



# Inclusion of women who are pregnant, lactating, or of reproductive potential in clinical trials: health, ethical, and regulatory considerations

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Randomised controlled trials have commonly excluded women who are pregnant, lactating, or of reproductive potential. When there is clinical equipoise, the exclusion of these women raises concerns regarding the principles of autonomy, beneficence, and justice. This exclusion also shifts evidence generation from the monitored setting of randomised controlled trials to clinical settings, where data can take several years to accrue. Here, we highlight key health, ethical, scientific, and regulatory considerations surrounding the inclusion of women who are pregnant, lactating, or of reproductive potential in clinical trials to guide further discussions. We offer recommendations for a judicious approach to inclusivity, highlighting regulatory, sponsor, and clinical trial design considerations. We highlight the need for patient engagement and interdisciplinary discourse throughout the research lifecycle.

## Background

Randomised controlled trials, considered the gold standard for the evaluation of the efficacy and safety of medical interventions, commonly exclude women who are pregnant, lactating, or of reproductive potential. This exclusion is often justified by an ideology of protection by exclusion, which arose in response to cases of drug-related fetal harm.<sup>1</sup> Such a stance prioritises fetal safety over maternal autonomy or health, despite evidence that supporting maternal health and autonomy can lead to better fetal outcomes. For example, thalidomide, a sedative and anti-emetic prescribed in dozens of countries from the late 1950s to the early 1960s, caused major fetal abnormalities in approximately 10 000 babies, as well as thousands of miscarriages.<sup>2</sup> However, exclusion from trials and reliance on post-market surveillance in pregnant women shifts potential risk to clinical settings where drug-related adverse effects or teratogenicity might become widespread before coming to attention, as in the thalidomide tragedy, which could have been smaller in scale and recognised sooner in the closely monitored setting of a randomised controlled trial and with oversight from a data safety monitoring board.

In this Viewpoint, we discuss the factors that have made it commonplace to exclude women who are pregnant, lactating, or of reproductive potential from clinical trials, and provide an overview of the medical, ethical, and regulatory considerations that govern their inclusion. We discuss how this exclusion creates knowledge gaps regarding the effect of contemporary therapies in pregnant or lactating women, perpetuating the use of outdated or minimally effective therapies for this population.<sup>1</sup> Acknowledging the justification for contraception requirements in some trials, we discuss medical and ethical considerations around blanket contraception mandates for inclusion of women of reproductive potential in randomised controlled trials. Although not intended to be a comprehensive medical, ethical, or regulatory guidance document, this Viewpoint suggests multilevel approaches that could foster the

inclusion of women who are pregnant, lactating, or of reproductive potential in trials. We use gender terminology (ie, women) throughout this Viewpoint to reflect the terminology used in many cited studies and in trial eligibility criteria, but recognise that pregnancy and lactation are biological conditions specific to the female sex rather than to gender.

## Exclusion of pregnant or lactating women from clinical trials without justification

Driven by a protection by exclusion culture that favours fetal safety over maternal autonomy or health, sponsors and investigators commonly exclude women who are pregnant, lactating, or of reproductive potential from trial participation. Although this approach prioritises doing no harm to the fetus, it falls short in showing beneficence towards the woman. Exclusions extend even to trials testing interventions of minimal risk<sup>3,4</sup> (table 1)<sup>5–11</sup>.

In a 2025 analysis of 4616 trials submitted for regulatory approval between 2019 and 2023, pregnant women were included in 1·1% of trials and breastfeeding women in 0·6%.<sup>12</sup> Further, only 22 (6%) of 400 clinical vaccine trials registered between 2018 and 2023 included pregnant women.<sup>13</sup> Among 367 industry-sponsored phase 4 clinical trials<sup>14</sup> with verified eligibility criteria, pregnancy was listed as an exclusion criterion without a specified reason in 348 (95%) trials.<sup>14</sup> Similarly, a review of 1333 randomised controlled trials found that pregnant women were eligible for 1·0% of trials and breastfeeding women were eligible for 0·5% of trials.<sup>15</sup> Furthermore, only 10·9% of trials that excluded pregnant women and 5·3% of trials that excluded breastfeeding women documented their rationale for exclusion.<sup>15</sup> This evidence gap affects clinical guidelines; in the 2018 European Society of Cardiology guidelines, over 90% of recommendations relating to pregnant or lactating women were informed by low-quality evidence, defined as consensus opinion of experts or small studies, retrospective studies, and registries.<sup>16</sup>

	Objective	Exclusion	Intervention	Reported reason for exclusion	Existing drug safety profile in pregnancy or lactation
<b>Behavioural or low-risk interventions</b>					
NCT02997943 <sup>5</sup>	To test whether a wireless feedback system yields non-inferior weight loss compared with telephone coaching in participants with a BMI of 27–45	Pregnant women	Behavioural weight loss lessons adapted from the Diabetes Prevention Program and a custom-built wireless feedback system based on self-regulation theory	Safety	NA
NCT05364476 <sup>6</sup>	To assess potential effectiveness and feasibility of a comprehensive digital intervention for people with poorly controlled type 2 diabetes	Pregnant and breastfeeding participants	16-week digital health intervention programme	None	NA
NCT03069716 <sup>7</sup>	To examine feasibility of an mHealth (mobile device) Fitbit Charge HR and mobile phone application intervention to improve step count and increase participant activity level compared with no intervention in pulmonary arterial hypertension	Pregnant women	A text messaging system linked to the Fitbit application programme that will send three texts per day to facilitate self-awareness, reinforce step targets, and link physical activity with a reward or memorable cue	None	NA
<b>Drug interventions</b>					
NCT02370680 <sup>8</sup>	To evaluate the safety and the length of effect on platelet aggregation of extended-release aspirin as compared with immediate-release aspirin or patient's current aspirin of choice in patients with type 2 diabetes and cardiovascular disease or multiple risk factors of developing cardiovascular disease	Pregnant and lactating women	One vs two capsules of extended-release aspirin	None	Low-dose aspirin is considered safe in pregnancy and associated with a low likelihood of serious complications; it is indicated for women with a history of pre-eclampsia or risk factors for it <sup>9</sup>
NCT04329611 <sup>10</sup>	To assess whether hydroxychloroquine treatment for outpatients with COVID-19 could prevent hospitalisation, mechanical ventilation, or death	Patients who were pregnant or breastfeeding	Oral hydroxychloroquine	None	Hydroxychloroquine has been used to treat lupus in pregnant women for many years <sup>3</sup>
NCT04470427 <sup>11</sup>	To evaluate the efficacy, safety, and immunogenicity of mRNA-1273 to prevent COVID-19 for up to 2 years after the second dose of mRNA-1273	Pregnant or breastfeeding women and participants of reproductive potential who are not on contraception that is deemed adequate, who have not abstained from all activities that could result in pregnancy for at least 28 days before the first dose, or who have not agreed to continue contraception that is deemed adequate for 3 months following the last dose	mRNA-1273	None	No previous biological evidence or plausibility to support teratogenicity or neonatal harm in pregnant and lactating women <sup>3</sup>
NA=Not applicable.					
<b>Table 1: Examples of low-risk clinical trials that have excluded pregnant, lactating, or women of reproductive potential</b>					

This scarcity of evidence burdens clinicians with decision making based on opinion, anecdotes, or observational data that take years or decades to accrue. Women who are pregnant or lactating are therefore offered medications that are considered minimally effective for other patient populations, who instead receive contemporary, evidence-based therapies. Large-scale data collection systems on medication use in pregnant women and maternal–fetal outcomes, such as the prospective Belgian interdisciplinary initiative to enhance pregnancy-related data registration and research on medication use,<sup>17</sup> can be useful, but they are

not a replacement for well designed randomised controlled trials, which allow causal inferences to be made.

Another ethical challenge is the requirement for paternal consent for pregnant maternal trial participation in some jurisdictions.<sup>18</sup> For example, the US Food and Drug Administration (FDA) requires paternal consent in research involving pregnant women that has the potential to benefit the fetus alone. Those in favour of these policies cite paternal rights, whereas others raise concerns about the absence of maternal autonomy or regard for varying familial hierarchies.<sup>19</sup>

There are justifiable reasons, underpinned by an ideology of doing no harm, for excluding women who are pregnant or lactating from clinical trials.<sup>20</sup> Trials might exclude them if the diagnosis does not affect them; if the intervention has a known, likely, or plausible risk of maternal or fetal harm; if the intervention is indicated (ie, no clinical equipoise); if the intervention is unlikely to provide benefit based on existing evidence; or if there is no consent from the woman.<sup>20</sup> These principles also apply to lactating women if the drug or its metabolites are excreted in breastmilk.

In the absence of justifiable reasons, pregnant or lactating women must be included in trials so that the efficacy and safety of therapies are known before clinical adoption<sup>20</sup>—a matter not only of beneficence, but also of justice for pregnant or lactating women who, like other populations, ought to be afforded robust safety and efficacy data for any proposed therapies. The prevalence of maternal chronic disease has increased, and as many as 90% of pregnant women with a chronic condition take at least one medication.<sup>1</sup> Many of these prescribed medications have not been studied in pregnant or lactating women, and their dosing data were extrapolated from studies done on men and women who were not pregnant.<sup>1</sup> Drug pharmacokinetics and pharmacodynamics can be significantly altered in pregnancy, as shown by studies of amoxicillin for anthrax prevention.<sup>21</sup> Therefore, trial data from other populations might not be consistently generalisable. Pregnancy and lactation are often grouped together as a single exclusion criterion, even though substances that cross the placental barrier might not be secreted in breastmilk in clinically relevant concentrations, and substances secreted in breastmilk might not cross the placental barrier. The COVID-19 mRNA vaccine trials excluded pregnant or lactating women even though the

vaccine neither crossed the placenta nor was extruded into breastmilk.<sup>3</sup> The resulting evidence gaps had implications on care and contributed to vaccine hesitancy in pregnant women, despite the higher risk of COVID-19-related adverse outcomes in pregnant women than in women who are not pregnant.<sup>22</sup> Similarly, pregnant women were excluded from COVID-19 hydroxychloroquine trials, despite hydroxychloroquine being used to treat lupus in pregnant women<sup>3</sup> and to prevent congenital heart block in at-risk fetuses.<sup>23</sup>

When the study question is specific to antenatal care, it is appropriate and fair that clinical trials exclusively enrol pregnant women (table 2).<sup>24–27</sup> For example, trials focused on pregnant women with HIV informed novel antiretroviral regimens that have improved outcomes,<sup>25</sup> and an international trial showed that high-dose folic acid does not prevent pre-eclampsia among at-risk pregnant women, contrary to the findings of previous observational studies.<sup>24</sup>

### Exclusion of women of reproductive potential

The exclusion of women of reproductive potential from clinical trials is more common in phase 1 trials,<sup>28</sup> but also prevalent in phase 2 and 3 trials. Among 688 phase 2 and 3 trials in diabetes, 51 (7.4%) excluded all women of reproductive potential regardless of contraceptive use.<sup>29</sup> The exclusion might be related to mistrust from trial organisers and sponsors in the woman's adherence to contraception and fear of litigation in the event of adverse pregnancy outcomes. Sponsors might also prefer preclinical, non-human animal developmental and reproductive toxicology studies, even though this approach is not required by the FDA.<sup>28</sup> Sponsors often invest in developmental and reproductive toxicology studies later in the drug development process. With minimal evidence generated before phase 1 trials begin,

	Condition of interest	Intervention	Impact on clinical practice or guidelines
NCT01355159	Pre-eclampsia	High-dose folic acid	Contrasted with findings of previous observational studies and provides basis for change in clinical practice <sup>24</sup>
NCT03048422	HIV	Dolutegravir with emtricitabine and tenofovir alafenamide; or dolutegravir with emtricitabine and tenofovir disoproxil fumarate; or efavirenz and emtricitabine and tenofovir disoproxil fumarate antiretroviral therapy regimens	Findings led to further clinical trials as well as changes to the recommended antiretroviral therapy regimens during pregnancy <sup>25</sup>
NCT01828697	Recurrent venous thromboembolism in pregnancy	Intermediate-dose vs low-dose LMWH	The data inform optimal LMWH dosing among pregnant women <sup>26</sup>
NCT02299414	Mild chronic hypertension during pregnancy	First-line anti-hypertensive drugs for pregnancy (ie, labetalol or extended-release nifedipine) supplied by trial investigators or other medication (eg, amlodipine or methylodopa) if preferred by the patient	Findings led to the ACOG changing their recommendations of the threshold for initiating and titrating of medical therapy for chronic hypertension in pregnancy to 140/90 from 160/110 <sup>27</sup>

ACOG=American College of Obstetricians and Gynecologists. LMWH=low-molecular-weight heparin.

**Table 2: Examples of clinical trials that have affected clinical care in pregnant women**

excluding women of reproductive potential becomes normative.<sup>28</sup> Even when such preclinical studies exist and do not show evidence of fetal harm, some sponsors or investigators might find the uncertainty to be a justifiable reason for excluding women of reproductive potential.<sup>28</sup>

Later-phase trials commonly have contraception mandates for trial eligibility; these have ethical and medical implications for potential participants.<sup>3,30</sup> Trials testing interventions with unknown fetal safety effects typically require at least one form of highly effective female contraceptive.<sup>28</sup> This requirement is typically absolute, and does not allow for women to make informed decisions around contraceptive use; even women who are not sexually active are required to initiate what is deemed as acceptable contraception to participate in some trials.<sup>28</sup> This blanket approach undermines individual autonomy and can lead to unjust trial exclusion. The personal financial, cultural, and health factors that can influence the uptake of contraception are overlooked, possibly biasing the selection of participants.<sup>30</sup> Additionally, the use of contraception can affect the interpretation of interventions in the context of natural menstrual cycles and associated pharmacokinetics. Furthermore, what are considered acceptable contraceptives (oral contraceptive pills, intrauterine devices, and hormonal injections or patches) are themselves not without risk or side-effects (eg, weight gain, thromboembolism, and infection).

## Solutions

Increasing the representation of women who are pregnant, lactating, or of reproductive potential in clinical trials requires multifaceted solutions (figure).<sup>2,18,20,30,31</sup>

### Policy and regulations

In the USA, the FDA guidance on conducting research highlights that some predetermined criteria must be met before pregnant women can be included in phase 3 trials, but some deserve further consideration (panel).<sup>18,32–34</sup>

Because the FDA does not require research to be conducted in pregnant or lactating women, the guidance might not provide enough incentive for sponsors seeking regulatory approval to invest in research in pregnant or lactating women.<sup>2</sup> Furthermore, the FDA criteria are not easily met because animal studies are typically conducted exclusively in male animals, and early phase clinical studies are typically male-predominant. Additionally, paternal consent can be difficult to obtain.

In the EU, the Clinical Trials Regulation<sup>32</sup> stipulates that clinical trials conducted in pregnant or lactating women must offer direct benefit that outweighs the risk to the pregnant or lactating woman or to her fetus or newborn. This prerequisite is counterintuitive, given that treatment equipoise underpins the rationale for clinical trials; if benefits and risks were known, trials would not be necessary. Similarly, trials in women who are not pregnant should not preclude testing for maternal–fetal efficacy or

safety in women who are pregnant or lactating. Additional considerations and avenues for trial approval are provided in the panel.

In the UK, the Medicines and Healthcare products Regulatory Agency outlines requirements for the inclusion of women of reproductive potential in clinical trials, including a clear warning about the risks of harm to an unborn or breastfeeding child, and information on the need for pregnancy testing and the use of contraception before enrolment.<sup>33</sup> In Australia, the Therapeutic Goods Authority stipulates that in studies involving pregnant women, the wellbeing of the pregnant woman and her fetus takes precedence over research considerations. It outlines content that pregnant women should specifically be informed of, in addition to the usual requirements, for consent (panel).<sup>34</sup>

Regulatory requirements often guide the need for clinical trials that include pregnant or lactating women and can influence the feasibility of recruitment and participation rates. In June, 2025, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the European Medicines Agency released for public consultation a new guideline regarding the inclusion of pregnant and lactating people in clinical trials.<sup>35</sup> The finalised report may influence regulatory criteria established by national and continental regulatory bodies. Furthermore, a 2024 report by the US National Academies of Sciences, Engineering, and Medicine on advancing research in pregnant or lactating women provides recommendations to regulatory organisations.<sup>2</sup> One recommendation is the formation of a joint National Institutes of Health (NIH)–FDA taskforce to develop guidelines surrounding the conduct of drug safety studies for pregnant or lactating women. These studies would use safety information and annual status reports from existing pregnancy and lactation registries.<sup>2</sup> Another recommendation is that the US Congress passes legislation allowing the FDA to require research on medical products in pregnant or lactating women.<sup>2</sup> To

Women of reproductive potential	Pregnant or lactating women
<ul style="list-style-type: none"> <li>• Include women of reproductive potential at the earliest stages of research to identify sex-related differences</li> <li>• Remodel the contraception mandate and require an informed discussion around the risks of pregnancy and benefits of contraception</li> </ul>	<ul style="list-style-type: none"> <li>• Incentivise research in pregnant or lactating women at the regulatory and clinical trial design levels</li> <li>• Design trials specifically for pregnant or lactating women to assess efficacy and safety</li> <li>• Provide separate, valid justification for the exclusion of pregnant or lactating women</li> <li>• Include insurance costs for investigator-initiated trials that include pregnant or lactating women</li> <li>• Reconsider the requirement of paternal consent for trial participation</li> </ul>
<ul style="list-style-type: none"> <li>• Create an interagency taskforce to develop clinical trial guidelines</li> <li>• Pass legislation to require research in women who are pregnant, lactating, or of reproductive potential</li> <li>• Involve obstetric medicine specialists, maternal–fetal medicine specialists, paediatricians, and patients in trial design</li> <li>• Consult women in the development of information brochures and consent documents</li> </ul>	

Figure: Proposed multilevel solutions to increase the inclusion of women who are pregnant, lactating, or of reproductive potential in clinical trials<sup>2,18,20,30,31</sup>

### Panel: Regulatory criteria for the inclusion of women who are pregnant, lactating, or of reproductive potential in clinical trials

#### US Food and Drug Administration (USA)<sup>18</sup>

The predetermined criteria that must be met before the inclusion of pregnant women in phase 3 trials include but are not limited to:

- Preclinical animal studies and clinical studies in women who are not pregnant have been completed
- Any risk to the fetus is attributable only to interventions that have the potential to benefit the woman or the fetus
- Consent from the father of the fetus is obtained for research that has the potential to directly benefit only the fetus

#### European Clinical Trials Regulation (EU)<sup>32</sup>

The conditions that must be met before clinical trials can be conducted in pregnant or lactating women include but are not limited to:

- The trial is expected to offer a direct benefit (that outweighs the risks) to the pregnant or lactating woman, her fetus, or child
- If no direct benefit to the woman or fetus is expected, the trial can be conducted only if:
  - A similar trial cannot be conducted in women who are not pregnant or lactating
  - The results are likely to benefit pregnant or lactating women
  - The trial poses minimal risk to the pregnant woman or her fetus or child
  - For women who are lactating, measures are implemented to avoid adverse outcomes for the child
  - No financial incentives are provided other than compensation for expenses incurred through trial participation

#### Medicines and Healthcare products Regulatory Agency (UK)<sup>33</sup>

The general requirements for informed consent must be accompanied by a specific statement that outlines the reasonably foreseeable risks to the woman, embryo, fetus, or nursing infant. Details should include but are not limited to:

- The need for pregnancy testing or contraception
- What will happen should pregnancy occur, including how the pregnancy will be monitored

#### Therapeutic Goods Authority (Australia)<sup>34</sup>

The wellbeing of the pregnant woman and her fetus should take precedence over research considerations. In addition to general required elements of informed consent, the pregnant woman must also be informed of the following:

- That she should consider whether she should obtain consent from any other person, such as the other parent
- Whether it is possible to store the fetus or fetal tissues for later research use
- That she can withdraw consent at any time, whether before or after a termination or other fetal loss
- Whether there is potential for commercial application of research outcomes, including cell line development
- That she will not be entitled to a share in any commercial application profits
- Whether fetal organs or resulting stem-cell lines will be exported to another country

address the delay in completion of developmental and reproductive toxicology studies and resulting exclusion of women of reproductive potential, studies could be conducted and generate results earlier in the trial process.<sup>36</sup> Furthermore, clinical trial investigators could be better educated on how to interpret the results of these studies.<sup>36</sup>

Financial incentives play an important role in industry-sponsored research. Sponsors might not deem pregnant or lactating women a large enough market to justify the upfront risk of testing drug or device therapies. Public funding agencies should include insurance costs for investigator-initiated trials that include pregnant or lactating women.<sup>2</sup> In the absence of financial incentives, regulatory requirements with procedural guidance could help generate evidence, particularly in diseases that commonly affect pregnant or lactating women. The paediatric exclusivity programme, which awards 6 additional months of marketing exclusivity on a drug in exchange for conducting FDA-requested paediatric studies, has substantially increased paediatric drug labelling.<sup>37,38</sup> A similar financial incentive in pregnant or lactating women could facilitate their inclusion in clinical trials, but will need careful assessment. Conditions that commonly affect maternal–fetal health would be a strategic area to target. For example, given that bleeding and cardiovascular events are leading causes of maternal death, regulatory approval for treatments of these conditions could require evidence generation in pregnant or lactating women.<sup>2</sup> If randomised trials are not feasible, novel study designs with analytic approaches that enable causal inferences could be a requirement for regulatory approval.

The feasibility of solutions depends heavily on the political climate. Under the second Trump administration, the US NIH has terminated nearly 800 research projects worth over USD\$2.3 billion, including many focused on women's health.<sup>39</sup> Policies against diversity extend to the FDA. With ongoing policy considerations and legal proceedings, the future of NIH-funded research and regulatory decisions remains uncertain, and setbacks in including pregnant and lactating women in clinical trials are expected.

#### Clinical trial design and implementation

Women with reproductive potential should ideally be included in phase 2 and phase 3 clinical trials. In trials where there is potential for fetal harm, an informed discussion about the risks and benefits of trial participation in the event of pregnancy could be a more reasonable approach than exclusion or contraception mandates. The participant's individual circumstance, values, and preferences could then guide the decision for trial participation regardless of contraception use.<sup>30</sup> This risk-based approach would balance safety and liability without mandating contraception.<sup>30</sup>

Trials aimed at testing an intervention's effect in pregnant or lactating women could be restricted to pregnant or lactating women; including a few pregnant or lactating women in a large trial will not produce the statistical power necessary to assess efficacy or monitor safety in this group. Alternatively, for conditions that are specific to (or predominantly affect) women, a balanced

subgroup of pregnant or lactating women could be considered for meaningful subgroup analysis.

Any sex-specific exclusion criteria should be supported by valid justification.<sup>20</sup> Pregnancy and lactation (two separate biological states) should consistently be listed as separate eligibility criteria rather than combined;<sup>20</sup> depending on the circumstances, it might be appropriate to exclude one but not the other, and separation could reduce unnecessary exclusion. Maternal–fetal specialists could be included in trial advisory boards to explore how women who are pregnant, lactating, or of reproductive potential can be safely included as participants.<sup>20</sup>

### Partnerships and co-design

The RECOVERY trial, one of the few COVID-19 treatment trials that included pregnant women, used several strategies to navigate common barriers to participation and inclusion, including engaging with the UK Teratology Information Service.<sup>31</sup> Engaging individuals with lived experience as research partners can add an important perspective that is typically missed in drug or device development.<sup>31</sup> Advocacy groups led by those with lived experience have been instrumental in advancing the inclusion of women who are pregnant, lactating, or of reproductive potential in clinical trials. An example is the Pregnancy and HIV and AIDS: Seeking Equitable Study working group, which focuses on pregnant women with HIV.<sup>40</sup> In 2020, this group developed a comprehensive guidance document that has since influenced multiple international projects, including the UNAIDS–WHO ethics guidance for HIV prevention to accelerate the study of new drugs in pregnancy.<sup>40</sup>

### Conclusion

The persistent, categorical exclusion of women who are pregnant, lactating, or of reproductive potential from clinical trials raises concerns regarding maternal autonomy, beneficence, and justice. This default exclusion, in combination with the common blanket requirement of contraception use, can contribute to under-representation of women in clinical trials, gaps in high-quality evidence, and health-care disparities. System-level regulatory changes, changes to the design and execution of clinical trials, and emphasis on patient engagement and co-design can contribute to a more inclusive approach that promotes the health and safety of women.

#### Contributors

HGCVS conceptualised this Viewpoint. LM and AM conducted the literature search. All authors contributed to writing and revising.

#### Declaration of interests

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