

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

Margaret Waltz Anne Drapkin Lyerly Jill A. Fisher

Department of Social Medicine and the Center for Bioethics, UNC Chapel Hill

BACKGROUND

Phase I clinical trials test the safety and tolerability of investigational drugs, often in healthy individuals.

These trials also establish drug doses which translate to the clinic and have implications for **sex-based differences in adverse drug reactions**.

Yet **women are poorly represented** in Phase I trials, so pivotal safety information for females is insufficiently and inequitably captured.

To evaluate progress on inclusion of women in early trials, we conducted **interviews with key gatekeepers** on their perception of including women in Phase I trials.

METHODS

Conducted interviews with **10 IRB members** and **12 Phase I investigators**.

Interviews lasted 84 minutes on average, were audio recorded, and transcribed verbatim.

Interview **topics included reasons to exclude people** from participating as healthy volunteers, the process of **including or excluding people of childbearing potential**, as well as their perception of the **importance of including all sexes** in Phase I trials.

We identified the following **barriers to including women** in Phase I trials in our analysis.

RESULTS

The Structure of Drug Development

The **priority placed on speed** in drug development restricts women's inclusion:

"The pharmaceutical industry is a race... So pharma companies want to start testing as soon as possible." (Investigator)

This priority results in companies waiting to conduct reproductive toxicology studies, which are expensive and time-consuming. Yet they use the **absence of reproductive toxicity data** at the time of Phase I studies to **exclude women of childbearing potential**:

"A lot of times, they don't have all the reproductive toxicity studies back from preclinical in time. So it doesn't make sense to have women in that stage." (IRB member)

"Ethically and humanely, you can't enroll a women of childbearing potential [in Phase I]... There's...zero reproductive data. And, just for the sake of expediency, that's what happens." (Investigator)

Lack of Trust in Women

Women often faced additional hurdles to participate in Phase I trials, including **stricter contraceptive requirements** than men or **longer confinement periods** before trials begin.

While risks to *potential* fetuses were cited as a reason for this difference, **explanations extended beyond biological rationales** and illustrated a **lack of trust in women**.

"[There are often] rigorous requirements for women to agree to multiple forms of contraception even if they're not in an existing sexual relationship." (Investigator)

"We recruited a group of women who would reside with us [prior to the trial starting]. It was like cloistered nuns... And we did that for nine days... But one thing they didn't do was have sex with men... And at the end of that...they were negative for pregnancy." (Investigator)

"Despite how much you preach to the women about [preventing pregnancies], some women just don't do the precautions they should." (Investigator)

Concerns about Risks to Institutions

Risks of pregnancies for the institutions enrolling women in Phase I trials served as an additional barrier to including women:

"There's a concern both at the Phase I site level and at the sponsor level about...what liability might be possible... If there's a pregnancy that occurs and if it comes out badly, you will be sued." (Investigator)

"I have found there is a huge tendency... where people exclude women or pregnant women because of a fear of the regulatory implications, and that's the only reason." (IRB member)

Despite worries about liability, **interviewees rarely, if ever, encountered pregnancies or teratogenic effects**.

"I don't know if there's been a pregnancy for a Phase I healthy volunteer study." (IRB member)

"I don't know any outcome of an infant that was adverse." (Investigator)

CONCLUSIONS

Interviews demonstrate that the **justification for women's exclusion from clinical trials is based on structural barriers, problematic gender-based rationales, and a narrow focus on eliminating fetal risk**.

Data point to the need for stronger implementation and education around the **importance of representation** in research, approaches to **address gender disparities in the attribution of reproductive risk and contraception requirements**, and future research on **how the 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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