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

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### 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.

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**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.<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup> 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.<sup>4</sup> 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,<sup>5</sup> 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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> 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.”<sup>10</sup> 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.”<sup>11</sup> In research involving neonates, however, only one parent must consent to research involving neonates of uncertain viability,<sup>12</sup> while both parents must consent, with limited exceptions, to research involving nonviable neonates.<sup>13</sup> 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.<sup>14</sup> 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."<sup>15</sup> 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.<sup>16</sup> 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.<sup>17</sup> Manufacturers have also faced the threat of litigation from injured women whose grandmothers had taken DES, although those plaintiffs generally have been unsuccessful.<sup>18</sup> 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<sup>19</sup>—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.<sup>20</sup> 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.”<sup>21</sup> 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.<sup>22</sup> 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.<sup>23</sup> 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,<sup>24</sup> 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<sup>25</sup>; (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<sup>26</sup>; 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,<sup>27</sup> (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.

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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. §§ 46.201–46.207 <http://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. 2011 [http://www.semmes.com/publications\\_archive/litigation/pdf/off-label-use.PDF](http://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](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](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.

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