaining that “careful examination of past studies and historical events including thalidomide exposure, points to the need for more controlled evidence-based considerations in premarket research studies rather than research observations which come after the exposure of large numbers of pregnant women”).

66. Greenwood, *supra* note 24, at 287-91.

67. *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials*, *supra* note 53, at 4.

68. *Id.* at 2.

69. Sarah C.J. Jorgensen et al., *Inclusion of Pregnant and Breastfeed Women in Nonobstetrical Randomized Clinical Trials*, 4 AM. J. OBSTET. GYNECOL. 1, 1 (2022).

70. *Id.* at 2-3.

71. *Id.* at 3, 6.

72. Kristine E. Shields & Anne Drapkin Lyerly, *Exclusion of Pregnant Women from Industry-Sponsored Clinical Trials*, 122 OBSTET. & GYNECOL. 1077, 1080 (2013).

73. *Id.* at 6.

applicable federal regulations as interpreted by IRBs force experimental drug and biologics sponsors to justify the inclusion of pregnant women in clinical trials, there is no requirement whatsoever for them to justify their exclusion of that research population.⁷⁴ Indeed, “[s]ince the U.S. National Institutes of Health (NIH) began to require the inclusion of women, ethnic minorities, and children in research, pregnant [people] are the only population for which justification for exclusion need not be given.”⁷⁵

The ongoing exclusion of pregnant people from drug and biologic clinical trials is unjust, illogical, and health harming. The entire purpose of the FDA’s drug and biologic approval processes is to shift the risk-benefit assessment concerning the safety and efficacy of those medications from providers and patients to an expert oversight agency charged with protecting the public health.⁷⁶ While non-pregnant people reap the benefits of this regime, pregnant people and fetuses are denied meaningful regulatory protection. Instead, the exclusion of pregnant people from clinical trials leaves pregnant patients and their providers with two potentially risky choices: (1) consumption of a drug potentially harmful to maternal and/or fetal health or (2) medication avoidance even where use of a therapeutic might dramatically improve maternal and/or fetal health outcomes.⁷⁷ The FDA conceded the same in its 2018 guidance, explaining that

... to the extent there exists any drug or biologics labeling information for pregnant people, 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 pregnant patient reluctant to treat the underlying condition, which in some cases may result in more harm to the pregnant person and the fetus than would result if the pregnant person had been treated. In addition, pregnant people are often forced to use medically necessary drugs without a clear scientific understanding of the risks and benefits to themselves or their developing fetuses.⁷⁸

74. Sam F. Halabi, *Zika, Pregnancy, and the Law*, 70 ARK. L. REV. 707, 731 (2017).

75. *Id.*

76. See, e.g., Food & Drug Admin., *Benefit-Risk Assessment for New Drug and Biologics Products* (Oct. 2023), <https://www.fda.gov/media/152544>.

77. Waggoner & Lyerly, *supra* note 57, at 7; see also Lyerly, *supra* note 5.

78. *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials*, *supra* note 53, at 4.

As a result of this paradox, pregnant people have been characterized as the “last therapeutic orphans”⁷⁹ in the United States. This begs a critical question: why have American regulators historically taken the position that it is ethical to force pregnant people to subject themselves and their fetuses to the considerable potential risks to maternal and fetal health that attend to their uninformed decision to consume—or refrain from consuming—medications that were never tested in pregnant subjects yet unethical to facilitate the participation of pregnant people in clinical research trials? One of the more troubling things about this scenario, where the prevailing policies and incentives trust pregnant people to serve as drug test subjects post-approval, but largely exclude them as test subjects pre-approval is that we lose the benefit of the clinical safety and efficacy data about drug use during pregnancy that would be generated if the rules actively promoted the inclusion of pregnant people in clinical research.

The exclusion of pregnant people from clinical trials due to ethical concerns that “an intervention could cause harm to the fetus, and especially that the . . . medication under study could cause birth defects” is also scientifically nonsensical.⁸⁰ Pregnant people and their fetuses are physiologically interconnected in complex ways such that the physical experiences of pregnant people have considerable impacts on fetal health and development.⁸¹ This interconnectedness means that policies—like clinical trial exclusion—that make it impossible for pregnant people to obtain evidence-based health care often undermine rather than advance fetal health.⁸² In many instances, therefore, the ongoing exclusion of pregnant people and fetuses from clinical trials for so-called fetal

79. Lyerly, *supra* note 5.

80. Committee on Ethics, *Ethical Considerations for Including Women as Research Participants*, AM. COLL. OBSTET. & GYNECOL. COMM. OP. NO. 646, 5-6 (Nov. 2015), <https://www.acog.org/-/media/project/acog/acogorg/clinical/files/committee-opinion/articles/2015/11/ethical-considerations-for-including-women-as-research-participants.pdf>; *see also* McKiever et al., *supra* note 65, at 291 (observing that “fetal safety profile is the most cited reason for the exclusion of pregnant women and those who could become pregnant from research studies”).

81. *See, e.g.*, Zaina Mahmoud & Elizabeth Chloe Romanis, *On Gestation and Motherhood*, 31 MED. LAW REV. 109, 111 (2023) (explaining that “the fetus must be understood as part of a person’s physiology, rather than as a distinct creature existing within them. The fetus is completely integrated into the pregnant person’s physicality, functionality, and physiology . . .”).

82. Committee on Ethics, *supra* note 80, at 5 (noting that “[t]he unknown risk status of the vast majority of FDA-approved medications puts fetuses at risk” and “[h]ad these drugs been studied in pregnancy early in their use, data on risk may have provided an opportunity to better balance the risks and benefits of their use”).

protective purposes amounts to protecting pregnant people and fetuses to death.

III. THE URGENCY OF REFORM

There is an urgent unmet need to prioritize and expedite the inclusion of pregnant . . . women in research.⁸³

As previously noted, researchers have been advocating for reform of the collusive laws and policies that continue to disincentivize the inclusion of pregnant people in drug and biologic clinical trials. After decades of advocacy, federal regulators have shifted their view in favor of inclusion but, as the research illuminates, little has changed in practice.⁸⁴ This section argues that meaningful reform is urgent given three recent developments: (1) the exclusion of pregnant people the COVID-19 pandemic clinical trials, (2) the enactment of state abortion healthcare restrictions and enhanced pregnancy surveillance in the wake of the Supreme Court’s decision in *Dobbs v. Jackson Women’s Health Organization*; and (3) the ongoing legal challenges to the FDA’s approval and regulation of mifepristone.

A. COVID-19 Pandemic

For the reasons discussed above, pregnant people have long been excluded from clinical trials involving the development of experimental therapeutics, including vaccines, aimed at combatting and mitigating infectious disease public health emergencies.⁸⁵ A 2023 systemic review of emergency vaccine clinical trials conducted between 2009 and 2019 found that 90% of those trials explicitly excluded pregnant people.⁸⁶ Such exclusion even extended to diseases, like HIV, H1N1, Ebola, and Zika, for which the treatments of pregnant people ought to have been prioritized due to those diseases’ devastating impacts on maternal and/or fetal health.⁸⁷ It is well-documented that the lack of experimental therapeutic

83. Jorgensen et al., *supra* note 69, at 1.

84. *See, e.g.*, Smith et al., *supra* note 2, at 793 (observing that “[t]he current state of research in pregnancy and the pattern of excluding pregnant [people] from drug trials is dismal at best and has not significantly improved even with recent improvements in the regulatory area”).

85. Jamie Minchin et al., *Exclusion of Pregnant People from Emergency Vaccine Clinical Trials: A Systemic Review of Clinical Trial Protocols and Reporting from 2009 to 2017*, 41 *VACCINE* 5159, 5160 (2023).

86. *Id.* at 5161.

87. *Id.* at 5160; Halabi, *supra* note 74, 710; Anna C. Mastroianni, *HIV, Women, and Access to Clinical Trials: Tort Liability and Lessons from DES*, 5 *DUKE J. GENDER L. & POL’Y* 167, 169-70

and vaccine study in pregnant people during a public health emergency depresses the uptake of those treatments during pregnancy,⁸⁸ yet exclusion of pregnant people from clinical trials persisted even where fetal death was certain. Pregnant people, for example, “were excluded from Ebola vaccine trials even though all reported pregnancies in Ebola infected women ended in spontaneous miscarriage, stillbirth, and neonatal death.”⁸⁹

As a result of this history, there was a considerable push from international experts to include pregnant people in COVID-19 vaccine trials at the inception of the pandemic. The Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) and COVID-19 Vaccine Global Access (COVAX) Maternal Immunization Working Group, for example, each issued guidance regarding the inclusion of pregnant people in such research.⁹⁰ Their recommendations also cited to numerous studies indicating that pregnant people infected with COVID-19 were at enhanced risk of adverse health outcomes, “including illness resulting in ICU admission, mechanical ventilation, or death,” and adverse birth outcomes, including preterm birth and other pregnancy complications.⁹¹

Unfortunately, this inclusion advocacy on behalf of pregnant people was largely ignored early in the pandemic.⁹² A 2020 review of COVID-

(1998) (explaining that women of reproductive age were largely excluded from clinical studies of HIV and AIDS and that such exclusion “has had a significant impact on the health and welfare of women afflicted with the disease” and “also jeopardizes the health of their potential offspring”).

88. See, e.g., Stefania Triunfo et al., *Increasing Vaccine: Update During Pregnancy by Using Perinatal Education Classes: An Effective Tool for Health Communication and Promotion*, 10 CHILDREN 1, 2 (2023) (noting that “pregnant women generally have a negative attitude about being vaccinated” and “[i]nadequate information, concerns about safety, fear of harming the fetus, and underestimation of the risks related to both illness and infection are the most common explanations for vaccine hesitancy”).

89. Halabi, *supra* note 74, at 735.

90. Carleigh B. Krubiner et al., *Pregnant Women & Vaccines Against Emerging Epidemic Threats: Ethics Guidance for Preparedness, Research, and Response*, 29 VACCINE 85 (2021); COVAX MATERNAL IMMUNIZATION WORKING GROUP, CONSIDERATIONS FOR THE EVALUATION OF COVID-19 VACCINES IN PREGNANT AND LACTATING WOMEN (Feb. 2021), https://media.tghn.org/medialibrary/2021/04/12MAR2021_COVAX_MIWG_Project_report_final.pdf.

91. CONSIDERATIONS, *supra* note 90, at 4; Carla L. DeSisto et al., *Risk for Stillbirth Among Women With and Without COVID-19 at Delivery Hospitalization—United States, March 2020–September 2021*, 70 MORBIDITY & MORTALITY WEEKLY REP. 1640, 1640 (2021).

92. See, e.g., Terra A. Manca et al., *Vaccine Regulation Should Require and Enforce the Inclusion of Pregnant and Breastfeeding Women in Prelicensure Clinical Trials*, 18 HUMAN VACCINES & IMMUNOTHERAPEUTICS 1, 2 (2022) (noting that, while the “discussion about inclusion [of pregnant women] early in COVID-19 vaccine development marked a change from the past, systemic exclusion persisted”).

19 clinical trials that utilized a search of the World Health Organization (WHO) International Clinical Registries Trial Registries Platform (ICTRP) demonstrated that “less than 2% of all COVID-19 registered trials include pregnant women” despite the fact that only three of those trials even involved the use of a medication or supplement.⁹³ A separate 2020 study of 10 international registries found that pregnant people were expressly excluded from 75% percent of those trials.⁹⁴ Yet another study inclusive of 10 randomized controlled COVID-19 vaccine trials found that *all ten* expressly excluded pregnant people.⁹⁵

The exclusion of pregnant people from early COVID-19 vaccine trials was particularly pernicious. That exclusion generated inconsistent guidance from public health, regulatory, and professional authorities, which contributed to delays in vaccine access, vaccine hesitancy, and lower vaccine uptake in pregnant people.⁹⁶ The WHO, for example, initially recommended vaccine avoidance for pregnant people while the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SM-FM) shirked their responsibility by recommending that vaccination decisions should be left to pregnant people and their providers.⁹⁷ ACOG and SM-FM, in fact, waited until the end of July 2021 to recommend that pregnant people take the COVID vaccines.⁹⁸

This is particularly concerning given that it was clear well in advance of July 2021 that pregnant people were more likely to become very sick and die from COVID-19 than non-pregnant people.⁹⁹ It was also known that pregnant people with COVID-19 were at higher risk of hospital admission, oxygen therapy, intubation, pregnancy complications, and

93. Smith et al., *supra* note 2, at 795.

94. Melanie M. Taylor, *Inclusion of Pregnant Women in COVID-19 Treatment Trials: A Review and Global Call to Action*, 9 LANCET GLOBAL HEALTH e366, e366 (2020).

95. Sharon Einav et al., *Inclusion of Pregnant Women in Clinical Trials of COVID-19 Therapies: What Have We Learned*, 125 BRIT. J. ANAESTH. e326, e327 (2020).

96. Mary S. Tschann et al., *COVID-19 Vaccine Hesitancy in the Perinatal Period: A Survey Among Residents of Hawaii*, 3 AM. J. PREV. MED. FOCUS 1, 2 (2024) (pointing out that “COVID-19 vaccination among pregnant [people] has lagged behind the non-pregnant population nationally, even in states where general vaccine uptake is high”).

97. Harriette Gillian Christine Van Spall, *Exclusion of Pregnant and Lactating Women from COVID-19 Vaccine Trials: A Missed Opportunity*, EUR. HEART J. 1, 1 (2021), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7989536/pdf/ehab103.pdf>.

98. Amos Grunebaum & Frank A. Chervenak, *Physician Hesitancy to Recommend COVID-19 Vaccination in Pregnancy as a Cause of Maternal Deaths—Robert Brent was Prescient*, BIRTH DEFECTS RES. 1, 2 (Aug. 28, 2022).

99. *Id.*

stillbirth.¹⁰⁰ The failure to include pregnant people in vaccine trials and, consequently, to recommend that pregnant people take COVID-19 vaccines instigated vaccine hesitancy in pregnant people, “especially among persons of Black and Hispanic race and among younger women (aged 18-24 years),” which “led to a significant increase in maternal mortality at the end of 2021.”¹⁰¹ Unfortunately, the adverse health ramifications experienced by pregnant people due to their exclusion from COVID-19 clinical trials is just one of three recent developments that underscores the urgency to implement experimental research reforms. The second is the Supreme Court’s 2022 decision overturning *Roe v. Wade*, which is the subject of the next sub-section of this article.

B. *The Policing of Pregnancy Drug Use Post-Dobbs*

In 2022, the Supreme Court decided *Dobbs v. Jackson Women’s Health Organization*.¹⁰² *Dobbs* overturned *Roe v. Wade* and *Planned Parenthood v. Casey*¹⁰³ by holding that there is no right to abortion healthcare under the United States Constitution.¹⁰⁴ In anticipation of that ruling, various states began to restrict or criminalize abortion healthcare. Texas, Oklahoma, and Idaho, for example, enacted bounty hunter statutes that permitted private citizens to enforce state abortion laws.¹⁰⁵ Other states had in place dormant abortion-restrictive “trigger bans” that became enforceable once *Dobbs* was decided.¹⁰⁶ Yet others enacted new abortion-restrictive laws after the decision came down.¹⁰⁷

It has been well-documented that states habitually surveilled, policed, and criminalized the “behaviors” of pregnant people before the

100. *Id.* at 2; DeSisto et al., *supra* note 91, at 1640.

101. Grunebaum & Chervenak, *supra* note 98, at 2.

102. 597 U.S. 215 (2022).

103. *Roe v. Wade*, 410 U.S. 113, 164–66 (1973); *Planned Parenthood of Se. Pa. v. Casey*, 505 U.S. 833 (1992) (upholding the constitutional right to an abortion and creating the undue burden standard).

104. 597 U.S. at 302.

105. Emma Bowman, *As States Ban Abortion, the Texas Bounty Law Offers a Way to Survive Legal Challenges*, NAT’L PUB. RADIO (July 11, 2022), <https://www.npr.org/2022/07/11/1107741175/texas-abortion-bounty-law>.

106. See, e.g., Elizabeth Nash & Isabel Guamieri, *13 States Have Abortion Trigger Bans – Here’s What Happens When Roe is Overturned*, GUTTMACHER INST. (June 6, 2022), <https://www.guttmacher.org/article/2022/06/13-states-have-abortion-trigger-bans-heres-what-happens-when-roe-overturned> (listing those trigger-ban states as Texas, Arkansas, Idaho, Kentucky, Louisiana, Mississippi, Missouri, North Dakota, Oklahoma, South Dakota, Tennessee, Utah, and Wyoming).

107. See, e.g., Mitch Smith & Julie Bosman, *Indiana Governor Signs First Post-Roe Abortion Ban, with Limited Exceptions*, N.Y. TIMES (Aug. 5, 2022), <https://www.nytimes.com/2022/08/05/us/indianaabortion-vote.html>.

Dobbs decision.¹⁰⁸ “Pregnancy behaviors” in this context include “actions or conduct engaged in by pregnant persons that the state deems as harmful or potentially harmful to the pregnancy, including, but not limited to, actions or conduct during pregnancy that would not be criminal or punishable if they were engaged in by a non-pregnant person.”¹⁰⁹ States arrested or detained over 1,700 pregnant people in cases where being pregnant was a necessary element of the crime between 1973 and 2020.¹¹⁰

Prosecutors have invoked a litany of laws to charge pregnant people for a wide range of “pregnancy behaviors,” including but not limited to, child abuse, child endangerment, and fetal harm statutes.¹¹¹ Pregnant people are at heightened risk of such charges where their pregnancies end in miscarriage or stillbirth.¹¹² Prosecutors, however, have also brought these charges against post-partum people whose children were born perfectly healthy under theories of attempted child endangerment and attempted fetal harm.¹¹³

Without question, the most frequently targeted and criminalized pregnancy behavior is drug use.¹¹⁴ Although the vast majority of such cases involve the use of illicit drugs during pregnancy, state surveillance of pregnancy drug use includes the surveillance of licit drugs and biologics, particularly where, as is often the case due to the exclusion of pregnant people from drug and biologic clinical trials, prosecutors can advance questionable arguments that the use of a particular medication caused or contributed to an adverse fetal health outcome, miscarriage, or stillbirth. Moreover, there is nothing novel about the suggestion that states will increase their surveillance of licit drug use in pregnant people post-*Dobbs*. States were in the business of punishing pregnant people whose

108. See, e.g., Valena E. Beety & Jennifer D. Oliva, *Policing Pregnancy “Crimes,”* 98 N.Y.U. L. REV. ONLINE 29, 29-30 (March 2023).

109. *Id.* at 32 n.14.

110. ARRESTS AND PROSECUTIONS OF PREGNANT WOMEN, 1973–2020, PREGNANCY JUST. (Sept. 18, 2021), <https://www.nationaladvocatesforpregnantwomen.org/arrests-and-prosecutions-of-pregnant-women-1973-2020>.

111. Beety & Oliva, *supra* note 108, at 34.

112. See, e.g., Lynn M. Paltrow & Jeanne Flavin, *Arrests of and Forced Interventions on Pregnant Women in the United States, 1973–2005: Implications for Women’s Legal Status and Public Health*, 38 J. HEALTH POL. POL’Y & L. 299, 305–09 (2013).

113. See, e.g., *Whitner v. State*, 492 S.E.2d 777, 778–79 (S.C. 1997).

114. *Substance Use During Pregnancy*, GUTTMACHER INST. (Dec. 1, 2022), <https://www.guttmacher.org/state-policy/explore/substance-use-during-pregnancy>; Jeanne Flavin & Lynn M. Paltrow, *Punishing Pregnant Drug-Using Women: Defying Law, Medicine, and Common Sense*, 29 J. ADDICT. DIS. 231 (2010).

newborns tested positive for legally-prescribed drugs before *Dobbs* was decided.¹¹⁵

In sum, *Dobbs* gives the green light to states to enhance their surveillance, policing, and criminalization of drug use during pregnancy.¹¹⁶ As a result, the *Dobbs* decision and its collateral consequences demonstrate the need for urgent implementation of meaningful reforms that ensure the inclusion of pregnant people in drug and biologic clinical trials. Indeed, one of the more troubling *Dobbs*-inspired debacles that implicates the importance of reform in this context is the subject of the following subsection of this article.

C. *The War on Mifepristone*

The ongoing challenge to the FDA's approval of mifepristone currently pending before the United States Supreme Court is an unfortunate by-product of the *Dobbs* decision and particularly worrisome in a regulatory regime that continues to exclude pregnant people from clinical trials. In 2000, the FDA approved mifepristone as the first in a two-drug regime that is used to terminate early intrauterine pregnancies.¹¹⁷ FDA approval of mifepristone was based on three clinical trials conducted in pregnant people, which established the drug's safety and effectiveness for its intended use.¹¹⁸ Mifepristone has proven to be one the safest drugs that has ever gone to market in the United States. As experts have emphasized, it is safer than Tylenol and Viagra.¹¹⁹

The FDA nonetheless placed severe restrictions on mifepristone's distribution and use at the time of its approval. Among other things, FDA only permitted mifepristone to be prescribed by a physician to a patient during an in-person visit up to the forty-ninth day of gestation.¹²⁰ In 2016, the FDA lifted or modified several of mifepristone restrictions based on a

115. Shoshanna Walter, *They Followed Doctors' Orders. Then Their Children Were Taken Away*, N.Y. TIMES MAG. (June 29, 2023).

116. Beety & Oliva, *supra* note 108, at 34.

117. Alliance for Hippocratic Med. v. U.S. Food & Drug Admin., 78 F.4th 210, 223-24 (5th Cir. 2023); Food & Drug Admin., Information about Mifepristone for Medication Termination of Pregnancy Through Ten Weeks Gestation (Mar. 23, 2023), <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-about-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation>.

118. Mifepristone New Drug App, No. 20-687, Medical Officer's Review 2-3, 6 (Jan. 27, 2000), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf.

119. Christine Fernando, *Mifepristone "Safer than Tylenol," Experts Say Amid Court Battle Over Major Abortion Pill*, USA TODAY (Apr. 18, 2023), <https://www.usatoday.com/story/news/nation/2023/04/18/mifepristone-case-abortion-pill-drug-tylenol-fda/11687403002/>.

120. 78 F.4th 210.

litany of data concerning the drug's post-market safety and efficacy profile.¹²¹ It is important to note that the FDA also approved a new and *lower* dosing regimen for the drug in 2016 that is more effective than the initial regimen that the agency approved in 2000.¹²²

Approximately five months after *Dobbs* was decided, the Alliance for Hippocratic Medicine (Alliance), which is an umbrella group composed of physicians staunchly opposed to abortion healthcare, filed a lawsuit against the FDA in the United States District Court for the Northern District of Texas along with several other organizations and individual physicians.¹²³ The plaintiffs sought and received an order from that court enjoining the FDA's initial approval of mifepristone effectively rendering the drug unavailable on the market throughout the United States.¹²⁴ In that lawsuit, the plaintiffs contended that the FDA's approval of mifepristone exceed its authority under the Food, Drug, and Cosmetic Act (FDCA).¹²⁵

The plaintiff physicians involved in the case do not and refuse to provide abortion healthcare, so they are not in the business of prescribing mifepristone. Consequently, they argued that they had standing as a result of (1) the health harms to the very small number of patients who experience adverse events due to mifepristone use and (2) the harms to physicians and the medical system that result from these adverse events, which they contend "consume crucial limited resources . . . , physician time and attention, space in hospital and medical centers, and other equipment and medicines" and cause physicians who oppose abortion healthcare to "feel complicit" in medication abortion due to the need to treat a patient experiencing adverse events.¹²⁶

The FDA appealed the district court's order to the United States Court of Appeals for the Fifth Circuit.¹²⁷ The Fifth Circuit vacated the district court's injunction of the FDA's 2000 approval of mifepristone on the grounds that the plaintiffs' challenge was untimely.¹²⁸ It nonetheless

121. Amicus Brief for Food and Drug Law Scholars and Professors in Support of Petitioners at 7-9, U.S. Food & Drug Admin. v. Alliance for Hippocratic Med., Nos. 23-235 & 23-236 (Jan. 20, 2024) [hereinafter FDA Law Scholars Brief].

122. *Id.* at 7, 9.

123. Alliance for Hippocratic Med. v. U.S. Food & Drug Admin., 2023 WL 2825871 (N.D. Tex. Apr. 7, 2023).

124. *Id.*

125. *Id.* at *9.

126. *Id.* at *4-5.

127. 78 F.4th at 224.

128. *Id.* at 245-46.

affirmed the district court's injunction of the FDA's 2016 decision to (1) lift several of its initial restrictions on the drug's distribution and use and (2) lower the drug's dosing regimen to improve its efficacy.¹²⁹ The Supreme Court granted the FDA's petition for certiorari and the case is slated for oral argument in April 2024.¹³⁰

The mifepristone litigation demonstrates the urgent need to implement reforms that ensure the inclusion of pregnant people in drug and biological clinical trials for at least three reasons. First, if the Supreme Court rules that the respondent physician organizations have standing in this lawsuit, such a decision will open the door to all forms of challenges to the use of FDA-approved medications during pregnancy based on little more than the whims of practitioners morally opposed to various therapeutics. Second, if the FDA's decision to approve and lift restrictions on mifepristone, which is (1) particularly safe and effective relative to other approved drugs and (2) was tested on pregnant people in its clinical trials,¹³¹ can be successfully challenged as scientifically inadequate, most drugs, which (1) have a less desirable safety and efficacy profile than mifepristone and (2) were never tested on pregnant people, are even more vulnerable to challenge, at least insofar as their use by pregnant people is concerned. It is undisputed that all drugs cause adverse events in some subset of patients.

Finally, a Supreme Court decision affirming the Fifth Circuit's injunction of the FDA's 2016 mifepristone restriction and dosing regimen changes would have severe ramifications regarding the FDA's authority to rely on post-market surveillance data to make dosing and restriction adjustments to approved drugs. In reaching its 2016 decision to adjust mifepristone's use and distribution restrictions and lower mifepristone's dosing regimen, the FDA relied on a litany of post-marketing data, including 54 unique studies and 15 years of adverse event reporting.¹³² The Fifth Circuit, however, held that such data was insufficient because it did not include studies that "examined the effect of implementing all of [the] changes together."¹³³ In fact, the court enjoined the FDA's 2016 change in mifepristone's dosing regimen, which the data proves makes the drug *more effective*, on that very rationale.

129. *Id.* at 246.

130. *Food & Drug Admin. v. Alliance for Hippocratic Med.*, No. 23-235, 2023 WL 8605746 (Dec. 13, 2023); *Danco Laboratories v. Alliance for Hippocratic Med.*, No. 23-236, 2023 WL 8605744 (Dec. 13, 2023).

131. *Medical Officer's Review*, *supra* note 118, at 2-3, 6.

132. *FDA Law Scholars Brief*, *supra* note 121, at 7-9.

133. 78 F.4th at 224.

There is no requirement under the FDCA that the FDA examine cumulative effects to approve changes to an approved drug's restrictions or dosing regimen.¹³⁴ As a result, the Fifth Circuit crafted a new requirement out of thin air that would significantly increase the evidentiary burden on drug manufacturers seeking changes to approved drugs based on post-market surveillance data. Drug manufacturers will be even more reticent to seek FDA approval of dosing and other labeling changes to drugs that might better inform pregnant people about the risks and benefits of their use based on pertinent post-market surveillance data. Such a regulatory environment would make it even more difficult for pregnant people to make clinical decisions about drug use and obtain evidence-based care. Consequently, the ongoing mifepristone litigation shines a bright line on the urgent need to collect important pregnancy-related data on drugs and biologics during the pre-approval process.

IV. PROPOSED REFORMS

[R]eforming human research guidelines with a greater participation of pregnant and breastfeeding [people] represents the new paradigm which should allow shifting from protecting these populations from research toward protecting these populations through research.¹³⁵

The implementation of reforms that enhance the inclusion of pregnant people and fetuses in drug and biologic clinical trials are long overdue. Past and present public health emergencies, including the documented adverse health outcomes that resulted from the exclusion of pregnant people from COVID-19 clinical trials, teach that federal "recommendations" for inclusion and other statements of support are woefully insufficient to provoke real change. The prospect of enhanced policing of pregnant people for medication use and challenges to the use of safe and effective medication during pregnancy post-*Dobbs* further demand the immediate development of evidence-based safety and efficacy data regarding drug and biologic pregnancy use. The following section details three meaningful categories of reform aimed at incentivizing the inclusion of pregnant people and fetuses in future clinical research.

134. FDA Law Scholars Brief, *supra* note 121, at 9-10.

135. Librerata Sportiello & Annalisa Capuano, *It is the Time to Change the Paradigms of Pregnant and Breastfeeding Women in Clinical Research!*, 14 FRONT. PHARMACOL. 1, 5 (2023).

A. *Regulatory Reforms*

HHS should implement at least two reforms to the Subpart B regulations that apply to clinical research involving pregnant people and fetuses to harmonize those regulations with the agency's Subpart D rules that apply to pediatric clinical research. First, HHS should jettison from Subpart B the rule that demands dual parental consent where the direct benefit of the research is solely applicable to the fetus¹³⁶ and replace it with the Subpart D rule that permits pediatric research to proceed with single-parent consent.¹³⁷ There is simply no justification for imposing more onerous obstacles to research involving pregnant people and fetuses than the agency imposes on researching involving pediatric subjects. In addition, and as the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLC) explained in its 2018 enumerated recommendations to HHS, maternal consent should be sufficient under Subpart B “[g]iven the recognized autonomy of a pregnant [person and] the evolution of family structure.”¹³⁸

Second, HHS should strike the Subpart B rule that limits fetal research that lacks a direct benefit to no more than a minimal risk because that standard is narrowly interpreted by IRBs to exclude pregnant people and fetuses from the overwhelming majority of clinical research. Instead, and in lieu of the minimal risk rule, HHS should import into Subpart B the “minor increase over minimal risk” standard in Subpart D that applies to pediatric research that has no prospect of a direct benefit to individual subjects.¹³⁹ FDA should also harmonize its rules with or expressly adopt these proposed reforms to Subpart B.

B. *Statutory Mandates and Incentives*

Congress should adopt statutory reforms that mandate and incentivize the inclusion of pregnant people and fetuses in drug and biologic clinical trials. It is worth emphasizing that none of these proposed reforms are strangers to Congress or the FDA. All of them already exist in some form in American law to promote the development of various

136. 45 C.F.R. § 46.204(e).

137. 45 C.F.R. § 46.408(b).

138. Nat'l Insts. of Health, *List of Recommendations from the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)*, <https://www.nichd.nih.gov/about/advisory/PRGLAC/recommendations> (last accessed Feb. 3, 2024); *see also* Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) Report to Secretary, Health and Human Services, Congress (Sept. 2018), https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf.

139. 45 C.F.R. § 46.406.

novel and/or under-researched therapeutics. They simply remain inapplicable to research involving pregnant people.

As noted above, current federal law places additional onerous demands on drug and biologic sponsors who desire to include pregnant people and fetuses in clinical research trials. Worse yet, federal law does nothing to mitigate those additional demands by making them more cost-effective or otherwise appealing to researchers. As such, Congress should amend the FDCA to mandate that the FDA condition certain new drug and biologic applications on the inclusion of pregnant people and fetus in those products' clinical trials.

Congress passed an analogous law that authorizes the FDA to require pediatric testing for both new drugs and biologics and already approved drugs and biologics, subject to certain waivers and requirements, by enacting the Pediatric Research Equity Act of 2003 (PREA).¹⁴⁰ PREA also incentivizes pediatric research by requiring drug and biologic sponsors who seek a waiver from the statute's clinical trials mandate to expressly justify the exclusion of pediatric subjects from such trials.¹⁴¹ Congress should similarly amend the FDCA to require drug and biologic manufacturers seeking a waiver from any requirement to conduct clinical research in pregnant people and fetuses to provide a similar justification.

Congress should further amend the FDCA to permit the FDA to provide additional financial incentives to drug and biologic sponsors that include pregnant people in clinical trials. The FDCA and the federal tax code already authorize the provision of such carrots, such as new drug and biologics application fee reductions and waivers,¹⁴² tax credits,¹⁴³ priority review,¹⁴⁴ and extended market exclusivity,¹⁴⁵ to sponsors in exchange

140. Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, § 505B(a)(2), 117 Stat. 1936, 1936 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.) [hereinafter PREA]; see also Holly Fernandez Lynch, *Give Them What They Want? The Permissibility of Pediatric Placebo-Controlled Trials Under the Best Pharmaceuticals for Children Act*, 16 ANNALS OF HEALTH L. 79, 95-97 (2007).

141. 21 U.S.C. § 355c.

142. See, e.g., 21 U.S.C. § 379h(d) (authorizing the FDA to waive or reduce certain new drug application fees where, among other things, "such waiver or reduction is necessary to protect the public health" or "the assessment of the fee would present a significant barrier to innovation").

143. See, e.g., I.R.C. § 45C (authorizing tax credits for "qualified clinical testing expenses" for orphan drugs).

144. See, e.g., 21 U.S.C. § 360ff (authorizing the FDA to extend priority review to encourage the development of drugs for rare pediatric diseases).

145. For example, Congress amended the FDCA to authorize the FDA to grant an extra six months of market exclusivity to a drug when the drug sponsor conducts pediatric research trials. 21 U.S.C. § 355c; see also Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified at 21 U.S.C. §§ 351 et seq.); Best Pharmaceuticals for Children Act of

for a variety of important research undertakings, including conducting pediatric trials, protecting the public health, developing breakthrough therapeutics, and developing medications that treat rare diseases and conditions. Congress could simply extend these financial incentives to drug and biologic sponsors that agree to conduct research in pregnant people and fetuses. In addition, and as one legal scholar has persuasively argued, Congress also could enact legislation that permits the government to fund clinical trials that include pregnant people and fetuses, much like it funds trials that include pediatric subjects.¹⁴⁶

C. *Liability Reforms*

In addition to the problematic federal regulations detailed above, researchers and IRBs often contend that liability risk is a significant impediment to clinical research projects that include pregnant people.¹⁴⁷ As the literature makes clear, there is little evidence that supports that concern.¹⁴⁸ Moreover, “even if [such] evidence existed . . . the responsibility of the IRB is to protect subjects of research, not to protect researchers from legal liability.”¹⁴⁹ That stated, to the extent that the perception of liability risk continues to serve as a significant obstacle to the inclusion of pregnant people in clinical trials, it might be possible to address that issue by implementing liability reforms that borrow from the no-fault system that applies to certain vaccine injuries.¹⁵⁰

By the mid-1980s, American immunization programs were in peril.¹⁵¹ Vaccine manufacturers contended that vaccine production had become prohibitively expensive as a result of tort litigation and escalating

2002, Pub. L. No. 107-109, § 10, 115 Stat. 1408, 1415 (codified as amended in scattered sections of 21 U.S.C.) [hereinafter BPCA]. Congress also amended the FDCA to authorize the FDA to provide seven years of market exclusivity to orphan drugs. 21 U.S.C. § 360cc(a).

146. Greenwood, *supra* note 24, at 315-22.

147. Anna C. Mastrioianni et al., *Research with Pregnant Women: New Insights on Legal Decision-Making*, 47 HASTINGS CTR. REP. 38, 38 (2017).

148. See, e.g., Jacquelyn Kay Hall, *Exclusion of Pregnant Women from Research Protocols: Unethical and Illegal*, 17 IRB: ETHICS & HUMAN RES. 1, 2 (1995) (explaining that “no proof . . . is evident in the literature” to support “[t]he perception of researchers . . . that the inclusion of pregnant women in a protocol increases the risk of lawsuit to the researcher”).

149. *Id.* at 2.

150. Mastrioianni et al., *supra* note 147, at 42 (explaining that “[t]he literature has long suggested that the primary factor contributing to the exclusion of pregnant [people] from clinical trials is legal liability”).

151. Michelle M. Mello & Troyen A. Brennan, *Legal Concerns and the Influenza Vaccine Shortage*, 294 JAMA 1817, 1818 (2005); Subcommittee on Health and the Environment of the House Comm. on Energy and Commerce, 99th Cong., 2d Sess., Report on Childhood Immunizations 85 (Dec. 20, 1986).

liability insurance expenses.¹⁵² In response, Congress enacted the National Childhood Vaccine Injury Compensation Act of 1986 (NCVA).¹⁵³ The NCVA created the National Childhood Vaccine Injury Compensation System (VICP), which is a no-fault vaccine injury claims resolution system alternative to the traditional tort liability system.¹⁵⁴

Congress could enact legislation that creates a similar no-fault claims system to resolve injuries incurred due to maternal and fetal exposure to experimental drugs during clinical trials to mitigate the liability risk concerns that have been raised by IRBs and researchers to justify their exclusion of pregnant people from research. It is an open question, however, whether such a system would be effective in this context. The Institute of Medicine Women in Health Research Committee considered the adoption of a special no-fault compensation scheme to award damages to children who were injured due to parental clinical trial participation in 1994.¹⁵⁵ The committee declined to recommend the creation of such a system at that time, however, on the grounds that the specialized causation issues that attend to these types of injuries made quantifying the risk of liability especially difficult.¹⁵⁶

Scholars also have criticized the VICP for failing to comport with its intended purpose: ensuring the development and adequate supply of vaccines in the United States by mitigating liability risk for biologic manufacturers. Professors Mello and Brennan have argued, for instance, that the VICP failed to eliminate influenza vaccine shortages in 2004 because those shortages resulted primarily from other factors, such as the relatively low return on investment that attend to vaccines relative to other pharmaceutical products.¹⁵⁷ Mello and Brennan went on to warn American policymakers that they should be wary of arguments from drug and biologic manufacturers that typically blame problems on “mounting

152. *Id.* at 85-89; see also Randall B. Keiser, *Déjà Vu All Over Again? The National Childhood Vaccine Injury Compensation Act of 1986*, 47 FOOD & DRUG L.J. 15, 16 (1992).

153. Pub. L. No. 99 - 660, 100 Stat. 3755 (1986) (codified as amended at 42 U.S.C. § 300aa).

154. Greenwood, *supra* note 24, at 307 (explaining that “[t]he twin goals of the VICP are (1) to offer the families of children injured by vaccines a no-fault alternative to the tort system that provides prompt and fair compensation and (2) to protect vaccine manufacturers from the specter of crippling liability which was threatening the vaccine supply”).

155. INST. OF MED. COMM. ON ETHICAL AND LEGAL ISSUES RELATING TO THE INCLUSION OF WOMEN IN CLINICAL STUDIES, WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 169 (Vol. 1 1994), <https://nap.nationalacademies.org/catalog/2304/women-and-health-research-ethical-and-legal-issues-of-including>.

156. *Id.*

157. Mello & Brennan, *supra* note 151, at 1820.

litigation costs” because other non-litigation market factors are often the dominant drivers of manufacturer behavior.¹⁵⁸ At the minimum, such critiques of no-fault compensation schemes suggest that this reform is unlikely to guarantee the inclusion of pregnant people in clinical trials standing alone. It may, however, help move the needle in the direction of enhanced inclusivity if accompanied by the regulatory and statutory reforms enumerated in the previous sub-sections.

CONCLUSION

Although pregnant people often need to take medications to treat or mitigate health conditions that threaten maternal and fetal health, they have long been excluded from the overwhelming majority of drug and biologic clinical trials in the United States. The reasons cited for such exclusion range from the burdensome federal regulations that prioritize fetal health at the expense of maternal well-being to the lack of incentives to conduct research in this population to liability concerns. As a result, and unlike their non-pregnant counterparts, pregnant people with treatable health conditions are frequently left with two risky choices: take medications that lack adequate pregnancy-related safety and efficacy information or abstain from treatment. Pregnant people, therefore, are often deprived of access to evidence-based care. As the lessons of the COVID-19 pandemic and recent post-*Dobbs* developments teach, the implementation of meaningful reforms that ensure the inclusion of pregnant people in drug and biologic clinical trials are urgent and long overdue.

158. *Id.*