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The Pathway Forward: *Insights on Factors that Facilitate Research with Pregnant Women*

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ABSTRACT The near-routine exclusion of pregnant women from clinical research has resulted in evidence gaps that endanger the health of pregnant women and their future offspring. Although existing literature documents numerous obstacles along the clinical trial pathway that can stymie research involving pregnant women, there is little guidance on how to facilitate such research. This qualitative study aims to fill that void by examining the experiences of individuals involved in conducting, approving, or overseeing research involving pregnant women at one academic institution. The study identifies factors throughout the clinical pathway—from protocol development, to IRB review, and ultimately trial execution—that likely contribute to the successful conduct of research with pregnant women. Attention to those factors, coupled with agreement among stakeholders that research with pregnant women should and can be done ethically and legally, is critical to shifting the narrative from "why we cannot" do such research to "how we can."

KEYWORDS clinical trials, pregnant research participants, human subjects research, institutional review board (IRB)

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The use of prescription and over-the-counter medications during pregnancy is prevalent in the United States.[1] Most women (97%) take at least one medication while pregnant, and nearly one-third of women take five medications or more during pregnancy.[2] Despite their significant use of pharmaceutical interventions, pregnant women remain "drug orphans."[3] Their near-routine exclusion from clinical trials has resulted in scant scientific evidence to inform their care.[4] Recent studies have determined, for example, that fewer than 3% of medications approved by the U.S. Food and Drug Administration (FDA) have sufficient safety and pharmacokinetic data to guide their use during pregnancy.[5] The evidence gap not only raises ethical questions about fair inclusion in clinical research, but it also endangers the health of pregnant women and their future offspring.[6]

A variety of factors are thought to contribute to the historic and ongoing underrepresentation of pregnant women in clinical research. Society's collective memory of the thalidomide and diethylstilbestrol tragedies is frequently cited as a reason that clinical research with pregnant women lags behind that of other populations, though, ironically, the scope of both tragedies could have been mitigated if the drugs had been studied in pregnant women.[7] The literature also identifies other impediments, whether real or perceived, to conducting research during pregnancy.[8] Those potential obstacles include liability risk for pharmaceutical companies, research institutions, and investigators; difficulty interpreting regulations that pertain to research with pregnant women and fetuses; ethical complexities associated with conducting risk-benefit assessments that involve pregnant women and their potential offspring;

and financial disincentives that deter both public and private funding for pregnancy-related research.[9] Nevertheless, some clinical trials *are* conducted with pregnant women.[10]

Although studies have analyzed the diverse challenges of including pregnant women in clinical trials, we are unaware of any studies that have identified factors that facilitate such research. This qualitative study aims to fill that void by examining the experiences of investigators, institutional review board (IRB) staff members, university administrators, and ethicists at one academic institution who have conducted, approved, or overseen clinical trials involving pregnant women. This work complements and broadens our prior work on how various actors along the clinical research pathway—from protocol development and design to research review and approval and, ultimately, through trial execution and drug approval—affect the inclusion of pregnant women in research.[11] We hope that providing insights on myriad factors that facilitate research with pregnant women will advance the work of investigators, IRBs, and administrators who are struggling to conduct, review, or oversee such research.

STUDY METHODS

We conducted semistructured interviews with investigators, IRB administrators, and university administrators involved in the conduct or review of clinical research involving pregnant women at the University of Washington (UW). A single institution was chosen as the locus of the study to control for institutional factors that may affect the conduct and approval of clinical research. We selected UW because it is a leading U.S. academic research institution that receives significant research funding from the National Institutes of Health (NIH) and because of its proximity to the interview staff, which facilitated recruitment, data collection, and snowball sampling.

To qualify for this study, investigators must have successfully completed a clinical study involving pregnant women (as determined by authorship of a PubMed indexed article published within the five years preceding October 14, 2016) that reported results of a clinical trial of a pharmaceutical drug, device, biologic, or other product (including vitamin supplements) involving pregnant women and was approved by UW Human Subjects Division (HSD) IRBs. To ensure that investigators were likely to have sufficient depth of knowledge to share expertise and experience in response to interview questions, they must have received a terminal degree or foreign equivalent in or prior to 2007. To ensure access for interviews, investigators must have been employed by the UW at the time of interview request.

To identify investigators to interview for this study, we followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[12] (see figure 1, available online; see the "Supporting Information" section at the end of this article). PubMed article abstracts (n = 49) were each screened by two members of the study team. Articles were excluded (n = 28) if the study was not a randomized controlled trial, was nested within a randomized controlled trial, or was a pharmacokinetic study; if the intervention was not a pharmaceutical drug, device, biologic, or other product (including vitamin supplements); or if the incidence of pregnancy was documented but pregnancy-related outcomes were not assessed. Articles were not excluded based on the condition or health status studied.

Nearly all the investigators and noninvestigators we interviewed mentioned the value of consulting with IRBs, both domestic and foreign, throughout the protocol development and design stage.

Full-text articles (n = 21) were then each assessed for eligibility by two members of the study team and excluded (n = 7) if an IRB at UW did not approve the study intervention or protocol or if no pregnant women were enrolled or monitored in the study. The remaining articles (n = 14) revealed 94 independent authors, of whom 72 were excluded because they did not have a UW affiliation listed on the publication. The remaining authors (n = 22) were assessed and excluded (n = 10) using web-based resources to confirm that the author

had a current UW affiliation and had received a terminal degree or foreign equivalent in or prior to 2007. The remaining investigators (n = 12) were contacted via email to participate in this study. Nine responded affirmatively and were able to participate within the study time frame.

Using web-based resources, we determined that the nine investigators who participated in this study had a collective 187 years of experience since receiving their terminal degrees, with a range of 14 to 36 years. Seven of those investigators are women, and two are men. The investigators represent three schools at UW (Medicine, Pharmacy, and Public Health) and hold primary and secondary appointments in eight departments within those schools (Biostatistics, Epidemiology, Global Health, Medicine, Obstetrics and Gynecology, Pediatrics, Pharmacology, and Pharmacy).

Two potential noninvestigator interviewees were identified prior to the study based on their institutional roles and responsibilities as they pertain to the conduct, review, and oversight of research. Snowball sampling identified three more potential noninvestigator interviewees. All five noninvestigators were contacted via email to participate in the study, and all were able to do so within the study time frame.

In total, data were collected from 14 investigators and noninvestigators by in-person interview (n = 12), telephone interview (n = 1), and email exchange (n = 1). The interviews were guided by five open-ended questions (see tables 1 and 2), and responses were probed for clarification and illumination. All in-person interviews were conducted at the interviewees' offices at UW in Seattle, Washington. Interviews lasted between 30 and 60 minutes, were recorded with permission using an Olympus voice recorder, and were transcribed verbatim. Interview staff members also took written notes during interviews to record insights and observations. Study authors used an iterative and collaborative process to develop a detailed codebook and establish intercoder reliability. Two members of the study team coded each interview transcript to ensure consistency in coding. Study staff members then applied all agreed-upon codes to transcript excerpts electronically, using ATLAS.ti.

This study was determined to be exempt from IRB review by UW HSD IRB (UW HSD STUDY00001010). All participants provided oral consent to participation and the use of their titles and research backgrounds in publications. Any responses that participants identified as confidential were omitted from research findings and have not been referenced in this manuscript.

INVESTIGATORS' MOTIVATIONS AND COMMITMENTS

Research success, in general, depends on the sustained commitment of investigators at every stage along the clinical trial pathway. Research with pregnant women is understood to be a particularly thorny area, with potential obstacles arising throughout the pathway. Interviews with investigators revealed a set of common motivations and commitments that drive their interest in and ongoing dedication to research with pregnant women. Most investigators reported professional or personal experiences that influenced and continue to reinforce their decision to undertake research with pregnant women. They tended to share a nearly universal awareness of the scientific evidence gap, as well as a commitment to advancing women's reproductive health and decisions through efforts to close that gap. They also commonly referred to those commitments as

Table 1.
Interview Guide for Investigator Participants

1. Could you describe what prompted you to conduct research with pregnant women?
2. Could you describe your experiences getting approvals to proceed with your research with pregnant women?
3. What factors do you think enhance the likelihood of successfully conducting studies with pregnant women?
4. Could you describe what advice or guidance you would give others who want to conduct research with pregnant women?
5. Were there any documents or individuals you found particularly helpful during any phase of your research in ensuring that your research with pregnant women was ultimately conducted, completed, and reported?

Table 2.
Interview Guide for Noninvestigator Participants

1. Could you describe any of your experiences reviewing and ultimately approving biomedical studies with pregnant women?
2. What factors in the review and approval process of studies involving pregnant women do you think enhance the likelihood of approval?
3. To your knowledge, does the IRB ever contact the [attorney general's/legal] office on issues related to studies involving pregnant women? Vice versa, has the [attorney general's/legal] office ever contacted the IRB about those studies?
4. Could you describe what advice or guidance you would give to researchers submitting proposals or to IRB members or other IRBs reviewing and approving research with pregnant women?
5. Are there any documents or individuals that you have found to be particularly helpful during any phase of your review and approval processes in ensuring that research with pregnant women is allowed to proceed?

justifying the extra time and effort that, in their experience, research with pregnant women demands.

Early career experiences. Investigators frequently cited professional and personal experiences as motivating their research with pregnant women. A few investigators noted that their medical specialization drew them to the research. One, an obstetrician-gynecologist, explained, "[W]omen and their reproductive health concerns and issues are a natural part of what would be of concern and interest to me" (Investigator 8). Another investigator said that "understanding how infections are transmitted from women to children" is a central aspect of being a pediatrician with a subspecialty in infectious disease. "It was part of that clinical interest that got me interested in [research with pregnant women]" this investigator commented (Investigator 9).

Several investigators attributed their interest in conducting research with pregnant women to pivotal moments early in their careers. One investigator, who had worked in Africa during the 1990s when very few HIV+ women or their infants survived, referenced that experience as the start of a continuing focus on HIV prevention research with pregnant women. The investigator explained, "I really wanted to go back and work with that population. . . . The idea that you could prevent almost all of the infants from getting HIV . . . and prevent[] all kinds of maternal morbidity through identification of HIV and early treatment is very attractive" (Investigator 7). Another investigator said that early-career work with mentors who conducted studies with pregnant women had "a big impact" on their subsequent work with that population (Investigator 3). One investigator also said that the personal experience of being pregnant early in her career strengthened her interest in advancing research with pregnant women:

> I did my training with the intent of studying drugs that are used in the transplant population—rejection and drug interactions and that kind of thing. Then I got pregnant with my first child and was really ill and realized at that time that there was almost nothing known about drugs and pregnancy. And when I got pregnant with my second child, there was still nothing known, [and] the skill set I had was easily transferable [to research with pregnant women]. (Investigator 4)

Closing the evidence gap. Investigators' comments demonstrated awareness of the scientific evidence gap resulting from the underinclusion of pregnant women in research. Several investigators offered reasons for the historic and current underrepresentation of pregnant women. One noted that "until fifteen or twenty years ago, it was easy for a researcher to exclude all women from their research [because] they might get periods, [or] they might get pregnant . . . adding increased variability to a research outcome" (Investigator 2). The same investigator emphasized that, although the NIH Revitalization Act of 1993 led to the greater inclusion of women in clinical research,[13] the federal government has not taken the same initiative with regard to pregnant women in research. As that respondent explained, "There's no pregnancy health research institute at the NIH. A pregnancy-based study goes to the NICHD division, the National Institute of Child Health and Development. There's a statement there—there's no 'P' in there. And, well, you would think there's another divi-

sion but there's not. There's never been a [federal] division for pregnancy-based research" (Investigator 2).

Several investigators noted that pregnancy-oriented research has not traditionally received strong financial support from the public sector or private sector. As respondents mentioned, such research may have unfavorable economic outcomes for pharmaceutical companies and other institutions and is viewed by some stakeholders as carrying political or liability risks.

Investigators did not consider the evidence gap as a bar to conducting research with pregnant women but instead viewed it as a motivation and justification for advancing such research. As one investigator put it, "We have diseases that are common [in pregnant women] that we don't know how to take care of. . . . There are huge health care outcomes, quality-of-life outcomes, economic outcomes, and we don't have answers. . . . So that's how you get answers: you do research" (Investigator 2). With respect to the evidence gap, another investigator expressed frustration that when a pregnant patient comes into the clinic already taking medications, "even today . . . if I looked these medications up in my medical database, it wouldn't [include] pregnancy data" (Investigator 7). "If you don't do the research," the respondent continued, "then the problems still remain. They're just silent. Nobody knows about them."

Several respondents cited the potential risks of not conducting research with pregnant women as a reason that doing such research is important to them. One investigator emphasized that, while many pregnant women are prescribed and take FDA-approved drugs, very few of those drugs are FDA-approved *for use during pregnancy.* That distinction matters, the investigator explained, because "what we've found in our research, and [other investigators have] as well, is that the way drugs are handled in pregnancy . . . is probably substantially different than in a nonpregnant person" (Investigator 4). Without adequate information about how specific drugs are metabolized during pregnancy, a noninvestigator noted, pregnant women are "exposing themselves to meds, but they don't know if they [are] exposing themselves to more risk, because the dosage" of medications is neither uniform nor specific to the physiology of pregnancy (Noninvestigator 2). Echoing the sentiment expressed by others, that respondent "became convinced there was so much we didn't know in medicine [about medication use during pregnancy] that we were doing a harm by not doing the research." An investigator similarly observed, "[D]oing nothing has its own risks and benefits, and so that's the comparison" (Investigator 7).

Investigators also described nonmedical benefits of conducting research with pregnant women, including the ability to provide women with more information to guide their reproductive and health care decisions. As one investigator explained, "We can now go to populations and say, this medication has been used in women who have become pregnant while using it, and this is what we know about its safety. That's so much better than the sort of void of information for women who are deciding whether to become pregnant or who are not deciding but just happen to become pregnant when using an HIV prevention intervention" (Investigator 1).

Women's reproductive health and decisional autonomy. For most investigators, their awareness of the evidence gap was closely connected to their commitment to improving women's reproductive health and opportunities for informed reproductive decision-making. For some respondents, improving women's reproductive health was expressed as a critically important aspect of enriching women's health more broadly. One investigator asserted, "[P]retty much everything that I've done comes from a foundation of wanting to optimize or improve women's health" (Investigator 6). Other investigators viewed research during pregnancy as essential to providing women with information to make informed decisions throughout their reproductive years. An investigator whose work focuses on HIV prevention said,

> Women want to know that the product you're developing doesn't negate the contraception that they're on if they don't want to become pregnant. Women want to know that a product they're taking now doesn't have an impact on fertility in the near or, hopefully, in the far term. So, it's not just safety in pregnancy, but the ability to become pregnant. So some of the information that also is really part and parcel of the studies [with pregnant women] was the ability to say this pill didn't interfere with women's ability to use contraception effectively, their ability to become pregnant, and, because we worked in couples, we could say this pill did not interfere in men's ability to father a child. The entire reproductive health picture. (Investigator 1)

That investigator and others shared the view that pregnancy is "not just a condition" that occurs at one moment in time (Investigator 8) but instead is a potential future, present, and past health status that has implications for women's health and permeates women's decisions throughout their lives.

Patience and time. Several investigators suggested that research with pregnant women requires patience, stressing that, in their experience, such research takes more time than research with nonpregnant populations. In describing the IRB review process, for example, one investigator said, "[Y]ou should not expect that you're going to get the same turnaround and approval time frame as studies that you might have completed in the past in the nonpregnant population. I would say that it literally takes double the time." To avoid frustration, that respondent recommended that investigators "change their expectation timewise for [studies that involve] pregnant subjects" (Investigator 4). Another investigator urged similar patience with respect to making progress toward improved health for pregnant women: "You have to have a reasonable time frame. . . . [W]e can all see the second hand move on the clock. If we sit here long enough . . . we see the minute hand move. Does the hour hand move? I'm staring at it, but I can't see it. . . . But you come back in a little while, and you've made progress. You know, incremental progress" (Investigator 2).

Investigators generally justified the extra time involved in their research with pregnant women by referring to their dedication to doing such research. One investigator said, "If I decide I want to create a hepatitis C protocol in pregnancy, no one's going to give me a bunch of time to do that. I'm going to have to figure out how to get it done in between seeing patients and doing C-sections, and various other things. But if it's important enough to me, I'll do it" (Investigator 6). Collectively, investigators' comments suggest that their commitment to conducting research with pregnant women, their patience with what can be a time-consuming process, and their resilience in the face of potential obstacles are factors that propel their research through the clinical trial pathway.

PROTOCOL DEVELOPMENT AND DESIGN

The literature suggests that various features of the IRB review process influence the extent to which research with pregnant women is proposed and approved.[14] There has been little discussion, however, about whether such research is also affected by factors arising at earlier points along the clinical trial pathway. In this study, respondents independently identified aspects of protocol development and design as critical to the success of research with pregnant women. They highlighted consultations with academic colleagues, accounting for pregnant women's needs, building site-specific relationships, minimizing risk, and consulting early and often with the IRB as factors that positively affect subsequent research review, approval, and completion.

Consulting with academic colleagues. Both investigators and noninvestigators consistently referred to consultations with a range of stakeholders during the protocol development and design stage as a factor that contributes to successful research with pregnant women. All respondents viewed academic consultations as playing an important role. As an investigator explained, "[I] usually will check in with others as well to get their thoughts on [the feasibility of a study] because one person might feel that something is totally safe, but a person who's more conservative might say, well, I wouldn't go above this dose, or I wouldn't approach that. And I usually also consult with neonatology . . . on fetal safety and neonatal safety of drug studies" (Investigator 4).

Respondents emphasized the importance of consulting with colleagues outside of their specialty area, whether at UW or another medical center. A noninvestigator recommended "cultivating . . . relationships with other departments" as a first step toward ensuring that any proposed research translates not only across medical specialties (such as obstetrics and infectious disease) but also does so in a way that meets the needs of pregnant women (Noninvestigator 2). Several investigators described receiving similar collegial support from external research networks. One investigator expressed that the network provides a way to have "an ear to the ground [to get a] sense of what's going on," including access to data on exposures and outcomes in pregnancy, and to be "in touch with people who are at that same

leading-edge [as you] across the country" (Investigator 6).

Accounting for pregnant women's needs and daily lives. Most respondents, whether investigators or noninvestigators, expressed the view that successful research with pregnant women begins with, and is driven by, the health needs of that population. Although respondents reported relying on clinicians to inform their understanding of pregnant women's health needs, most respondents underscored the importance of talking with pregnant women directly. Doing so is essential, one investigator said, "[t]o form the research questions and to form the moral arguments behind the research. . . . So, if you ground and aim your research toward the pregnant women's needs, it is both going to be more beneficial for the women and feasible" (Noninvestigator 2).

In addition to soliciting the views of pregnant women directly, or in cases where doing so is infeasible at early stages of study development, another investigator pointed to the usefulness of community advisory boards in eliciting the health needs and interests of pregnant women (Investigator 6). These boards can provide a forum for community members—including pregnant women and women who have been or plan to become pregnant—to participate in the process of planning research to meet their specific needs. The same investigator stated, "If [the research is] relevant to the woman and asks a question that women want the answer to, it's going to be so much easier to do it well" (Investigator 6).

Several respondents suggested that designing research studies that account for the reality of pregnant women's daily lives is equally important. One investigator stressed that an "intervention may be really simple, but the lives of the people in your intervention are very complicated. And you can't divorce those things—they're all part of the same thing . . . so you need to factor all that into the design of the study from the beginning" (Investigator 7). Investigators referred to long study visits, frequent blood draws, onerous surveys, and invasive exams as examples of study requirements that warrant attention during the study development phase because they may prevent or limit pregnant women from participating in or completing the study. Although those activities may be essential to safety or data collection in some studies, respondents emphasized that such requirements should always be driven by "patients in need . . . not an investigator trying to get a publication" (Noninvestigator 2).

Building site-specific relationships. Investigators who have successfully conducted research with pregnant women outside of the United States also stressed the value of building relationships with local stakeholders during the study's development and design stage. In describing why those relationships matter from an early point in the clinical pathway, one investigator said, "It's finding out where the gaps are. It means you need to have some knowledge of the local population, so you know what challenges, what health concerns, what their problems are. If you understand the gap, then you're trying to fill a gap. If you don't understand the gap, then you're . . . [not] addressing the needs of a particular population" (Investigator 8).

In addition to noting the importance of learning about pregnant women's needs, respondents observed that having relationships with local stakeholders also helps investigators think through the implications and perceptions of their proposed research in a particular community. As one investigator put it, conducting research with pregnant women requires "thinking hard and long about the ethics behind it. One has to do a lot of soul searching and discussion with one's colleagues, and people not just at UW, but in the field where you're going to be doing that work, because it's not always clear what adverse effect one might have in another setting—you know, with cultural differences and how something might be perceived, might be stigmatized" (Investigator 3).

Respondents emphasized that initiating early relationships with local team and staff members has other advantages as well. One investigator, who described including local clinicians and researchers in study design, commented that "by the time my project goes to the IRB in [the foreign country] and in the U.S., I feel like it's been vetted by many, many people" (Investigator 7). Other investigators felt that early involvement of local researchers and staff led to a strong collaborative bond that sustained the research study. One said, "I think it's important to have a coresearcher who's at the local site, and that's always been the case on any of our studies. Hopefully, a local lab person, local study coordinators, and that we really have it be a team effort all the way across" (Investigator 6).

The emphasis on "team" planning was shared by other investigators, who used the words "we" and "our" in speaking of the wide-ranging relationships they had initiated and cultivated at trial sites prior to IRB review. One investigator who conducts research with pregnant women in multiple foreign countries and in the United States commented that successful research with pregnant women requires early input from a "very big 'we' . . . the investigators on the study in all the geographies, . . . [t]he IRBs in both places, the drug regulatory authorities in all the places, stakeholders, scientists, governments, civil society . . . then in the places where the work is being done" (Investigator 1). That respondent concluded by noting the importance of "really listening to the stakeholders who'll be most affected" during the early stages of study development and design.

Minimizing risk. Several respondents suggested that research with pregnant women is more likely to receive IRB approval and to enroll participants when investigators have taken steps during the study development and design phase to minimize potential risks to pregnant participants and their potential offspring. One investigator, who referred to the safety of research participants as the "top priority," stressed that minimizing risk "requires more thought than maybe trying to find the answer to the same question in the nonpregnant population" (Investigator 4). In some cases, the respondent explained, minimizing risk may involve, for example, "developing very sensitive assays [that allow] highly capable analytical facilities to study drugs and give very low amounts" of those drugs to pregnant study participants.

Investigators also reported using multipronged approaches to assess risk and provide information about risk and benefit to IRBs and others. Respondents mentioned reviewing relevant publications, requesting data from drug companies and the FDA, and consulting pregnancy-specific exposure and outcome registries and programs.

Consulting with IRBs. Nearly all investigators and noninvestigators mentioned the value of consulting with IRBs, both domestic and foreign, throughout the protocol development and design stage. Multiple investigators viewed the IRB as a valuable resource and described their comfort discussing or identifying controversies or potential study risks with IRB members prior to protocol submission. "One of the things I found helpful," an investigator said, "is that many IRBs are open to discussion before you submit your protocol. You can ask questions. But that's something that most researchers don't make use of" (Investigator 8).

Another investigator described having "lots of conversations with participating IRBs, both here at the UW, but most importantly in the two countries where the study was done, about . . . the extent to which we would take on risk in working with populations who could become pregnant, would become pregnant, and were pregnant, and were breastfeeding. We collectively reached a space [of consensus]" (Investigator 1). Those conversations, the respondent explained, allowed the research team to tell the IRB at the time of submission, "'This is the total package.' Rather than just saying, 'Here's a submitted application,' [the team is] saying 'Here's a submitted application, *and* we'll talk to you,'" throughout the study, from design to completion.

Noninvestigators involved in IRB review similarly commented on the benefits of early-stage discussions with investigators about research with pregnant women. One noninvestigator described those conversations as "collaborative" (Noninvestigator 4). Another noninvestigator urged early consultations with the IRB, noting that fears around IRB review should not deter investigators from pursuing research with pregnant women: "To the researchers, I just would say, 'Do it.' Just do it. You know, ask for the money and the grant support to do it. Consult with the [human subjects research office] if you're worried about it . . . to get a better idea of the criteria and what the rules are . . . and we'll work it out together" (Noninvestigator 5).

RESEARCH REVIEW AND APPROVAL

The scholarly literature often characterizes the research review and approval process as an obstacle along the pathway to conducting research involving pregnant women.[15] In this study, however, both investigators and noninvestigators identified aspects of the review and approval process as facilitating ethical research with pregnant women and mitigating potential barriers to such research. Respondents suggested that regulatory clarity and consistency, institutional efforts to address the complexity of risk and benefit, and a culture of mutual respect between study teams and the

IRB are factors that likely contribute to the successful review and conduct of research with pregnant women.

Regulatory clarity and consistency. Although regulatory ambiguity and inconsistent application of regulatory requirements are potential impediments to research involving pregnant women,[16] several respondents referenced UW policies and procedures as facilitating that research by fostering a common institutional understanding of regulatory requirements and, in turn, promoting consistency in regulatory implementation. Among the materials mentioned were UW's web-based standard operating procedures (SOPs) and worksheets that are readily accessible online.[17]

UW HSD's SOP "supports the policy of providing pregnant women with the same opportunities as nonpregnant women to participate in research unless the individual meets exclusionary criteria or the study poses more than minimal risk to the fetus."[18] That policy, which requires justification for the *exclusion* of pregnant women from research, is supplemented with worksheets that offer procedures and checklists to assist IRBs, investigators, and administrators in applying and interpreting applicable regulations.[19]

Two noninvestigators separately mentioned UW's "flexibility policy"[20] as a significant aid in attempts to increase efficiency in regulatory review and to clarify regulatory interpretations affecting the participation of pregnant women in research. That effort flows from UW's affiliation with the Flexibility Coalition, a multi-institutional group of IRB managers, which was established in 2011 at the University of Southern California. The coalition identifies and shares best practices in interpretation of human subjects regulations to enhance the efficiency of review while ensuring appropriate protection of participants.[21]

The UW "flexibility policy," which applies to research involving pregnant women,[22] articulates the university's interpretations and applications of research regulations based on funding source (such as federal or nonfederal, and also by federal department, such as the Department of Health and Human Services or the Environmental Protection Agency), risk (for example, physical or nonphysical or minimal or more than minimal), and target population (for example, the target of the research or incidental to the research).[23] That guidance, which is translated into simplified expressions of regulatory interpretations and reflected in the aforementioned SOPs and worksheets, allows investigators and reviewers to readily apply UW's official interpretation of federal regulations by answering a stepwise series of questions. As respondents noted, implementation of regulatory requirements is, in turn, more consistent.

Addressing the complexity of risk and benefit. Considerations of risk and benefit are central to ensuring the safety of research participants and are reflected in requirements for regulatory compliance. Nevertheless, the task of applying the two concepts to a proposed study involving pregnant women can prove challenging. The relevant federal regulations governing research with pregnant women and fetuses, collectively referred to as "Subpart B," offer two standards under which the imposition of fetal risk in research with pregnant women is permissible: (1) If the proposed research has "no . . . prospect of direct benefit" for the pregnant woman or fetus, and "the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means," then the research may proceed if the "risk to the fetus is not greater than minimal."[24] (2) If the proposed research offers the "prospect of a direct benefit" to the pregnant woman, the fetus, or both, then risk to the fetus may exceed minimal risk, provided the "risk is the least possible for achieving the objectives of the research."[25]

Respondents commented that, generally, in the absence of further guidance, reviewers tend to "consider the risks to the fetus" only when applying the regulatory standards (Noninvestigator 2). That practice, one noninvestigator remarked, can lead to an "overly conservative" interpretation of what constitutes minimal risk and, ultimately, to the denial of research proposals that include pregnant participants (Noninvestigator 5). The respondent added that, although UW had made such judgments in the past, its institutional approach to minimal risk determinations has evolved and has been informed by input from federal regulators.

UW now provides training to those charged with applying regulatory definitions of risk, a factor some respondents perceived as improving the likelihood that research with pregnant women is approved and conducted. The training includes attention to "the dimensions of risk, [including] the probability that something's going to happen, but also the magnitude of what

can happen . . . how immediately serious the problem is, . . . how recoverable it is, . . . how treatable [it is], [and] what kind of impact will it have on their life" (Noninvestigator 5). In addition, the training instructs reviewers "to take into account not just the absolute risk, but the risk in the context of the protections that the researcher is going to provide" (Noninvestigator 5).

In describing their assessments of risk and benefit, many respondents took a multifactorial approach that accounts for risks to the pregnant woman and fetus of *not* conducting the research, as well as benefits to the fetus that flow from improved maternal health. One noninvestigator, who was involved in a clinical trial of the H1N1 influenza vaccine said, for example, "I think everyone's first question was asking, 'Will this hurt the fetus?' But if we don't give the vaccine, what is the woman's risk of getting the flu? Because . . . then we are allowing other harms to happen [to the pregnant woman and her fetus]" (Noninvestigator 2). An investigator similarly emphasized that many people "only consider the risks to the fetus, but . . . you have to be weighing it against . . . the risks of the underlying [maternal] condition that you're treating. [Research drugs] do have some risks, but it's much lower for both the mother and the fetus than the disease itself" (Investigator 4).

In characterizing their assessments of research with pregnant women, most respondents highlighted the potential downstream benefits of improved maternal health for the fetus. One investigator said, "[I]t's pretty straightforward, really, because if you're thinking about maternal health benefit, you're obviously thinking about fetal health benefit as well" (Investigator 6). Acknowledging that connection, another remarked that the research team "saw the fetus's health was dependent on the woman's health" (Noninvestigator 2).

Culture of mutual respect. Although human subjects research regulations and review are frequently cited in the literature as a perceived obstacle to conducting research with pregnant women,[26] none of the respondents in this study expressed that view. Nearly all respondents perceived UW IRBs as playing a positive and constructive role during the research review and approval stage, and many investigators articulated their respect for the IRB and the work it does. Comments from noninvestigators involved in the research review and approval process suggest that they hold investigators and clinicians in similarly high esteem.

Most investigators acknowledged that IRBs are commonly portrayed as a barrier to research with pregnant women but said that description did not align with their experience, and they cautioned investigators against operating from that premise. One investigator said, "I think people see [the IRB] as the policeman or the big stick at the end of the road, and you avoid them as much as possible until you have no option but to deal with them, and then when you deal with them, and they hit you on the head, you hope it's not too hard" (Investigator 8).

That investigator and others emphasized, however, that IRBs are "not the enemy" (Investigator 2). While some people may have a "them-against-us mentality," another investigator said, "I have never seen it that way" (Investigator 4). A different investigator said, "I'm actually a big fan of the IRB process" because it is "incredibly important for looking ahead, transparency, and intention" (Investigator 1).

Several investigators, in describing their interactions with a UW IRB, referred to their appreciation of its role in protecting various stakeholders. One investigator commented, "You have to realize, first that they're trying to do a good job at protecting [pregnant women]. They're also trying to do a good job protecting the university from outside review and sanction. . . . They're protecting me. And so, in that role, you just have to respect what they're doing—the prima facie evidence that they're collecting—they're just doing their job" (Investigator 2). Echoing that sentiment, another investigator explained, "I think that if you take the stance that [the IRB] is on the same side as the investigator, they're not there to fight you; they're there to help you and better what you're doing. And their interest is in the safety of everyone involved. And in the end, their suggestions are going to protect not only the patients but also you" (Investigator 4).

Investigators' comments suggest that the IRB's familiarity with reviewing pregnancy research engenders trust in the review process, as does the diversity and expertise of IRB members. "I think we have an IRB that's very comfortable doing reviews on pregnancy. They're helpful in guiding language," an investigator said. "There are other IRBs that find that they just don't want to do

anything . . . . [T]hey're not as sophisticated, and [they think] pregnancy is just too complicated" (Investigator 2). Another investigator stressed the value of having various types of expertise among IRB members: "[A]ll the studies I've done have always had an [obstetrician] as one of the committee members in reviewing our studies, and they have either themselves done research in pregnancy or seen enough research in pregnancy to know what's minimal risk and what's not. And I think that's one thing that's good about the UW IRB [process]. . . . There are also people on the IRB who are not clinical people and are intentionally there to get the non-health care provider perspective on it" (Investigator 4).

Noninvestigators expressed respect for the work of clinicians and investigators. One noninvestigator pointed to the value of having clinicians and investigators who have experience in pregnancy research on the IRB, noting that they are "a great resource . . . especially on the practical and logistical challenges of doing research on pregnant women" (Noninvestigator 5). Respect for investigator expertise also influenced each noninvestigator's openness toward and willingness about working with investigators to advance research with pregnant women. As one noninvestigator said, "I start with the assumption that the researchers want to do it this way for some reason. How can we get this study approved? And generally, it works out. . . . In [other] cases, we've actually had to talk to [investigators] and say, 'You know, we aren't going to be able to approve that.' So, I have found that to always be in negotiation—when you're in these situations between us and the researcher—to try to find the best path forward" (Noninvestigator 4). Another noninvestigator commented, "Obviously, this must be done ethically and legally, but we want researchers to be able to do their work" (Noninvestigator 3).

CLINICAL TRIAL EXECUTION

Investigators and noninvestigators emphasized that even after an IRB approves research with pregnant women, certain factors arising during the trial may affect whether the research is successfully completed. An investigator analogized,

> The IRB is kind of like a driver's license—you can get a driver's license but be a terrible driver. And being a good driver is not just about knowing the rules of the road—there's a lot more that goes into being a good driver besides knowing what all the signs mean. And I feel like the IRB is the same thing. Conducting ethical research—the IRB is just one small piece of paper, and there's a whole other thing that goes into it that's way more than IRB approval (Investigator 7).

Respondents cited the following factors as having a positive impact on the conduct and completion of research with pregnant women: efforts during the protocol design stage to account for the realities of pregnant women's daily lives, transparent communication with pregnant women, working with a data safety monitoring board (DSMB), and having an injury compensation program for research participants.

Both investigators and noninvestigators noted that studies designed to account for the daily lives of pregnant and postpartum women have greater recruitment success and higher completion rates than studies that do not make those adjustments. As one investigator explained, "If study visits are lengthy or complicated, that's definitely a barrier [for pregnant women] to being involved in the study" (Investigator 7). Another investigator acknowledged, "It's hard for someone to come in for a bunch of hours and get blood draws. So, if it's an easier study to do, it's obviously easier for the patient to participate in" (Investigator 6). That respondent added that "multiple, 24-hour PK [pharmacokinetic] visits, including after delivery . . . can be very onerous."

While protocol design can anticipate and preemptively address study requirements that may be incompatible with pregnant women's daily lives, investigators commented that flexibility is often required during the study. One investigator, whose research requires postpartum follow-up, expressed it this way: "Really, you stayed up all night breastfeeding for the last three weeks? Do I really want to make you come in several times?" (Investigator 7). Another investigator noted that pregnant women "don't want to come back to clinic all the time. So, we try to piggyback everything [related to the trial] onto the visits they're already coming to" (Investigator 6).

Investigators acknowledged that attentiveness to the unique needs of this population may create "tension between the intensity or quality of the data [and] the burden to the patient" (Investigator 6), which may surface in efforts to publish study results. As one investigator recounted, "I just submitted a paper, and they said,

'I don't understand why you didn't do daily sampling of the women.' I'm like, 'Well they're not mice in a cage!' Daily sampling of women in this [overseas] environment would be very stressful. . . . And the idea that a woman with a two-day-old baby is going to come to clinic every day is not realistic" (Investigator 7).

Most investigators expressed the view that transparent communication with pregnant women throughout the trial is critical to its successful completion. "Once you get all your ducks in a row and everyone lined up and all the permissions," one investigator said, "then you need to have a relationship with the women to recruit them . . . [and] people that can effectively communicate with pregnant women" about the study (Investigator 2). Effective communication, another investigator explained, means "saying what is known and what is not" about study interventions, including that "we have some information about its safety, but not the totality of information about safety. So we're in this . . . shared decision-making about what [the pregnant woman's] reproductive health decisions are and what [her] trial participation decisions are that are going to be balanced and fit [her]" (Investigator 1).

Investigators also highlighted working with a DSMB as a factor that likely contributes to the successful completion of trials involving pregnant women. DSMBs have data and safety monitoring and oversight functions that "are distinct from the requirement for study review and approval by an IRB."[27] As an independent expert committee tasked with periodically assessing study data for participant safety, a DSMB can make data-driven recommendations for the continuation, modification, or early termination of a trial. One investigator explained that "having that something in place to intermittently make sure that risk-benefit [assessments are] there and you're not seeing harm" requires "twice the work in terms of reporting" but "is even more important in studies of pregnant women because of safety to the woman [and] safety to the fetus" (Investigator 5). Intermittent monitoring, other investigators noted, also contributes to communication and transparency, factors that respondents independently associated with successful research involving pregnant women.

In addition, respondents' comments suggest that UW's Human Subjects Assistance Program likely facilitates the conduct and completion of research involving pregnant women. The program is "a discretionary [injury compensation] program that may provide limited medical and other assistance to subjects who experience a research-related medical problem that is more likely than not caused by UW-conducted research."[28] One noninvestigator explained that in the face of concerns about liability for research-related injuries, the program offers "researchers more comfort that they are not going to suffer any ill effects . . . if something happens to go wrong. If they do something like malfeasance or negligence . . . that's a different story, but in any research, things can go wrong that are really nobody's fault. . . . [T]he compensation program is designed to help the subjects and also to protect our researchers" (Noninvestigator 5). That respondent added that, although there are no data about whether the Human Subjects Assistance Program influences decisions about research participation, the UW Medical Center has fewer research-related lawsuits and tort claims than do comparable institutions (Noninvestigator 5).

MOVING BEYOND THE TRADITIONAL NARRATIVE

The scholarly literature documents the long-standing narrative that research involving pregnant women can be stymied at every step of the clinical trial pathway. Although there are calls to facilitate the inclusion of pregnant women,[29] to our knowledge, there has been little insight, if any, on how to support and sustain research with this admittedly "complex"[30] population. This study reveals that a variety of factors throughout the pathway—protocol development and design, research review and approval, and clinical trial execution—likely contribute to the successful conduct of research with pregnant women. Given that some of the factors (such as soliciting views of the population under study, building site-specific relationships, and having and following clear policies) could be considered best practices for any type of research that is otherwise routinely approved, it may be that pregnancy-specific attention to most or even all those factors is essential to overcome the established reticence and well-documented litany of obstacles specific to research with pregnant women. What is patently clear is that efforts to overcome those challenges require that stakeholders throughout the clinical trial pathway be in fundamental agreement that including pregnant women in research

is important and that it should and can be done ethically and legally. This study also suggests that longer-term cultivation of mutual respect among investigators, the IRB, and institutional officials is essential.

Toward this end, our study points to concrete actions that other institutions willing to support such research should consider in order to foster success in this area. Those actions include the following: developing and implementing formal written policies that both express a commitment to research involving pregnant women and delineate a transparent process for its review, developing and requiring formal IRB training on risk assessment and its application to research with pregnant women, and including an obstetrician in institutional research review. Once these actions are carried out or ongoing, a follow-up practical step includes offering consultation opportunities for investigators prior to protocol submission to the IRB.

Implementing these proposals will require arriving at a shared understanding of regulatory interpretations, a process that can take time and entail negotiation among stakeholders, including institutional administrators. A clear tangible longer-term benefit is enhancement of efficiency. Further, over time, actions that promote fair and consistent treatment of research applications should also provide intangible benefits that our findings suggest are crucial to research success, ultimately engendering trust among stakeholders.

The study also suggests that fostering investigators' motivations and commitments throughout the clinical trial pathway is important to success. One practical suggestion is to consider whether institutional incentives need to be developed to foster—or, more neutrally, not discourage—the efforts of investigators and their mentees who are committed to a comparatively time-intensive area of research, the complexity of which results in incremental and important public health successes, rather than revolutionary pharmaceutical blockbusters.

This study underscores that there is no simple fix to address the dearth of research available to support evidence-based decisions involving the health of pregnant women. Attending to just one aspect of the concrete suggestions above is unlikely to ensure success, as respondents respectively attributed success to several factors, which likely incrementally and iteratively lead to success.

This study does not intend to suggest that responsibility for advancing research with pregnant women lies solely with investigators, IRBs, and institutions. We acknowledge that each stakeholder along the clinical trial pathway (public and private funders, research agenda setters, regulators, outside collaborators and IRBs, and participants associated with the research studies discussed in the interviews) could have important insights on factors that facilitate research. Accessing those insights—though beyond the scope and time constraints of this study—is worthy of investigation. Nonetheless, a consensus on the core point reflected in our interviews—an acknowledgment of the importance and feasibility of this research—is arguably implied by the success of the research studies represented in our interviews.

The insights emerging from our interviews may be limited by the relatively small sample size. We chose to interview those who had been successful in areas of research known to be most challenging in this population, that is, trial interventions involving drugs, devices, biologics or other products (versus behavioral and observational trials). Further, because we intentionally focused on learning from research successes, our findings do not reflect data from investigators who have been unsuccessful in pursuing this research, who, if recruitment difficulties were overcome, might present a counterview. Lastly, there may be features specific to this one institution that may facilitate the conduct and completion of research with pregnant women, such as UW's Human Subjects Assistance Program, which may shift the traditional narrative about liability to support this research.

The ethical principle of justice demands the inclusion of pregnant women in research. Their ongoing underrepresentation leaves health care providers without adequate evidence to make treatment decisions, an outcome that unfairly denies pregnant women and their potential offspring the benefits of health research.[31] The comments and experiences of respondents in this study align with previous conceptual work on the implementation of the ethical principle of justice in human subjects research more generally.[32] That work emphasizes the collective need for attention to issues of equity throughout the clinical trial pathway. "[W]hat I say all the time," one of our respondents asserted, "is that there

is a pathway for this, the regulations have a path for this, let's walk down that path" (Noninvestigator 4). The traditional narrative of "why we cannot" must shift to "how we can." ♦

SUPPORTING INFORMATION

The figure is available in the "Supporting Information" section for the online version of this article and via *Ethics & Human Research*'s "Supporting Information" page: https://www.thehastingscenter.org/supporting-information-ehr/.

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DISCLOSURE

The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of BluePath Health, Hyman, Phelps & McNamara, or any of their clients.

REFERENCES

1. Wyszynski, D. F., and K. E. Shields, "Frequency and Type of Medications and Vaccines Used during Pregnancy," *Obstetric Medicine* 9, no. 1 (2016): 21-27.

2. Haas, D. M., et al., "Prescription and Other Medication Use in Pregnancy," *Obstetrics & Gynecology* 131 (2018): 789-98.

3. Scaffidi, J., B. W. Mol, and J. A. Keelan, "The Pregnant Woman as a Drug Orphan: A Global Survey of Registered Clinical Trials of Pharmacological Interventions in Pregnancy," *BJOG: An International Journal of Obstetrics & Gynaecology* 124, no. 1 (2017): 132-40, at 132.

4. Shields, K. E., and A. D. Lyerly, "Exclusion of Pregnant Women from Industry-Sponsored Clinical Trials," *Obstetrics & Gynecology* 122 (2013): 1077-81.

5. McCormack, S. A., and B. M. Best, "Obstetric Pharmacokinetic Dosing Studies Are Urgently Needed," *Frontiers in Pediatrics* 2 (2014): doi:10.3389/fped.2014.00009; Adam, M. P., J. E. Polifka, and J. M. Friedman, "Evolving Knowledge of the Teratogenicity of Medications in Human Pregnancy," *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 157C, no. 3 (2011): 175-82.

6. Van der Graaf, R., et al., "Fair Inclusion of Pregnant Women in Clinical Trials: An Integrated Scientific and Ethical Approach," *Trials* 19, no. 1 (2018): doi:10.1186/s13063-017-2402-9; Baylis, F., "Pregnant Women Deserve Better," *Nature* 465 (2010): 689-90.

7. Van der Graaf et al., "Fair Inclusion."

8. Van der Zande, I. S. E., "Fair Inclusion of Pregnant Women in Clinical Research: A Systematic Review of Reported Reasons for Exclusion," in *Clinical Research Involving Pregnant Women*, ed. F. Baylis and A. Ballantyne (Switzerland: Springer International Publishing, 2016), 65-94.

9. Krubiner, C. B., et al., "Advancing HIV Research with Pregnant Women: Navigating Challenges and Opportunities," *AIDS* 30 (2016): 2261-65; Strong, C., "Minimal Risk in Research Involving Pregnant Women and Fetuses," *Journal of Law, Medicine & Ethics* 39, no. 3 (2011): 529-38; Greenwood, K., "The Mysteries of Pregnancy: The Role of Law in Solving the Problem of Unknown but Knowable Maternal-Fetal Medication Risk," *University of Cincinnati Law Review* 79, no. 1 (2010): 267-322; Ells, C., and C. Lyster, "Research Ethics Review of Drugs Trials Targeting Medical Conditions of Pregnant Women," in *Clinical Research Involving Pregnant Women*, ed. F. Baylis and A. Ballantyne (Switzerland: Springer International Publishing, 2016), 95-118.

10. Wickremsinhe, M., et al., "Beyond 'Vessels and Vectors': A Global Review of Registered HIV-Related Clinical Trials with Pregnant Women," *Journal of Women's Health* 28, no. 1 (2019): 93-99.

11. Mastroianni, A., et al., "Research with Pregnant Women: New Insights on Legal Decision-Making," *Hastings Center Report* 47, no. 3 (2017): 38-45.

12. Liberti, M. D., et al., "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement," *PLoS Medicine* 6, no. 7 (2009): e1000097.

13. National Institutes of Health Revitalization Act of 1993, Pub. L. No. 103-43, 107 Stat. 122 (1993).

14. Blehar, M. C., et al., "Enrolling Pregnant Women: Issues in Clinical Research," *Women's Health Issues* 23, no. 1 (2013): doi:10.1016/j.whi.2012.10.003; van der Zande et al., "Fair Inclusion of Pregnant Women"; Sahin, L., "The FDA Perspective on the Ethical Barriers of Conducting Research in Pregnant Women," *AJOB Primary Research* 2, no. 1 (2011): 13-14.

15. Blehar et al., "Enrolling Pregnant Women"; Levine, R. J., "IRB Perspective on Inclusion of Pregnant Women in Clini-

cal Research," in *Enrolling Pregnant Women: Issues in Clinical Research*, ed. M. Blehar (Bethesda, MD: National Institutes of Health, Office of Research on Women's Health, 2010), 37-43; Krubiner et al., "Advancing HIV Research"; Mastroianni et al., "Research with Pregnant Women"; Saenz, C., et al., "Ethics, Regulation, and Beyond: The Landscape of Research with Pregnant Women," *Reproductive Health* 14 (2017): doi:org/10.1186/s12978-017-0421-3. For documentation of a more general critique of IRBs, see Silberman, G., and K. L. Kahn, "Burdens on Research Imposed by Institutional Review Boards: The State of the Evidence and Its Implications for Regulatory Reform," *Milbank Quarterly* 89 (2011): 599-627.

16. Mastroianni et al., "Research with Pregnant Women."

17. University of Washington, Human Subjects Division, "Worksheet: Pregnant Women," in "Policies, Procedures and Guidance," December 13, 2019, at https://www.washington.edu/research/forms-and-templates/worksheet-pregnant-women/; University of Washington, Human Subjects Division, "Pregnant Women, or Fetuses," in "Policies, Procedures and Guidance," last updated November 15, 2019, at https://www.washington.edu/research/policies/sop-pregnant-women-2/.

18. University of Washington, Human Subjects Division, "Pregnant Women, or Fetuses."

19. University of Washington, Human Subjects Division, "Worksheet: Pregnant Women."

20. "eNews re: IRB Review—June 3, 2014—Flexibility Is Coming to HSD," University of Washington, Office of Research, June 4, 2014, https://www.washington.edu/research/announcements/enews-re-irb-review-june-3-2014-flexibility-is-coming-to-hsd/; University of Washington, Human Subjects Division, "Policy: Regulations," in "Policies, Procedures and Guidance," implemented December 28, 2018, at https://www.washington.edu/research/policies/policy-regulations/.

21. "Flexibility Coalition," University of Southern California, accessed April 25, 2020, https://oprs.usc.edu/hspp/flexibility-coalition/.

22. University of Washington, Human Subjects Division, "Policy: Regulations."

23. Ibid.

24. 45 C.F.R. 46.204(b).

25. 45 C.F.R. 46.204(b)-(d).

26. Mastroianni et al., "Research with Pregnant Women."

27. "Policy for Data and Safety Monitoring," National Institutes of Health, June 10, 1998, https://grants.nih.gov/grants/guide/notice-files/not98-084.html.

28. University of Washington, Human Subjects Division, "Human Subjects Assistance Program," in "Policies, Procedures and Guidance," updated February 5, 2018, at https://www.washington.edu/research/policies/human-subjects-assistance-program-2/.

29. Lyerly, A. D., M. O. Little, and R. Faden, "The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research," *International Journal of Feminist Approaches to Bioethics* 1, no. 2 (2008): 5-22; Little, M. O., and M. N. Wickremsinhe, "Research with Pregnant Women: A Call to Action," *Reproductive Health* 14, supplement 3 (2017): doi:10.1186/s12978-017-0419-x; Baylis, F., "Pregnant Women Deserve Better," *Nature* 465 (2010): 689-90.

30. Blehar et al., "Enrolling Pregnant Women," 4.

31. Van der Graaf et al., "Fair Inclusion of Pregnant Women"; Lyerly, Little, and Faden, "The Second Wave"; Baylis, F., and A. Ballantyne, "Missed Trials, Future Opportunities," in *Clinical Research Involving Pregnant Women*, ed. F. Baylis and A. Ballantyne (Switzerland: Springer International Publishing, 2016), 1-16.

32. Kahn, J. P., A. C. Mastroianni, and J. Sugarman, "Pursuing Justice in Research," in *Beyond Consent: Seeking Justice in Research,* 2nd ed. (New York: Oxford University Press, 2018), 208-15; Mastroianni A., R. Faden, and D. Federman, eds., *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies* (Washington, DC: National Academies Press, 1994), 203-11.

ERRATUM

In the May-June 2020 issue, the article "The Importance of Engaging Children in Research Decision-Making: A Preliminary Mixed-Methods Study" (*Ethics & Human Research* 42, no. 3 [2020]: 12-20, doi:10.1002/eahr.500049) listed the authors' names in incorrect order. The correct order is Erin Talati Paquette, Hannah Palac, Elizabeth Bair, Blake Schultz, Nicole Stenquist, Avani Shukla, and Steven Joffe.

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