DALHOUSIE UNIVERSITY
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Novel Tech *Ethics*
Faculty of Medicine

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Interagency Panel on Research Ethics
350 Albert Street
Ottawa, ON Canada
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To Whom it May Concern:

As the Interagency Panel on Research ethics (PRE) is considering revisions to the TCPS, we are writing to draw your attention to a longstanding problem with the TCPS as concerns research involving women, pregnant women, and breastfeeding women.

While there is much we could suggest to improve the TCPS with respect to these study population we here draw your attention to two pressing issues: Research in women of childbearing potential and research in pregnant and breastfeeding women.

We are pleased to have this letter and my comments posted on the Panel on Research Ethics Website

Sincerely,

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Chris Kaposy, PhD
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Please include these comments in the public record of the consultation process on the Panel on Research Ethics Website

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Chapter 4 Fairness and Equity in Research Participation

I. CURRENT TEXT and reason for proposed change:

Article 4.2 Women shall not be inappropriately excluded from research solely on the basis of gender or sex.

> The TCPS 2 does not include a sufficiently strong directive to researchers regarding the inclusion of women in research. It also fails to stress the importance of gender and sex-based analysis.

PROPOSED CHANGE:

Article 4.2 Women (including women of childbearing capacity) shall be included in research, unless there is a valid reason for exclusion.

II. CURRENT TEXT and reason for proposed changes:

Article 4.3 Women shall not be inappropriately excluded from research solely on the basis of their reproductive capacity, or because they are pregnant or breastfeeding.

> TCPS2 inappropriately clusters information about research in women who may become pregnant (i.e., women of childbearing capacity), with research in women who are pregnant or breastfeeding. It is imperative that there be discrete research guidelines for these discrete populations.

PROPOSED CHANGES:

(i) Mandatory contraception:

It is common practice in Canada and elsewhere for researchers to mandate the use of contraception by women of childbearing capacity while enrolled in clinical trials. This practice is deeply problematic for several reasons, not the least of which is that this privileges the potential interests of *potential* fetuses over the autonomy interests of women research participants. Also, this practice is often over-inclusive. Consider, for example, women who are not sexually active (e.g., nuns), are not sexually active in a heterosexual relationship (e.g., lesbians), or are sexually active in a heterosexual relationship with a male partner who has had a successful vasectomy. Or, consider women who have had a hysterectomy or a successful tubal ligation, women with certain types of infertility, or women with male partners who have certain types of infertility. Requiring these women to use birth control as a condition of research participation is offensive and should not be permitted under any circumstances.

Current practice with respect to mandatory contraception is also often discriminatory in its exclusive application to women. There is no ethical justification for the blanket requirement of contraceptive use only by women of childbearing capacity. If the worry is the risk of fetal harm, then it is important to recognize potential male contributions to this harm.

TCPS2 offers little guidance on contraceptive requirements in clinical trial protocols. It only includes the following general statement "researchers should not require participants to use oral contraception, unless there is a valid reason for doing so." The guidelines should clearly state that routine *mandatory* contraception is *not* a legitimate standard inclusion criterion. Mandatory contraception must be ethically justified.

- It is ethically offensive to require all women (including those who abstain from heterosexual activity and women with infertile sexual partners) to use contraception as a condition of research involvement.

- Contraceptive requirements place greater emphasis on protecting the potential interests of *potential* fetuses than on respecting the autonomous judgments of women research participants about their need for contraception. The potential interests of nonexistent beings should not be prioritized over the real interests of women.

- Contraceptive requirements imposed exclusively on women research participants are inequitable, since damage to a fetus can be caused by teratogens that attach to sperm.

- Mandatory contraception can deter women from participating in research for financial or personal reasons.

Proposed Change to Article 4.3

Article 4.3 Research participants shall not be inappropriately required to use contraception as a condition of research participation.

Application Researchers should not require research participants to use contraception without a valid, compelling reason for doing so that is fully documented and evidence-based. For example, requiring the use of contraception can be justified if it is already known that the agent being studied is teratogenic, and if the research participant plans to engage in sexual activity that is likely to lead to pregnancy. When there is adequate justification for requiring research participants to use contraception, such requirements should apply equitably to all participants. There is, for example, evidence that damage to a fetus can be caused by teratogenic agents that transfer via sperm.

> Those who abstain from procreative sexual intercourse for personal, religious, or cultural reasons shall not be required to use contraception. Furthermore, research participants shall have the option of (i) abstaining from procreative sexual intercourse rather than using mandated contraception, or (ii) terminating adversely affected pregnancies that may occur while participating in research. These options shall be made known to research participants as part of the consent process.

(ii) Research in pregnant and breastfeeding women

It is widely recognized that pregnancy is a near-automatic exclusion criterion for research participation, "regardless of the costs of exclusion or the magnitude or likelihood of the risks of participation." The near complete exclusion of pregnant women from research on drugs and biologics means that there is little clinical trial data on the basis of which health care providers can make treatment recommendations for pregnant women. This includes women with underlying health conditions who become pregnant, and healthy pregnant women who become sick.

There are several reasons to pursue research involving pregnant women. These include:
• Developing effective treatments for pregnant women
• Promoting fetal safety (avoiding clinical use of drugs and biologics that are harmful to the fetus)
• Reducing harm from the reticence to prescribe potentially beneficial drugs and biologics (suboptimal care)
• Allowing access to benefits of research participation

Justice requires that if pregnant women are going to use drugs and biologics to manage their health, then it is imperative to study these drugs and biologics in that population. More generally, we need to learn to make reasoned decisions about risk in pregnancy (which may include taking responsible and calculated risks), both with respect to pregnant women and developing fetuses. We also need to recognize that there are responsible ways in which to manage risk.

TCPS2 makes no improvement on the original TCPS regarding research involving pregnant women. In fact, TCPS2 simply reiterates the text in TCPS that, "In considering research on pregnant or breastfeeding women, researchers and REBs shall, however, take into account risks and potential benefits for the woman and her embryo, fetus or infant" (Application, Art. 4.3).

This requirement provides no substantive guidance on which benefits and harms to consider, or how these should be weighted. A useful source of information is the Health Canada *Guidance Document: Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences*. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/womct_femec-eng.php

Moreover, this requirement is ineffective for the purposes of promoting the involvement of pregnant women in research (when such research is appropriate by virtue of clinical equipoise). The requirement appears to place the burden of justification on those who would include pregnant women, rather than on those who would exclude pregnant women from research trials.

Pregnant women need to be included in research because their exclusion has led to serious knowledge gaps about the safety and efficacy of drugs and biologics currently used during pregnancy. The absence of information also precludes the possibility of women giving informed consent when a medication is suggested. At present, only a handful of drugs have been approved for use in pregnancy, and of the thousands of drugs on the market only about 100 have a demonstrated safety record in pregnancy. This means that in most situations, pregnant women are forced to choose between taking medications with uncertain safety and efficacy or declining treatment for illnesses that may compromise their health or the health of their fetuses.

Excluding pregnant women from research is usually framed as a way to protect fetal health. This is certainly important, but the need to protect fetal health should not disqualify pregnant women from research participation when it is appropriate. There are responsible ways to reduce the risks of research involving pregnant women, just as there are responsible ways to reduce risks associated with research involving other populations, such as children. We should not let fear prevent us from conducting necessary research when it is ethically sound.

Pregnant women should be treated like all other prospective research participants insofar as they should be able to enroll in responsible well-designed clinical trials that abide by the established norms of research ethics and have been approved by an REB.

Proposed Change to Article 4.3

Article 4.4 Pregnant and breastfeeding women shall be appropriately included in research unless there is a valid reason for exclusion.

Application Researchers should not exclude pregnant and breastfeeding women from research, unless there is a valid, compelling reason for their exclusion. Exclusions should be based on clear criteria that reflect attention to (i) the risks of teratogenicity and (ii) the potential benefits of the interventions (including drugs, biologics, and medical devices) under study for the health of women, fetuses and newborns. A useful reference is the Health Canada *Guidance Document: Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences*. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/womct_femec-eng.php

The ability to offer pregnant women and fetuses, breastfeeding women and newborns effective and safe evidence-based treatments depends on

information obtained from well-designed, ethically sound clinical trials involving pregnant and breastfeeding women.

Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility.