Exclusion of Women from Phase I Trials: *Perspectives from Investigators and Research Oversight Officials*

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ABSTRACT Over the past 30 years, progress has been made in increasing women's representation in clinical research. However, women continue to be underrepresented in phase I clinical trials—those trials that test the safety and tolerability of investigational drugs, often on healthy individuals. As sex-based differences in adverse drug reactions are often linked to drug dose, pivotal safety information in phase I trials is often insufficiently—and inequitably—captured for females. Yet there has been little attention to how clinical investigators and those charged with overseeing the ethical conduct of these trials perceive the barriers to women's inclusion in phase I trials. To address this gap, we report on 22 interviews with U.S. phase I investigators and institutional review board (IRB) members. Our findings indicate that although these investigators and IRB members acknowledged the importance of including women in clinical trials, they justified women's exclusion from phase I trials by citing the need to manage their reproductive potential. In particular, we identified four key themes that informants used to warrant women's exclusion from phase I trials: the structure of the drug-development system itself, fears about risks to potential fetuses, distrust of women to prevent pregnancy, and concerns about risks and burdens to institutions from resulting pregnancies. We argue that these rationales reflect structural and cultural barriers to women's inclusion in clinical research that ultimately fail to respect female research participants as persons, highlighting the need for broad-based solutions.

KEYWORDS phase I clinical trials, women, respect for persons, inclusion, risk, androcentrism

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The National Institutes of Health (NIH) established the Revitalization Act nearly 30 years ago, requiring women and members of racial and ethnic minority groups to be included in NIH-funded clinical research.[1] Since then, women's participation in NIH studies has increased to over 50% overall, although gender disparities remain.[2] Moreover, women are still poorly represented in industry-sponsored research and in early phases of clinical research, especially phase I studies.[3] From the early 1990s to 2010, for instance, women accounted for just 22% of phase I participants.[4] A more recent study found that from 2013 to 2015, still only 29 to 31% of phase I participants were women.[5]

Phase I clinical trials test the safety and tolerability of investigational drugs, often in healthy individuals. Healthy volunteers, who have no possibility for direct medical benefit from participating, are enrolled to help investigators determine a drug's safety profile without the ambiguity that could arise from symptoms associated with an underlying disease or condition.[6] Participants are often required to be confined to a residential research clinic during the trial, and they are incentivized to participate through monetary compensation.[7] While the inclusion of women is important in later-phase clinical trials to determine drug efficacy across different populations, it is critical for women to be in-

cluded in phase I trials because these studies establish drug doses that carry forward into later-phase trials and clinical use. As sex-based differences in adverse drug reactions are often linked to drug dose, pivotal safety information in phase I trials is often insufficiently—and inequitably—captured for females.[8] However, this has been an underexplored issue in the literature on the ethics of early-phase clinical trials.

Previous research has examined the motivations of healthy volunteers who enroll in phase I research,[9] and some of these studies have specifically explored the experiences of healthy volunteers who are women.[10] Those latter empirical studies highlight the important barriers unique to women's phase I participation. For instance, women who want to enroll in phase I trials face the hurdle of having to prove repeatedly that they are not pregnant.[11] As a result of the pervasiveness of trial protocols that exclude or severely restrict the participation of women of "childbearing potential," some women have even undergone sterilization to be eligible to participate and earn income through these clinical trials.[12] Once enrolled, women also face "more subtle forms of discrimination that act as impediments to participation" stemming from an unwelcoming environment within the clinic.[13] Jain and colleagues found that healthy women volunteers report being seen by research staff as more "difficult" participants because of their menstrual cycles and purported worse venous access compared to men.[14] In addition, clinics do not always provide women sleeping quarters that are separate from men, which can cause women to feel stressed, unsafe, or uncomfortable during studies' clinic confinement period.[15]

While women's experiences of phase I participation have been examined, attention to how clinical investigators and research oversight committees perceive the inclusion of women in biomedical research and to the associated ethical issues that emerge is lacking. To address this gap and to evaluate progress on inclusion in the particular context of early-phase trials, we report

Table 1.
Demographic Characteristics of Interviewees (N = 22)

	Variable	*Frequency*	*Percentage*
Interviewee group	IRB	10	45.5
	Phase I investigator	12	54.5
Institution type	Private academic institution	6	27.3
	Public academic institution	3	13.6
	Institution other than academic	13	59.1
Gender	Man	14	63.6
	Woman	8	36.4
Race	More than one race	1	4.5
	White	21	95.5
Ethnicity	Hispanic or Latino	2	9.1
	Not Hispanic or Latino	20	90.9
Education	Some college	1	4.5
	Bachelor's degree	4	18.2
	Graduate degree	17	77.3
Time in the field	2-5 years	1	4.5
	6-10 years	3	13.6
	11-20 years	6	27.3
	20+ years	12	54.5

on interviews with U.S. phase I investigators and institutional review board (IRB) members on their perceptions of barriers to including women in phase I healthy volunteer trials and clinical trials more generally. We show how these identified barriers serve as rationales for the continued exclusion of women from phase I trials. Based on these findings, we argue that these rationales reflect structural and cultural barriers to women's inclusion in clinical research that ultimately fail to respect female research participants as persons.

STUDY METHODS

This study was nested within a broader research project on comparative research ethics in phase I healthy volunteer trials and nonhuman animal research.[16] For the phase I portion of the study, we conducted a total of 22 interviews with phase I investigators (12) and IRB members (10). Interviews were conducted via telephone between October 2018 and January 2019. The Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill reviewed and approved the study.

We identified potential participants through online searches of U.S. phase I clinical research units and central IRBs, as well as IRBs associated with academic medical centers that conduct a large volume of phase I healthy volunteer trials. Potential participants were contacted by email, given an information sheet about our study, and invited to take part in a phone interview. For those who scheduled an interview, verbal consent was given before the interview commenced. On average, interviews lasted 84 minutes. All interviews were audio-recorded and transcribed. Identifying information was stripped from transcripts to protect participants' confidentiality.

Although the interviews covered a diverse array of topics related to phase I trials, such as the risks to healthy volunteers, recruitment and selection of healthy volunteers for trials, and the research oversight system, questions about sex as a biological variable and the inclusion of female participants in clinical trials were central to the study. Specifically, we asked about reasons to exclude people from participating as healthy volunteers in phase I trials, the process of including or excluding people of childbearing potential from trials, the contraception restrictions or requirements and pregnancy-testing procedures used in studies, the protocol employed when a healthy volunteer becomes pregnant during a trial, and perception questions about the importance of including all sexes in phase I trials.

So that we could analyze the transcripts, detailed notes that included summaries of participants' answers to each of the domains of the interview were written for all the interviews. We used these memos as the basis for an initial discussion about the findings and to identify major themes that emerged related to the inclusion of females in phase I trials. Next, we read the portions of the transcripts relevant to this topic to further explore those themes, and we again discussed the findings, adding nuance to the identified themes and selecting quotations that best illustrated them. This iterative process allowed us to attend both to what people said in the interviews and to the implications of the information and opinions they provided.

Our data suggest that many of the cultural themes that contributed to the underrepresentation of women across clinical trials prior to the 1990s still shape sex-based research exclusions.

STUDY RESULTS

Twenty-two interviews were conducted with IRB members (10) and phase I investigators (12). Of the IRB members, half (5) worked at universities. The other half (5) worked at central IRBs. Most phase I researchers (8) worked for private-sector research clinics. The majority of interviewees (12) had more than twenty years of experience in their respective fields. Over half of the interviewees identified as men (14), and 8 identified as women. Additional demographic characteristics are presented in table 1.

Overall, interviewees expressed support for the inclusion of women in clinical trials and acknowledged the importance of diversity among phase I participants. For instance, one phase I investigator said, "I think in

general it's important to include women in the studies because [of] just differential effects that a drug can have depending on sex. So, I think it's very important to make sure that women are included from a very early stage" (PI10). Another investigator echoed this sentiment, saying that including women in phase I trials is "more equitable. You get safety data on women, which may be different than safety data on men, sooner. So, in the grand scheme, the thought is if done well, you're doing the research process better" (PI03). Other interviewees recognized the importance of including women not just in phase I trials but also in clinical trials more generally. As an IRB member said, "Not really specific to phase I trials …, we certainly want women to be enrolled in trials, phase I or other" (IR02).

Despite acknowledging the importance of including women in phase I trials and clinical trials more generally, interviewees emphasized or alluded to various barriers to enrolling women in early-phase trials that ultimately warranted their exclusion. Central to their concerns was managing women's reproductive potential. Phase I trials, especially first-in-human trials, often include healthy individuals only between the ages of 18 and 45, an age bracket corresponding to the average adult female's reproductive years. As we document in what follows, phase I investigators and IRB members often characterized decisions to exclude women from such trials as ethically reasonable or responsible, justifying such exclusion because of the structure of the drug-development system itself, fears about risks to potential fetuses, distrust of women to prevent pregnancy, and concerns about risks and burdens to institutions from resulting pregnancies.

The drug-development system. According to interviewees, a major barrier to women's inclusion in phase I trials is the structure of drug development itself. A phase I investigator stated, "What limits participation of women of childbearing potential in phase I clinical trials is the structure of the process …. As you know, [the] pharmaceutical industry is a race. Okay? So, pharma companies want to start testing as soon as possible" (PI05). Within this race, efficiency is often valued over inclusion. Preclinical, nonhuman animal developmental and reproductive toxicology (or DART) studies are not mandated by the U.S. Food and Drug Administration (FDA) prior to human testing, but they may be required before women of childbearing potential can be enrolled.[17] DART studies can be expensive and time consuming, so companies may opt to conduct them later in the drug-development pipeline. Absence of reproductive toxicity data at the time phase I trials commence has been, and is still, used as a reason to exclude women of childbearing potential from phase I studies. The same phase I investigator explained, "Very often, when they [pharmaceutical companies] are ready to do a first-in-human study, for example, right, their reproductive tox is not completed. So, at that time, *ethically and humanely, you can't enroll a woman of childbearing potential* …. There's no data, zero reproductive data. And, just for the sake of expediency, that's what happens" (PI05; emphasis added).

An IRB member echoed this point, explaining that "a lot of times, they don't have all the repro-tox—reproductive toxicity—studies back from preclinical in time. So, *it doesn't make sense to have women in that stage*" (IR07; emphasis added). However, a phase I investigator noted shifts in the drug-development system over time, saying, "There was a little bit of a renaissance, and I don't know if this was because of the FDA's rules or different perspectives, but … there were different guidances put out about women of childbearing potential, and some of the preclinical studies were advanced sooner. It used to be those studies weren't done until later in the development pipeline. Now they're done a little bit sooner, so [women are] more eligible" (PI03). Notwithstanding these changes to drug-development timelines, preclinical studies are still not always completed early enough to militate against the exclusion of women in phase I trials.

Even though the priority placed on speed within drug development restricts or excludes women's inclusion, most interviewees did not express concern about women's absence in phase I trials. Instead, they trusted that the drug-development system would ensure that women were included in later phases. Summarizing this sentiment, one IRB member said that "by the time it gets into patients and before the FDA's going to put it on your shelf, it's got to have included women" (IR07). Therefore, she continued, "phase I in healthies [healthy volunteers] as a subset or as a phase, they don't have to always have women." She justified this position by adding, "So again, we're just seeing if something is safe [in phase I trials]. We're not trying to see if it works. So, re-

ally, where women benefit is if it works for them" (IR07). In other words, according to this interviewee, including women mainly matters in later phases for sex-based determinations of efficacy, not safety. Another IRB member described how internal processes at her IRB support the inclusion of women in later phases of trials, but not necessarily phase I. When asked about protocols that exclude women of childbearing potential, she said, "I wouldn't say we push back too, too much on investigators to justify that. We *have*. Every once in a while, we will get a team that just does not want to adhere to our pregnancy-testing policy, and they will say, 'We don't want to enroll women of childbearing potential.' We will definitely push back and say, 'What's the rationale here?' Again, we wouldn't do that for a phase I study, but we definitely would query the study team if they were just trying to enroll for a convenience reason" (IR02). Thus, this interviewee's IRB did not necessarily challenge the exclusion of women from phase I trials overall, but it would require a scientific reason to do so, and as we have already noted, the lack of preclinical reproductive toxicity data is typically a sufficient—if not compelling—reason for that choice.

Fear of fetal and reproductive risks. Underlying the exclusion of women of childbearing potential from phase I trials—particularly when there is a lack of preclinical data—is the fear of possible reproductive risks for women of childbearing potential. When articulated by our informants, these risks extended to, and often centered on, risks to potential fetuses. Embedded in this construction of risk is another key barrier—the presumption that any reproductive-aged woman may become pregnant during a clinical trial. In this view, excluding all women of childbearing potential from phase I trials is the only way to control risk to potential fetuses. For example, when asked how the participation of women of childbearing potential should be managed in phase I trials, a phase I investigator said, "If it's a drug that is known to have effects on a developing fetus, it just doesn't make any sense to put people at risk that way …. When you're talking about a first-in-human trial, and you don't—even if all your preclinical data doesn't point to anything, you really don't know [the risk to fetal development]. And consequently, I tend to prefer enrolling people that are not of childbearing potential in trials like that … . So, the less I know about the drug, the more potential for fetal harm, the more I would tend to want to dose only women not of childbearing potential" (PI07).

For this interviewee, even if preclinical studies had already been completed without generating any signals of fetal harm, potential risks to a possible fetus still justify excluding women of childbearing potential. In other words, uncertainty about fetal harm is interpreted as unacceptable risk in phase I trials. The point about protecting possible fetuses was taken even further by an IRB member who said, "There may be a concern related to future birth defects, if there's something that lingers around in the system for a long time. Or you just don't know and you want to do this first because it's a feasibility, pilot-y kind of project in the very beginning and you want a uniform study population. Those are all like scientific reasons that I think you can justify" (IR03). Thus, in addition to concern about pregnancies that could occur during a phase I trial, the fear of reproductive harm extended to future potential fetuses, providing some interviewees a further reason to exclude women of childbearing potential.

Other interviewees raised concerns about risks to women's future fertility. One phase I investigator described conducting a study in which early preclinical data showed no genotoxicity effects, so they enrolled women who were using contraception. However, he said additional preclinical data later revealed a "concern that there may be longer-term impact on fertility of women, so we had to exclude enrolling new women of childbearing potential" (PI03). As a result of such concerns about the possibility of harm to women's fertility as well as to potential fetuses, some interviewees preferred not to enroll women of childbearing potential in early-phase trials at all. This is clearly illustrated by the phase I investigator who said, "In general, I believe that women of childbearing potential should be enrolled later [rather than earlier] in the clinical trials [process] as much as possible, because as it is, we have drugs with very poorly defined reproductive risk" (PI05). None of our informants discussed similar concerns about or exclusion criteria for men.

Lack of trust in women of childbearing potential. Fears of risks to potential fetuses translate into contraceptive requirements that are stricter for women who want to participate in early-phase trials than for men—

an additional barrier to including women that our informants illustrated is based in mistrust rather than objective risk mitigation. Contraceptive requirements, however, often do not include conventional hormonal contraceptives, so some of the most effective forms of preventing pregnancy also exclude women from participating out of concern about drug-drug interactions. Instead, contraceptive requirements focus on surgical sterilization or menopause confirmed by blood hormone levels. Notably, these requirements also remove any doubt about women's fertility given that they do not rely on participants' word about their sexual or contraceptive practices. Nonetheless, women of childbearing potential may be allowed to enroll in phase I trials if they are using a double-barrier method of contraception (i.e., a condom or occlusive cap with spermicide) or, albeit more rarely, if they are abstinent. As other authors have noted, there is no FDA or international guidance that specifies what contraceptive requirements are used in clinical research protocols,[18] and there is considerable variation in what pharmaceutical companies and IRBs require.[19] More broadly, requirements tend to assume women are heterosexual and sexually active.[20]

Interviewees acknowledged the major differences in contraceptive requirements for men and women in phase I trials. Standard practice in informed consent documents, as our informants confirmed, is to include separate paragraphs about contraception for female and male participants. An investigator emphasized that there are often "rigorous requirements for women to agree to multiple forms of contraception even if they're not in an existing sexual relationship" (PI09). Many respondents cited the prospect of harms of fetal exposure to a drug if a participant became pregnant during the trial as the main reason for these different contraceptive requirements by sex. However, explanations for why they differed also extended beyond biological rationales. For instance, one IRB member referred to the varying requirements as "an unfortunate societal thing" (IR02). Another expanded on this point, saying, "I guess the first thing that comes to mind is just, you know, sociologically in the culture of the United States, whether it's good or bad, I would say that because usually it is the woman who traditionally takes responsibility for contraception, so that's probably why there is a difference that's rolled over into research" (IR01).

Because contraceptive requirements are influenced by social norms and assumptions, sponsors may even push back on additional requirements for men enrolled in studies. Another IRB member explained, "Sponsors were already pretty well trained to be clear about what the birth control requirements were for women, but when you came in and wanted to put in a warning about potential defects from sperm and not permitting sperm donation for a certain period, that sometimes required more pushback against the sponsors … . Because most of them were men [laughs]… Men are very protective of their little spermazoids [*sic*]" (IR07).

Importantly, phase I investigators' descriptions of the stricter contraceptive requirements for women revealed a lack of trust in women of childbearing potential to prevent pregnancies. Putting the contraceptive requirements in context, one investigator said that "the system inherently does not trust the women" (PI09). This distrust caused some sponsors to steer clear of enrolling women of childbearing potential, but rather than excluding all women, those sponsors sought out women who could not get pregnant instead. One phase I investigator illustrated this dynamic, saying, "A lot of sponsors … [specify that women] have to be no longer of childbearing potential—postmenopausal or had a tubal ligation. And even that, then they have to show medical history, or we could request documents from their caregiver showing that they've had this procedure done" (PI01). In other words, for this informant, even when enrolling women who are not of childbearing potential, the sponsors require additional proof rather than allowing investigators to trust women's word that they have actually had a tubal ligation or are postmenopausal.

One study that did allow women of childbearing potential to enroll provided a striking example of the industry's distrust of women. Explaining why women of childbearing potential were included, the investigator of that study said, "It was actually fairly important to the development of the drug that we know a lot about metabolism in women of childbearing potential" (PI02). Nonetheless, because of the systems-level distrust in these women not to become pregnant, the trial imposed considerable additional burdens on the women who participated (and, thereby, dramatically increased the cost of the clinical trial). The interviewee explained, "And so … we recruited a group of women who could

come in and basically just reside with us [prior to the trial starting]. It was like being cloistered nuns. Seriously. And we did that for nine days. They just sat with us and did crochet and played games and read books, and they sat around. But one thing they didn't do was have sex with men. And at the end of that, we tested them at nine days in, they were negative for pregnancy, and then they got the study drug. And that's how we did it. Because this sponsor was just tremendously concerned because it was a hormonal drug, especially because of that, that it might have an effect on very early conception" (PI02).

While the system itself may try to take trust in specific individuals out of the equation by mandating strict methods of contraception for all women of childbearing potential (or sequestration in a study facility), investigators also express distrust in the actual women who enroll as participants. For instance, when asked how participation of women of childbearing potential should be managed in phase I trials, an investigator expressed doubt in women participants, saying, "If they're using a highly effective form of birth control like a birth control pill or a hormonal IUD [intrauterine device] or implantable or injectable, then I'm less concerned, assuming that they're reliable with their method" (PI07). Other investigators noted that "despite how much you preach to the women about caution [to prevent pregnancy], some women just don't do the precautions they should" (PI06), and "I know that in the places I've worked before we have had people go home in between [confinement] periods and come back pregnant, where they weren't pregnant the first time. So, it happens no matter how much you tell them" (PI01). Moreover, other interviewees expressed judgment of women who become pregnant during a trial, with one investigator asserting that pregnancies that occur during clinical trials are the result of "people basically being stupid and reckless" (PI05).

Risks and burdens to institutions. While interviewees relayed a significant narrative around the risks to potential fetuses from clinical trials and the importance of contraception, they also described the risks of pregnancies *for the institutions* that enroll women of childbearing potential—an additional barrier to the inclusion of women. For instance, when asked about the exclusion of women of childbearing potential from phase I trials, one investigator said, "It has to do with risk and how much risk the sponsor wants to take" (PI01). Importantly, this language of risk extended beyond direct fetal risk to refer instead to legal and financial risk. Another investigator expanded on this sentiment, explaining, "I think there's a concern both at the phase I site level and at the sponsor level about just what's possible, what liability might be possible … . If there's a pregnancy that occurs, and if it comes out badly, you will be sued. If it comes out badly—and that is, say, a damaged child—and you are a big pharma company, or a big CRO [contract research organization], and you've got a deep pocket, and this poor family has this kid that's going to need care that will not be optimal if they have to live on Medicaid. This child will require care into adulthood. Many, many millions of dollars later, neither the pharma company, if it's a small company, nor the [trial] site has enough insurance to cover that. If that happens, if Murphy's law strikes and that happens, they're dead. The business is dead. And the jury may find that they are liable even if logic and science are totally against it. So that's one big concern" (PI02). Later, this interviewee added, "It's not that I don't have a principle-based feeling that women of childbearing potential ought to have access to being involved in these studies. It's a matter of … mitigating the risk and ensuring the financial safety of the other players, of the other stakeholders" (PI02).

In addition to the potential for institutions to be sued by a participant who becomes pregnant, the logistical burdens of dealing with such an event were described by some interviewees. For example, when asked what happens if a participant gets pregnant during a trial, a phase I investigator replied, "You've gotta follow them throughout the pregnancy and the outcome of the child, and there's all kinds of paperwork you've got to fill out for the sponsor. The sponsors are not happy about it because it's a hassle for them as well as for the [trial] site" (PI06). Another phase I investigator similarly said, "Obviously, the sponsor is notified. The IRB is generally notified. And then we have to follow the pregnancy until the end of the term. Either they terminate it, or, if the child is born nine months later, we generally have to follow up with them every month and confirm that everything's going okay with the pregnancy, and then once the baby's born, that there are no congenital anomalies

or anything like that. So, it creates lots of headaches for everyone" (PI07).

These logistical burdens can further disincline organizations from including people who may become pregnant. As an IRB member revealed, "I have found there is a huge tendency—not just related to phase I healthy volunteer trials but studies in general—where people exclude women or pregnant women because of a fear of the regulatory implications, and that's the only reason" (IR03).

Although interviewees described their worries about potential pregnancies, teratogenic effects, and liability for institutions, IRB members and phase I investigators rarely, if ever, encountered either. For instance, when asked if a pregnancy had ever occurred during a trial they were overseeing, an IRB member responded, "I don't know if there's been a pregnancy for a phase I healthy volunteer study" (IR03). For those who could recall pregnancies that had occurred, not a single informant had an experience of adverse outcomes. One IRB member said, "I don't recall any, over the years, babies that have been born that have had any concerns that were noted" (IR01). Another reflected, "I've never heard of any kind of birth defects or any kind of awful ending. I've never heard of that" (IR07). Similarly, a phase I investigator stated, "I don't know any outcome of an infant that was adverse. You know, no brain damage or weird things, or both with one leg or two legs, or five legs, or whatever. They all seemed to be pretty normal, thank goodness" (PI06).

DISCUSSION

Despite improved representation of women in biomedical research over the last three decades, they are often excluded from or underrepresented in phase I trials.[21] Our interviews with key gatekeepers to these studies—investigators and research oversight officials—revealed barriers to and opportunities for advancing their responsible inclusion. Although participants voiced general support for gender parity in research, interviews revealed structural barriers as well as enduring patterns of reasoning and errors in logic that help to explain why we have made only modest progress on inclusion in early-phase trials. Indeed, our data suggest that many of the cultural themes that contributed to the underrepresentation of women across clinical trials prior to the 1990s still shape sex-based research exclusions today.[22]

The structural barriers identified were primarily within the drug-development system, specifically requirements for preclinical DART studies prior to inclusion of women "of childbearing potential" in biomedical research studies. Consensus recommendations have encouraged pharmaceutical companies to conduct required studies earlier in the drug-development process to foster equitable study.[23] Yet the FDA has not updated its guidance to industry, and researchers and IRB members voiced a general acceptance of such delays in phase I research as both reasonable and ethical. They noted that IRBs generally accept decisions to conduct research with all-male samples as long as there is a scientific rationale and that the absence of reproductive toxicity data (albeit a product of market forces) is a sufficient reason to do so. On closer inspection, these "scientific" justifications reflect systems of *value* as much as they do extant rules, procedures, and results of preclinical research.

Indeed, participants' responses reflected a range of cultural barriers—sometimes identified explicitly, though often captured by patterns of reasoning within their comments—to equitable inclusion of women in phase I trials. First, comments of some informants reflected an enduring tendency to trust in the male body as the human norm, which is an often hidden but prominent bias known as "androcentrism." Androcentrism posits man as the tacit standard for human—"the measuring stick, the unstated point of reference, for what is normal for humans."[24] Such androcentrism was conveyed in several responses: for instance, that a male-only sample could be viewed as sufficient to generate foundational safety, dosing, and side-effect data for development of a drug that will be used in all sexes; that a representative cohort of "healthies" in a phase I trial could reasonably include only men; or that specific requirements for inclusion of women be viewed as an additional and avoidable burden, rather than as a requisite challenge (among many) that are normative in the conduct of clinical trials. That these androcentric views were voiced demonstrates the limited range of influence of the NIH's attempt to change scientific practice through their "sex as a biological variable" ("SABV") funding criterion in which investigators must attend to

potential sex-based differences or provide "strong justification … for studies enrolling only one sex" across preclinical and clinical research.[25] As phase I trials are key to determining safety, side effects, best dose, timing, and route of delivery for new drugs, failure to include women or attend to sex as a biological variable in such trials may contribute to excess drug-related adverse events among women in postapproval settings.[26] For instance, the FDA significantly lowered the recommended initial dose of the drug zolpidem (Ambien) in part due to the potentially harmful lasting effects of the sleep medicine (e.g., car accidents) that appear to affect women more substantially than men.[27] Yet among researchers and IRB members, we observed an exceptionalism around the ethical requirement for representativeness in phase I trials.

Second, our data reflect a tendency within the culture of biomedicine to focus on female reproductive potential without due regard for the reproductive status or activities of their male counterparts. This took many forms. One was a marked emphasis on *future* female fertility. Indeed, the potential that a drug might curtail future reproductive prospects was offered as a reason to exclude women, but not men, from clinical trials—despite a long list of drugs on the market that are known to affect sperm or male fertility more generally.[28] Another was an emphasis on *current* female fertility—reflected in a tendency to require more burdensome and documented contraception for women than for men—and even, as one respondent noted, resistance to male contraceptive requirements or warnings. No doubt risks to offspring are of relevance (morally and legally) to those designing studies, but prevention via exclusion of women from studies turns a blind eye to the potential for male-mediated developmental toxicity, reinforcing the tendency to blame mothers for birth outcomes attributable to a wide range of factors, including the health and exposures of fathers.[29]

Third, our data reflect a widely recognized tendency to focus on the fetus and prioritize avoidance of fetal harm in research without regard for the likelihood of such harm or the costs of eliminating it.[30] What is particularly curious here, however, is that the research under consideration is with *nonpregnant* participants; what appears to justify exclusion is the duty to protect a fetus who does not yet—and may not ever—exist. The risks, too, are theoretical, looming large for some even where preclinical data are reassuring. Such distortions point to two cultural tendencies. One is to view women primarily as persons who bear children—to link inextricably female sex with pregnancy and motherhood. In a 1993 analysis of justifications for pregnancy exclusions among researchers, legal scholar Vanessa Merton described a "fundamental misconception—[that] *all women are always pregnable and therefore* (through the magical operation of the mind characteristic of unconscious sexism) *always pregnant*" as driving exclusionary policies and rationales.[31] More broadly, sociologist and bioethicist Miranda Waggoner posited a broad cultural ethic of "anticipatory motherhood" that "positions *all* women of childbearing age as pre-pregnant" and responsible for ensuring that their bodies are always in optimal condition to grow a fetus.[32] The second tendency is the pursuit of zero risk to the fetus, the notion that any risk whatsoever to a fetus is unacceptable, and the view that medicines (in both research and clinical context) are presumed too poisonous—assumptions unmoored from the actual possibility of congenital harm and inattentive to the harms, to women and fetus both, of failing to effectively treat or prevent maternal disease.

Finally, we observed a worrisome mistrust by phase I investigators of women as research participants. This manifested, for instance, in access to trial participation based on results of preclinical reproductive toxicology data (which most participants endorsed) rather than on the facts and trajectories of participants' lives, reproductive and otherwise. Or more starkly, it was illustrated in the example of quarantining female research participants, as one interviewee noted, "like cloistered nuns" to ensure that they did and could not have (heterosexual) sex. This is reminiscent of Schiebinger's characterization of the FDA's pre-1993 prohibition on women of childbearing potential as "support[ing] the portrayal of women as 'walking wombs,' unable or unwilling to control their fertility."[33]

Conversely, respondents voiced trust in the pharmaceutical industry to gather data later in the drug-development process to ensure the safety of marketed drugs for women—yet, for this industry, earning the trust of participants and the public is generally understood to be an ongoing challenge.[34] Moreover, mistrust of participants translated into practices and policies of

consequence for them: required use of burdensome, risky, and unnecessary contraception; periods of isolation to ensure abstinence; and exclusion from trials. Relevant too were moral hazards of failing to treat participants as ends in themselves. As the American College of Obstetricians and Gynecologists' Committee on Ethics stated in a 2015 opinion, "Requiring birth control use by a woman who is not sexually active violates a commitment to respect her as a person."[35] More research is needed to understand the impact of trust or mistrust of research participants on research design, the experiences of people who choose to participate in research, and the degree to which gender, race, and socioeconomic status may inform these views.[36]

CONCLUSIONS

Our study on phase I investigators and IRB members demonstrates that the justification for women's continued exclusion from clinical trials is based on problematic rationales. Our findings have several implications for the inclusion of women in phase I healthy volunteer trials and clinical trials more generally. First, the cultural barriers and biases we observed were often implicit in the participants' responses. Making them visible is critical to redressing their impacts. Second, despite progress on inclusion of women in later phases of research, appreciation of the importance of preclinical and early-phase data was lacking, suggesting a role for stronger implementation and education around the importance of representation in research, including the science and ethics that support inclusion at all stages of preclinical and clinical research. Third, our data point to the need for approaches to address gender disparities in both attribution of reproductive risk and contraception requirements. As others have argued,[37] a risk-based approach to contraceptive requirements could help address both gender bias and ethical violations of contraception requirements, especially the imposition of risk in the absence of benefit and the failure to respect research participants as persons. Finally, there is the critical task of understanding how mistrust of women informs biomedical research. Without these interventions in biomedicine, androcentric biases will continue to permeate clinical research, hinder advances to women's health initiatives, and limit autonomy of and respect for women in research and health care. ♦

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