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RESEARCH PAPER

Disadvantaged, outnumbered, and discouraged: women's experiences as healthy volunteers in U.S. Phase I trials

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ABSTRACT

While enormous strides have been made in the representation of women in clinical trials, the percentage of women enrolling in Phase I trials still remains low, which both raises public health concerns about the safety of new drugs and social justice concerns regarding their inclusion in research. As part of a longitudinal study of healthy volunteers in the United States, our inquiry aimed to examine impediments to women enrolling in Phase I trials as well as their experiences participating in these studies at residential research clinics. We analyzed 111 semi-structured interviews conducted with 47 women who had enrolled in at least one Phase I trial. Our study indicates that women face discrimination during all stages of their participation in Phase I trials from their ability to qualify for studies, the treatment they receive in the clinic facilities, and a lack of social support. Specifically, we found that (1) study designs disadvantage participants of childbearing potential, (2) women feel vulnerable in the clinic space when outnumbered by men, and (3) heterosexual women are often discouraged from participation by their husbands or significant others. Placing these findings within the scholarly literature on barriers to women's clinical trial participation, we argue that diverse strategies attending both to physiological and social factors are needed to combat inequalities in U.S. Phase I trial participation.

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Introduction

In order for drugs to be approved by the U.S. Food and Drug Administration (FDA) for market use, they must be tested to evaluate their safety and efficacy. Such testing is required to proceed through three phases of clinical trials (Carpenter, 2010). Phase I trials are designed to evaluate the safety, dose, and side effects of investigational drugs on a small number of typically healthy participants. In addition, Phase I trials routinely require a 'confinement' period in a residential research clinic as part of the controlled nature of these studies (Fisher, 2015a). Phase II trials collect further safety data as well as provisional evidence of efficacy, using a small number of patients with the targeted disease. Phase II trials can be thought of as proof-of-concept studies that help pharmaceutical companies determine if their product is promising enough for larger-scale testing in Phase III trials. For the approximately one-third of investigational drugs that make it to Phase III trials (DiMasi, Feldman, Seckler, & Wilson, 2010), these studies are designed to enroll hundreds or thousands of patients as research participants to assess the efficacy of the drug (i.e., compared to existing treatments or a placebo). After

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securing results from all three clinical trial phases, pharmaceutical companies can then apply to the FDA for approval to market their drugs.

Increasing the diversity of clinical trial participants has been a national public health priority in the United States since the early 1990s. Catalyzed by widespread recognition of the under-representation of women enrolled in clinical trials, the National Institutes of Health (NIH) issued guidelines on inclusion of women, as well as minority groups, as a condition of extramural funding (Epstein, 2007). Policies such as these combine attention to both sex and gender, wherein sex is the biological category defining whether people are born male or female and gender refers to the social roles individuals fill as men or women. On one hand, these policies aim to increase scientific knowledge about sex-based differences, and on the other, they seek to promote health equity and justice by ensuring that diverse groups are included in research. This nomenclature, however, tends to elide differences between sex and gender by privileging the term 'women.'[1] While women now make up more than half of all participants in NIH-funded clinical trials (NIH Office of Research on Women's Health, n.d.), these metrics include only Phase III efficacy trials. Additionally, no similar mandates exist for the inclusion of women in non-federally funded trials. While FDA regulations oblige pharmaceutical companies to analyze their clinical trial data by sex, race, and age (Bren, 2005), the under-representation of female participants often leads to a lack of statistical power to detect variations in sex-based drug effects (Parekh, 2010).

Phase I trials, in particular, continue to have poor representation of women (Chen et al., 2018; Fisher & Kalbaugh, 2011). Although the FDA barred women of childbearing potential as Phase I participants from 1977 to 1993 out of concern for unknown reproductive effects of investigational drugs, no such regulatory restrictions currently exist (Corrigan, 2002). Many pharmaceutical companies nonetheless continue to limit the participation of female participants in Phase I trials, often requiring them as part of the trial protocols to be surgically sterile or postmenopausal (Mazure & Jones, 2015). These companies justify such inclusion–exclusion criteria for safety reasons, noting the harms that could occur to a fetus should participants become pregnant during the clinical trial, or for economic reasons, citing the costs incurred by using broader inclusion criteria in studies (Holdcroft, 2007). At the same time, because Phase I trials seek healthy subjects who do not take prescription medications, participants who use oral contraceptives – and therefore at less risk of becoming pregnant – are also excluded from participating (Fisher & Ronald, 2010).

Exclusion of women of childbearing potential in Phase I trials creates both social inequalities of access to research and scientific blind spots about population-based issues of drug safety and efficacy (Merton, 1994). First, in being denied the equitable opportunity to enroll in Phase I trials, women of childbearing potential are excluded from the economic benefits of participation as well as from making a contribution to drug development (Abadie, 2010; Fisher et al., in Press). Second, female and male physiology does not always respond to pharmaceuticals in the same way (Bennett, 1993; Miller, 2001). This can be due to physiological variations in pharmacokinetics (i.e., the action of the body on the drug, such as through absorption, metabolism, and excretion) that lead in some instances to greater drug exposure in female compared to male bodies (e.g., McGregor et al., 2014; Meibohm, Beierle, & Derendorf, 2002). Yet, due to the inequalities in the system of clinical testing, these effects might remain unknown until a drug is widely circulating on the market and disproportionately causing harm to female patients (U.S. General Accounting Office (GAO), 2001). These drug safety problems underscore the seriousness of the public health need for ensuring adequate representation of the sexes in Phase I trials.

The exclusion of participants of childbearing potential from clinical trials can also lead to a lack of sex-based evidence. This can result in overlooked symptoms and poorer clinical care of female patients. For example, even though there are significant differences in the way coronary heart disease presents itself across female and male patients, government-mandated guidelines for treatment are not tailored to sex categories (Holdcroft, 2007). In addition, the diagnosis and treatment of endometriosis, a condition in which menstrual tissue migrates and affixes to areas outside of the uterus, is fraught with gendered interpersonal dynamics. Medical practitioners may dismiss patients' symptoms, and both experts and sufferers alike can come to see endometriosis as

an illusion, bearing similarity to past medical practices that framed women as hysterical (Seear, 2014). Sex, as a socially agreed upon categorization system that uses anatomy, chromosomes, and/or hormones to classify bodies into female and male, cannot be fully disentangled from the social definitions of femininity and masculinity that make up gender.

Thus, it is critical to both increase the number of healthy volunteers of childbearing potential in Phase I trials and to take women's clinical trial experiences and concerns seriously. To this end, the existing scholarly literature has focused on FDA guidelines and clinical trial protocols or women's willingness to enroll in research (e.g., Mazure & Jones, 2015; Pinnow, Sharma, Parekh, Gevorkian, & Uhl, 2009). These are obviously important focal points to change the current system of clinical research, but there is also a need to better understand the empirical reality of women's participation in clinical trials. Examining the processes of screening for and enrolling in Phase I trials reveals the discriminatory practices that also contribute to the under-representation of women, even those who are very willing to participate, in pharmaceutical research.

Methods

This study investigates women's perceptions of their involvement in Phase I trials. It is based on three waves of data collected between 2013 and 2014 as part of a longitudinal study on the participation of healthy volunteers in U.S. Phase I clinical trials (Edelblute & Fisher, 2015). These clinical trials were for any therapeutic area in which an investigational drug was being tested, which included more than 40 aggregate illness categories. Investigational drugs for pain, cancer, autoimmune diseases, diabetes, and hepatitis C constituted nearly a third of the 1,138 Phase I trials for which participants screened while enrolled in our study. This larger study enrolled 180 cisgender men and women who had participated in at least one Phase I clinical trial. In order to recruit individuals for our study, we received permission from seven Phase I clinics in the U.S. (three on the East Coast, two in the Midwest, and two on the West Coast) to recruit healthy volunteers enrolled in a clinical trial at their facility. As part of their three-year participation in our study, healthy volunteers consented to up to five interviews about their involvement and experience in clinical trials and to report on any clinical trials for which they screened or enrolled while participating in our study. The study was reviewed and approved by the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill.

After enrollment and an initial 'baseline' interview with participants, we randomized 20% into a control arm to assess whether our study might have an unintended intervention effect on participants. Those individuals allocated to the control arm had limited contact with the study team for the three years after their enrollment, participating only in one baseline and one final interview and not reporting their clinical trial involvement during that time. All other participants were in what we call our full-participation arm, and we interviewed them again 6-months, 1-year, 2-years, and 3-years after their baseline interview. We compensated participants for each interview. All participants received a $20 Visa gift card after completion of their baseline interview. Individuals in the full-participation arm received a $50 check for completion of their 6-month interview, a $100 check for completion of their 1-year interview, and a second $100 check for completion of their 2-year interview. All participants (full-participation and control) were compensated $200 for completing the final, 3-year interview. Because we did not want to encourage screening for Phase I trials to receive payment from our study, we did not compensate participants for reporting their clinical trial activity. We retained 92.2% of our sample (91.1% of the full-participation arm and 97.1% of the control arm). The current investigation includes interview data from women participants' baseline, 6-month, and 1-year interviews.

Sample

As with Phase I trials more generally, our overall sample was demographically diverse but was predominantly men, with women making up only 26.4% (n = 47). Roughly 90% of the healthy volunteers we invited to participate in the study enrolled (see also Cottingham & Fisher, 2016).

Table 1 provides detailed information on the sociodemographic characteristics of the women in our study. A slightly higher percentage of women (25.5%) were randomized to the control arm, which left us with 35 women in the full-participation arm and 12 in the control arm. Forty-five percent of our sample was Non-Hispanic white, 32% African American, and 19% Hispanic, and they ranged in age from 19 to 64 years old, with nearly 60% being older than 40 years old. Over half of the women identified as having childbearing potential while 30% were surgically sterile and 13% were post-menopausal. More than 70% had at least one child, and they were nearly evenly distributed based on marital status with 28% reporting being single, 32% married, and 34% separated or divorced. We did not collect information about sexual orientation, but the majority of women in our sample explicitly discussed their heterosexual relationships and two women described being involved in same-sex relationships. As for their experience participating in Phase I trials, 23% were in their first study, 40% were in their second through fourth study, 21% were in their fifth through tenth, and 15% were in their eleventh through forty-fifth study. To provide a fuller picture of our sample, Table 1 also presents the women's household income, employment status, and educational attainment. Of the scheduled 6-month and 1-year interviews with the 35 women in the full-participation arm, we completed 32 at each phase. Two of the women were lost to follow-up between their baseline and 6-month interviews, and one woman voluntarily withdrew from the study before her scheduled 6-month interview. We retained all participants between the 6-month and 1-year interviews.

Data and analysis

The data analyzed for this article come from the 111 semi-structured interviews we collected with women as part of their baseline (n = 47), 6-month (n = 32), and 1-year (n = 32) interviews. The interviews followed an interview guide but allowed the interviewer to pose different questions based on the information the participant provided during the interview (Patton, 2002). The advantage of this method is that it allows probing of unprompted themes that are important to study participants (Weiss, 1994). The baseline interview was conducted in-person by one of the investigators in a quiet space in the clinic facility and covered a range of topics, including: background information on each participant's employment, education, and family life, along with detailed questions about the types of studies she had enrolled in, her perceptions of the risks and benefits of Phase I trials, and her experiences and motivations for participating in clinical trials. Baseline interviews lasted approximately 70 minutes.

The research team conducted 6-month and 1-year interviews by telephone. The 6-month interview was primarily a retention interview, reminding participants that they were enrolled in our study and collecting any clinical trial information that participants had not provided in the 6-month period since their enrollment in our study. Additionally, the interview guide included questions about the risks and benefits of Phase I trials, general questions about how the participants perceived their health, and their thoughts about their future participation in clinical trials. These 6-month interviews lasted approximately 30 minutes. The 1-year interview explored in greater depth participants' understanding of the risks and benefits of Phase I trials; their perceptions of the research clinics, pharmaceutical companies, and the FDA; and their perceptions of the clinical research enterprise, including how competitive it is to qualify for and enroll in studies. The 1-year interviews were an average length of 1 hour.

A transcription company transcribed all interviews, and we verified and corrected these transcripts for accuracy. Two members of the research team then coded each transcript. Our coding structure included both a priori codes developed from the literature on clinical trials and our preliminary research on healthy volunteers as well as emergent codes. In the larger study, we were particularly interested in participants' perceptions of trial risks and benefits, their decisions about which trials to pursue or avoid, as well as their concrete experiences in completed trials. Relevant to this analysis, we created a code for 'gender issues' and included participants' largely *unprompted* reflections on the gender dynamics in the clinic and their perceptions of sex and/or gender differences among men and women. As part of the first wave of analysis,

Table 1. Demographics of women study participants (N = 47).

	n	%
Arm of Study		
Full-Participation	35	74.5%
Control	12	25.5%
Clinical Trial Experience		
1 study	11	23.4%
2–4 studies	19	40.4%
5–10 studies	10	21.3%
11–45 studies	7	14.9%
Race/ethnicity		
Non-Hispanic white	21	44.7%
Black	15	31.9%
American Indian	1	2.1%
Asian	1	2.1%
More than one race	2	4.3%
Hispanic[a]	9	19.1%
Age		
18–21	1	2.1%
22–29	8	17.0%
30–39	11	23.4%
40–49	16	34.0%
50+	11	23.4%
Marital Status		
Single, never been married	13	27.7%
Married (or marriage-like, long-term relationship)	15	31.9%
Separated or divorced	16	34.0%
Widowed	3	6.4%
Number of Children		
0	13	27.7%
1–2	18	38.3%
3–4	13	27.7%
5–6	3	6.4%
Fertility Status at Baseline		
Childbearing potential	24	51.1%
Post-menopausal	6	12.8%
Sterile	14	29.8%
Unknown/missing data	3	6.4%
Educational Attainment		
Less than high school	2	4.3%
High school or GED	5	10.6%
Some college	16	34.0%
Trade/Technical/Vocational training	4	8.5%
Associates degree	9	19.1%
Bachelor degree	10	21.3%
Graduate degree	1	2.1%
Employment Status[b]		
Full-time/Business owner (self-employed)	18	38.3%
Part-time/Independent or Irregular Contractor	8	17.0%
Unemployed/Retired	21	44.7%
Household Income		
Less than $10,000	10	21.3%
$10,000 to $24,999	13	27.7%
$25,000 to $49,999	17	36.2%
$50,000 to $74,999	5	10.6%
$75,000 to $99,999	1	2.1%
$100,000 or more	1	2.1%

[a]The category Hispanic includes all racial groups, of which we had participants in our sample who identified as white, more than one race, and American Indian.

[b]These data are based on consolidated definitions of each employment category that we used to standardize self-reported data from participants.

we took an inductive approach and identified relevant excerpts based on any and all references to impediments to participation that women uniquely face and ways in which women felt discriminated against through the screening process or clinic confinement. In a second round of analysis, these select

excerpts were scrutinized further to reveal the specific themes surrounding the relationship between women and clinical trials discussed below. In the presentation of our findings, we use pseudonyms to protect the confidentiality of our participants. We also situate all quotes using women's self-reported race/ethnicity, age, and number of clinical trials at the time of enrollment in our study and indicate the interview from which the quote was taken (i.e., baseline, 6-month, and 1-year interviews).

Results

Participation in Phase I trials can be difficult for myriad reasons. Qualifying as a healthy volunteer can be challenging when trials include narrow inclusion–exclusion criteria. In addition, being confined to the clinic requires coordination to ensure that caregiving responsibilities are met for families and that, for those who are employed, permission for time off work has been obtained. These elements, however, pertain both to women and men. Our interest for this inquiry was to explore how women's experiences in trying to qualify for studies or being confined to the research clinic were uniquely shaped by their biological sex or gender roles. Unlike in interviews with men, women explicitly discussed how being female or being a woman shaped the experiences they had in Phase I trials. Overall, participants' views varied based on their specific circumstances, such as the length of their involvement in Phase I trials and the relationships they had within and outside of the clinic, yet they identified common impediments to and discrimination against women participating in clinical trials. We focus here on three critical themes that appear unique to women's experiences: (1) study designs limit or disadvantage participants of childbearing potential, (2) women feel vulnerable in the clinic space when outnumbered by men, and (3) heterosexual women are often discouraged from participation by their husbands or significant others.

Sex-based disadvantages

A primary theme in interviews with women is the perception that they face physiological disadvantages as females when trying to qualify for Phase I trials. Specifically, women emphasize how much more difficult it is for women than men to find trials for which they are eligible. As one might expect, many of these comments focus on exclusion from many trials based on one's childbearing status. For example, Evonne, an African American woman in her 30s who had participated in three trials at baseline, discusses how her childbearing status has prevented her from participating in several studies:

> Sometimes the issue that we've run into is a lot of times the studies are for men or it's for postmenopausal women or surgically sterile women… so it's like, we're kinda last on the list, the women that can still have children. But I kinda understand that because you don't wanna have kids… [that] come out all messed-up looking because you were on a drug [trial] or something like that… I don't plan on having any kids anytime soon, but… I don't wanna go through no [sterilization] surgery… [because] I might change my mind down the line, so. (baseline)

Evonne understands why women of childbearing potential face restrictions on their Phase I participation, but she perceives it as unfair that studies are limited to her unless she were to pursue the undesirable option of becoming surgically sterile.

Beyond differential access to trials based on reproductive status, women identify other ways in which their physiology impedes their trial participation. In particular, menstruation can negatively affect their ability to qualify for Phase I trials. For example, Renee, a biracial woman in her 30s who had participated in 9 trials at baseline, complains about a recent study for which she had passed the screening but was discharged from the study due to results from her pre-trial lab work at check-in:

> It's just [that] I got let go of that study 'cause my period was on and my hemoglobin got low… I mean, it sucked! [laughs] It sucked, and I wasn't happy about it, but, you know, it is what it is. (1-year)

Renee's frustration at being discharged is coupled with a sense of powerlessness, knowing there is nothing she can do when she simply does not meet the criteria for a healthy volunteer outlined in the trial protocol.

Other women are more proactive in ensuring that their blood matches the required criteria. Natasha, a white immigrant from Russia in her 30s who had participated in 45 trials at baseline, describes her experiences:

> When female… have period, you're low on iron, your hemoglobin is low. And you just do take iron pills to get your levels in certain levels, so [you're] not low on your iron. Very important because… a lot of the studies, that's how you get your data is from blood, so that's the main ingredient right there. (1-year)

Like Natasha, other women also make behavioral changes to combat this perceived physiological disadvantage and increase their chances of qualifying for a clinical trial. Tina, a white woman in her 40s who had participated in 30 trials at baseline, enumerates the changes she has made to her diet:

> At one of the clinics, they had said – more than one clinic – they had said, you know, 'You like red meat, and definitely before you come and screen, you should do that [i.e., consume red meat] and continue to do it before you come in [for the study check-in] because we're gonna be taking a lot of blood. You know, we don't want you anemic and, you know, we don't want you to be knocked out for studies, so that's maybe a change you need to have.' … They would say, Take, you know, take an iron pill. Absolutely take that for at least a week after and especially with women who are still menstruating.' (1-year)

Here Tina describes the research staff coaching her in ways to combat anemia, even explicitly acknowledging the effects of menstruation on female participants' blood levels.

Women also experience difficulty with blood collection, which is a common method of obtaining data about the effects of the investigational drug. On one hand, they complain that veins in the female body prove more challenging for venipuncture, and on the other, they voice concerns that the volume of blood required takes more of a toll on them than it does on men. Helen, a white woman in her 30s who had participated in 4 studies at baseline, expresses negative feelings about the frequency and volume of blood taken:

> I think studies could improve if they didn't have to take so many blood draws. Like if they could, you know, span out the blood draws to, you know, maybe once or twice a day. … I mean, give me a break, you know. I mean you've got to be able to reproduce that blood back, and it takes hours, you know. And especially women, we lose a fourth of our blood count every month through our menstrual [cycle]. (1-year)

Helen is particularly concerned about the effect of blood loss on her health, seeing herself as more vulnerable because of her female body. Furthermore, Bree, an African American woman in her 30s who had participated in 40 trials at baseline, believes that clinics' practice of vein assessment tends to work as a form of discrimination against women. According to her, the research staff:

> consider us not to have the best of veins. So there's that as well against women versus men. They're supposed to have the better veins, so then they look towards men for that as well' (baseline).

Outnumbered in the clinic

Another important theme that emerged in interviews centers on women's experiences of being confined to the Phase I clinic. Indeed, women often discuss how men radically outnumber women in clinical trials. When the clinic space is dominated by men, women may feel uncomfortable or vulnerable when staying in the facility. For example, Becca, a white woman in her 30s who had participated in nine clinical trials at baseline, relays her experiences:

> Yeah, there's an open bedroom… and there were a total of 12 people. I was the only girl. There was a completely empty bedroom [in the clinic], and I was not allowed to stay in that one… I mean, I wasn't like concerned, but I mean, I thought it was a little silly 'cause, you know, it's a little awkward just staying, you know, in a room with 12, well, 11 guys. (baseline)

Becca is no longer surprised by being one of very few women in studies but obviously remains unsettled by the accommodations the clinics provide.

When clinical trial facilities are disproportionately occupied by men, this may implicitly and explicitly affect women's willingness to participate in future studies. Bree feels anxiety about the types of men in these studies and the unwanted attention she has received:

> I'm just going to say this 'cause most studies are just basically men. Men who literally were fresh out of jail, men who [were] fresh off the streets… So, you have that, but you still have that mentality. There's this like, 'Oh my gosh, there's a woman. I haven't seen a woman in like two hours.' (baseline)

Women are not only outnumbered, but Bree plays into the common, and unsubstantiated, stereotypes about healthy volunteers as dangerous criminals, either coming from prison or their current illegal activities on 'the streets.' Similarly, Sherrie, a white woman in her 30s who was enrolled in her second study at baseline, recalls a past clinical trial where concerns for her safety emerged from the clinic's coed bedrooms:

> I'm assuming they let felons in because… the staff has said before that they worry sometimes because they have rapists that are there – you know, convicted rapists who stay the night. And they put us all in the same room together, men and women, so. And the last study I'm in, one girl was in a room with all guys, and then the rest of the girls were mixed in a room with a few other guys in the other room. So, she was in that room all by herself with like eight other guys. So, I wouldn't, I wouldn't have done it. (1-year)

Regardless of the veracity of Sherrie's beliefs, her statement highlights the vulnerability she feels in the clinic. Indeed, at the time of her 1-year interview, Sherrie had stopped participating in Phase I trials, saying,

> I don't even want to stay the night [in the clinic] anymore… I don't feel like I need to do it [participate]. But it's also the fact that, little things that… they don't have to do, that they do anyway, like not separating us [men and women]. … Little things like that bother me. (1-year)

Discouragement from heterosexual partners

A final theme we found in women's experiences involved the opposition they face to their clinical trial participation from their significant others. While enrolling in clinical trials has been described in the literature as being a stigmatized activity, especially for racial and ethnic minorities (Corbie-Smith, Thomas, Williams, & Moody-Ayers, 1999; Fisher, 2015a; George, Duran, & Norris, 2014), experiences of women suggest an additional gendered component to public perceptions. Many of the women in our sample hint at this type of stigma, but interestingly, several of the heterosexual women portray the men in their lives as having negative attitudes toward their trial participation or trying to prohibit them from participating altogether. For example, Penny, an African American woman in her 40s who had participated in six studies at baseline, acknowledges that her future participation in clinical trials will likely be curbed when she is married. She describes her fiancé as 'leery' of her participation. He explicitly told her that he does not want her to enroll in more trials. Reflecting on this, Penny states, 'This one'll probably be my last one. … Because once I get married, then I'm gonna have to listen to my fiancé, I guess. I'll have to listen to my-my husband' (6-month). Penny is not the only one to cede authority to her partner. Becca, too, indicates that her participation in clinical trials is heavily influenced by her fiancé: 'He gets the final say if I can do the study or not. He always looks and checks it out first, so if he nixes it, then I'm-, then I'm out' (6-month). This 'agreement' occurred after Becca had completed a Phase I trial for an investigational drug that had psychological side effects: 'I'd just be spaced out like woo, crazy, hyper, moody, just like nutty. … He [fiancé] told me after the last, crazy drug one, he's like, "No more of those." Like he told my parents on me' (baseline). Penny and Becca illustrate how traditional heterosexual gender norms affect their trial participation. In both cases, their fiancés try to exert control over, and even forbid, their participation.

Worry about a significant other's disapproval could also lead heterosexual women to keep parts of their clinical trial participation a secret. Jackie, a Hispanic woman in her 40s who was in her first trial at baseline, had anticipated that her husband would be angry with her decision, so she was selective about the information she divulged before she enrolled:

> I didn't tell my husband I was doing it until after I qualified. Because I thought, 'Oh my gosh, he would be so mad.' He's like, 'What're you doing? I think it's crazy! Do you know what you're getting yourself into?' So, I thought, 'Okay, I won't tell him until I qualify.' (baseline)

Jackie did not try to keep the study itself a secret from her husband, but she had avoided the risk of angering him before receiving confirmation she qualified for the study. Similarly, Jennifer, a white woman in her 20s who was also participating in her first study at baseline, recalls that after she scheduled her screening appointment, she wondered, 'And then in my head, I'm like, "How am I going to convince my husband that this is a good idea?"' (baseline). Later, she was able to get him to accept her participation by withholding information: 'I don't think I told him like *all* about it… I think I was a little bit fuzzy about like it [the investigational drug] being injectable.'

Study participation can create tension within heterosexual relationships because these women's partners might feel apprehensive about them being alone in a setting dominated by other men. For example, Myra, an African American in her 40s who had participated in eight studies at baseline, said that her husband feels insecure when she spends time in the clinic:

> 'Cause my husband, he doesn't like it, of course. I'm not there with him every night. But he's grown to accept it. He gets a little, he gets a little, I guess you can call [him] insecure every now and then. But, you know, I talk to him all the time so he's okay… I mean, he would love it if there was no men in the study. [laughs] (baseline)

Becca's fiancé has similar concerns, so she lies about the accommodations: 'I told my fiancé I had my own room. I was like, "Yeah, I'm not even gonna stress him about that"' (baseline).

Discussion

In spite of efforts to increase the representation of women in clinical trials, Phase I trials continue to enroll a disproportionate number of men as healthy volunteers, presenting an issue of gender equity for women as well as broader concerns about the scientific and clinical consequences of limited safety data from female participants (Chen et al., 2018; Fisher & Ronald, 2010). Our study indicates that women face discrimination during all stages of their participation in Phase I trials from their ability to qualify for studies, the treatment they receive in the clinic facilities, and a lack of social support. Additionally, these forms of discrimination also serve as impediments to clinical trial participation that have not previously been considered in the literature. Beyond the exclusion or restrictions based on childbearing potential, we found that Phase I trials are set up to discriminate against female participants' normal physiological states, such as fluctuations in iron during menstruation, or their putatively worse venous access. We also discovered that Phase I trial facilities do not always create separate sleeping quarters for women and men, which causes significant discomfort for women who are outnumbered by men in these confined spaces. The lack of separate spaces for women and men in Phase I trials can be seen as a clear issue of gender-based discrimination, which stem from clinical trial facilities' logistical or financial rationales. Finally, we also found that the partners of heterosexual women use traditional gender norms to mobilize their masculine authority to try to limit or prohibit these women from enrolling in trials. Rarely did other family members or friends try to influence their participation in these ways, so this dynamic appears unique to heterosexual relationships. Our participants were both explicit and implicit in their reflections on how these three forces of discrimination influenced their decision to enroll in studies. Even when women chose to participate in spite of these impediments, they often did so with a negative view of clinical trials or reluctance to participate in future trials.

Our findings point to the complex interconnections between sex and gender in biomedical research. Some women might undergo surgical sterilization or menopause with the result that they may qualify for more clinical trials, yet this does not mean that their experiences in the clinic become more comfortable or that partners or husbands begin to support their trial participation. Moreover, when more women are included, but only those who lack childbearing potential, it is difficult to see this as a true sign of progress. It is only when fully informed female participants are permitted to take on the risks of clinical trial testing without being defined by their relationship to potential children (or 'phantom fetuses,' Waggoner, 2013, p. 347), that knowledge gaps in drug metabolism and systemic inequities for women as participants and patients might be simultaneously rectified.

Critical public health scholarship has sought to bridge the gap between feminist and medical ethics in a way that grapples with the gendered and sex-based elements of health inequities (Rogers, 2006). Following Rogers' (2006) call for 'actions that are grounded in concern for the wellbeing of women, and that aim to achieve the goals that they themselves determine' (p. 353), we offer some practical suggestions that focus on institutional change. In order to avoid adverse drug reactions that pose greater risks to female patients after drugs are available on the market (U.S. General Accounting Office (GAO), 2001), it is critically important to decrease the sex- and gender-based barriers to women's enrollment in early-phase clinical trials. Changes need to be made not only at the level of policy and regulation to encourage pharmaceutical companies to accommodate participants with childbearing potential, but we need to address the discrimination that women who want to enroll in Phase I clinical trials routinely face. This means that changes to the structure of these trials are needed. Specifically, the Phase I clinic should actively foster women's sense of safety and comfort, even in a space that is dominated by men. These clinical trial settings can be quite stressful and unwelcoming for women to spend extended amounts of time. Sex-segregated bedrooms and a general emphasis on privacy and safety for women who might feel vulnerable could improve the environment for women. Further research should investigate how environmental stressors can also affect clinical trial results, particularly for women and other minority groups. Additionally, trial protocols could become more flexible to encourage the enrollment of women when their laboratory results (e.g., iron and hemoglobin levels) might fall outside the optimal range desired by a pharmaceutical company but are nonetheless clinically insignificant. While public perceptions of clinical trials are more difficult to change, making women's experiences in clinical trials more positive could help bolster the support of their partners.

The primary limitation of our study is that our findings are part of the secondary analysis of data for a larger research study. As such, we did not design and conduct a study to discover the discrimination that women face in Phase I trials. Instead, these themes largely emerged in an unprompted and unsystematic way. Yet, because all the women in our study were actual healthy volunteers rather than women who had never considered enrolling in a Phase I trial, we know the scenarios they shared with us were not hypothetical; they described the difficulties they have had qualifying for studies, their own experiences in Phase I clinics, and the reaction of their significant others to their enrollment in a trial. Future research can delve more deeply into these topics to further explore what additional barriers women might face as well as how they overcome them.

By focusing on women's experiences overall in Phase I trials, our study looks beyond their reproductive potential to understand more subtle forms of discrimination that act as impediments to participation. Based on these findings, clinics and regulators can create more equitable conditions for healthy women to enroll in Phase I clinical trials.

Note

1. Because the NIH and FDA use the word 'women,' we tend to reproduce this language to mirror how these issues appear in policies and guidelines. For example, the thrust of these policies is technically to encourage the inclusion of 'female' participants but 'women' is nonetheless the preferred term. In Phase I trials, sex is the important variable of analysis. Participants are classified based on their biological sex as female or male regardless of their gender identity. In a previous study of Phase I trials, a transwoman was treated as male,

both for data collection and her treatment by the research clinic (Fisher, 2015b). We use women/men and female/male in other instances to be more precise about these policies or to support our findings and analysis. Our reference to women in this context is specific to cis-gendered women.

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