

Women who are pregnant, lactating, or of childbearing potential: overdue for inclusion in CV trials

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Relevant disclosures

- I serve on international committees that aim to increase representativeness in clinical trials
- Research funding: Canadian Institute of Health Research, Heart and Stroke Foundation of Canada

Cardiovascular disease: a leading cause of death during pregnancy

- CVD is the leading cause of maternal mortality
 - Cardiomyopathy, HF, MI, and stroke account for **> 33% of pregnancy-related deaths**
- Burden of CVD during pregnancy is expected to increase
 - rising maternal age, earlier onset CVD, and increase in CV risk factors
- Pregnancy a period of hemodynamic changes, heightened CV risk
- ~32% of pregnant women with CVD use cardiovascular medications during their pregnancy

CVD care during pregnancy and lactation is guided by low-quality evidence

- Most CV guideline recommendations in pregnancy and lactation informed by level C evidence
 - consensus of expert opinion, small studies, retrospective studies and/or registries
- 2018 ESC 'Guidelines for the Management of Cardiovascular Disease During Pregnancy' provides the most comprehensive recommendations
 - 90% of recommendations derived from level C Evidence

Sex-specific exclusion criteria are common in RCTs

- A systematic review of RCTs published in high-impact medical journals found that female biology was the **basis of exclusion in 39% of trials**, and that these sex-specific eligibility criteria were largely unjustified.
- In a review of 317 heart failure RCTs, **26% used sex-specific eligibility criteria** and excluded women on the basis of existing pregnancy or childbearing potential - **none provided a rationale** for these exclusion criteria.
 - Independently associated (OR 2.1) with under-enrollment of women in the RCTs (PPR < 0.8)
 - Potential reasons
 - Time / testing for pregnancy
 - Conversations around intent / sexual activity / birth control / menopause

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Sex-specific exclusion criteria were present in at least 81 of 317 (26%) HF RCTs 2000-2020

Sex-related eligibility criteria reported in 81 RCTs	% of trials with exclusion criterion that under-enrolled females
Must not be pregnant (75% of trials)	83.6
Must be on a scientifically accepted method of contraception (43% trials)	83.0
Must not be lactating or nursing (32% trials)	69.2
Must be without childbearing potential based on surgical treatment (21% trials)	94.1
Must be confirmed post-menopausal (20% trials)	87.5
Must not have a desire to become pregnant during study period (10% trials)	75.0
Must not be of childbearing age (5% trials)	75.0

There are benefits of including pregnant and lactating women in cardiovascular RCTs



Fetal Benefits

- Direct benefits of careful fetal monitoring
- Indirect benefits of careful maternal monitoring and care



Maternal Benefits

- Autonomy in providing informed consent to trial enrollment
- Direct health benefits of careful monitoring and care



Societal Benefits

- Reliable estimates of treatment efficacy and safety
- Improved understanding of pathologies and treatment for conditions that occur at greater frequencies in pregnancy
- Improved fetal outcomes via evidence-based maternal care
- Representative inclusion of women in cardiovascular trials
- Reduction in disparities in cardiovascular care

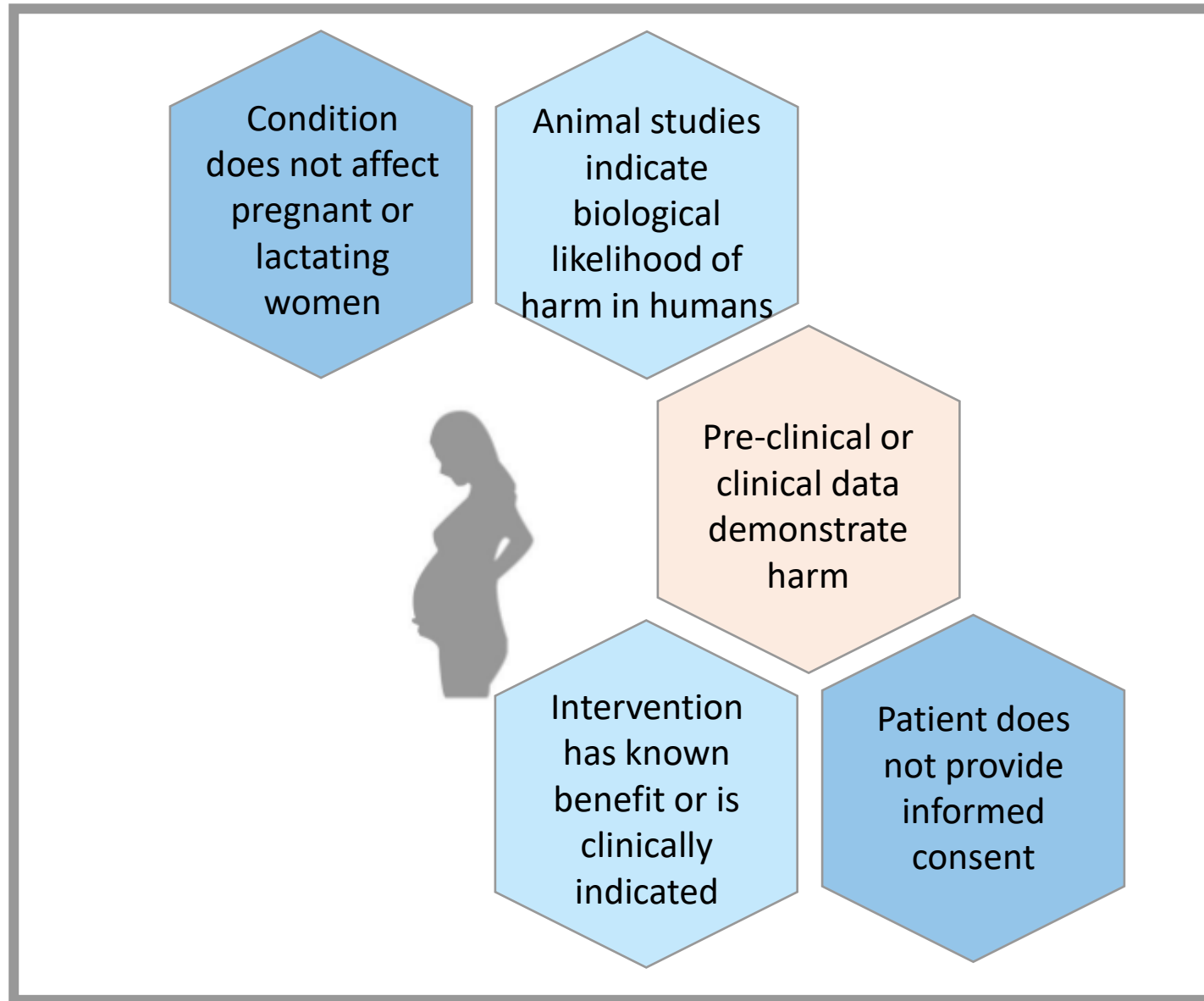
Unjustified exclusion from trial participation violates ethical principles

- Exclusion of women who are pregnant, lactating or of childbearing age from trials driven '**protection by exclusion**' ideology
 - Aims to protect fetus >> mother from potential harm (lack of fetal consent)
- Exclusion without justification violates
 - **Autonomy**
 - best preserved with informed discussion and consent
 - **Beneficence**
 - limited high-quality evidence regarding safety and efficacy, increasing susceptibility of harm
 - **Justice**
 - associated with under-enrollment of all women
 - pregnant and lactating women deprived of potentially beneficial therapies

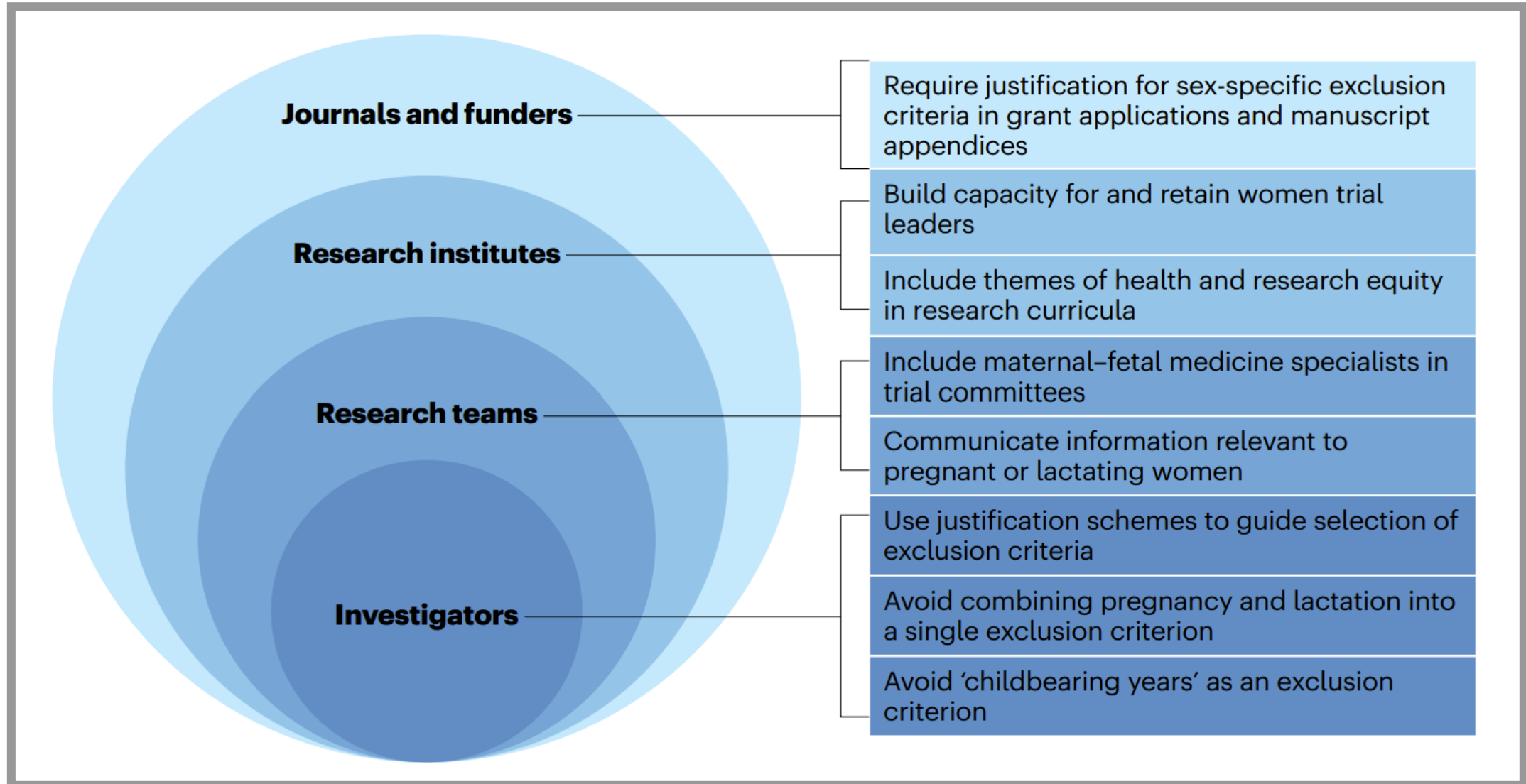
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Some exclusion criteria are justified



Recommendations to increase representation of pregnant and lactating women in cardiovascular trials



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