

Professor Rieke van der Graaf  
University Medical Center Utrecht  
Secretary of the Working Group on the Revision of the CIOMS Guidelines  
[R.vanderGraaf@umcutrecht.nl](mailto:R.vanderGraaf@umcutrecht.nl)

**Re: Consultation on CIOMS Guideline 15**

May 25, 2015

Dear Prof. van der Graaf,

Thank you for the invitation to comment on the draft revised text for CIOMS "Guidelines 15: Pregnant and lactating women as research participants". Revisions to these guidelines are timely and we are very pleased to be able to contribute. Attached are select recommendations prepared by me and my colleague Dr. Robyn MacQuarrie.

You will note that one of our key recommendations is not to address research in pregnant women in the same Guideline as research in lactating women. These are very different research populations and the concerns regarding potential harms for the developing fetus are different from those for the newborn. Grouping these populations results in guidelines that do not maximally serve either population.

We hope you find the comments helpful and would be very happy to answer any questions you may have. The CIOMS Guidelines are already widely regarded as progressive in their positive statement that pregnant women should be presumed eligible to participate in research and we are very pleased to see continued leadership in this vein.

Also attached, for your consideration, is our forthcoming book chapter "Why physicians and women should want pregnant women included in clinical trials." We think you may find this helpful.

Sincerely,



Françoise Baylis, PhD, FRSC, FCAHS  
*Professor and Canada Research Chair  
in Bioethics and Philosophy*



Robyn MacQuarrie, MSc, MD, FRCS(C)  
*Obstetrician and Gynecologist,  
Cumberland Regional Health Care Centre,  
Amherst, Canada*

**CIOMS “Guidelines 15: Pregnant and lactating women as research participants”**  
**Comments prepared by Françoise Baylis and Robyn MacQuarrie**

	Original Text	Justification for Change	Suggested Text
<b>Title</b>	Guideline 15: Pregnant and Lactating women as research participants	<p>Grouping pregnant women and lactating women in one category is problematic. The risk profiles of these groups are entirely different, as are the reasons for caution.</p> <p>In the current draft of Guideline 15, some statements apply to pregnant women alone and some to both pregnant and lactating women. This shifting provides evidence in support of the recommendation for a separate guideline on pregnant women.</p>	<p>Guideline 15: Pregnant women as research participants</p> <p>Guideline 16: Lactating women as research participants</p>
<b>First Sentence</b>	Pregnant and lactating women have distinct physiologies and health needs that require research in this population.	As above, separate out pregnant and lactating women, as these are two separate populations.	Pregnant women have distinct physiologies and health needs that require research in this population.
<b>Second sentence</b>	Pregnant and lactating women should be presumed to be eligible for participation in health-related research on conditions that affect these women.	<p>As above, separate out pregnant and lactating women, as these are two separate populations.</p> <p>The phrasing “health-related research on “conditions that affect these women” is potentially ambiguous and incomplete. It should be clear that pregnant women should be presumed eligible to participate in: (i) research about conditions specific to pregnancy (e.g., nausea and pre-eclampsia), as well as (ii) research about conditions that affect the general population</p>	Pregnant women should be presumed eligible to participate in health-related research on: (i) interventions for conditions resulting from pregnancy; (ii) interventions for conditions that affect the general population that can be reasonably expected to be used off-label during pregnancy; (iii) interventions for conditions that affect the developing fetus; and (iv) interventions

		<p>including women during pregnancy, (e.g., where drugs that are not intended to treat pregnancy would reasonably be expected to be used in pregnancy, such as diabetes, depression and so on). As one of us has argued elsewhere (FB) “pregnant women get sick and sick women get pregnant.”</p> <p>Also, it is important to remember that research in pregnancy is sometimes about the health of the fetus, or even the health of the subsequent infant/child (e.g., vaccines).</p> <p>At the present time, clinical trials in pregnancy frequently focus on issues in and around pregnancy. While this is a positive step in the right direction, all clinical research, however, should allow for the appropriate inclusion of pregnant women, and not exclude women based on pregnancy alone.</p>	<p>occurring during pregnancy with the infant/child as one of the research participants. In brief, pregnant women should not be excluded from research solely on the basis of pregnancy.</p>
<b>Third sentence</b>	<p>Biomedical Research in this population should be performed following evidence obtained from pregnant or lactating animal experiments, when relevant (confer guideline 1)</p>	<p>Pre-clinical research in pregnant animal models may not be the most appropriate (or only) research to consider. For example, it may be appropriate to move forward with research in pregnant women after an intervention has demonstrated a reasonable safety profile in human trials involving non-pregnant persons.</p>	<p>Research in pregnant women should be initiated pursuant to a careful consideration of the best available data from: (i) pre-clinical research in pregnant animal models; (ii) research in non-pregnant women; (iii) retrospective observational studies; and (iv) adverse events registries.</p>

		<p>Additionally, retrospective databases should be used to determine if there is an increased risk to the fetus before pregnant women are included in biomedical research. Finally the pharmacology of a drug needs to be considered to determine how it is likely to be metabolized in pregnant women (i.e. renal excretion, dosage, crossing the placental).</p> <p>It is not clear why there is a precise reference to biomedical research in this sentence, but nowhere else in the document.</p>	
<b>Fourth sentence</b>	<p>Researchers and research ethics committees must ensure that prospective participants 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.</p>	<p>It is important to clarify that the benefits of research are at best a potential outcome, not a guarantee. "Risk" is a probability statement (i.e., potential harm) and the corollary is potential benefit.</p> <p>Placing the reference to risks and benefits "to their fertility" after the reference to subsequent offspring implies that the fertility is that of the offspring, and not the pregnant women.</p> <p>While it is important to highlight special issues unique to pregnancy, it is important that this be worded in such a way as to be clear that all prospective research participants must be adequately informed, not just "prospective</p>	<p>Researchers and research ethics committees must ensure that prospective research participants are properly informed of the risks and potential benefits of research. With research in pregnant women, disclosure must include best available information about possible consequences for pregnant women (including future fertility), their pregnancies, their fetus(es) and their future offspring. Disclosure should also include information about what has been done to maximize potential benefits and</p>

		<p>participants who are pregnant”.</p> <p>With research in pregnancy there is no way to entirely mitigate all risks to the fetus. While researchers should do all they can to minimize risks to the fetus, research is about addressing/resolving uncertainty and as such it is not possible to disclose all risks, only those risks that can be anticipated.</p>	<p>minimize potential harms.</p>
<p><b>Fifth and sixth sentences with bullets below</b></p>	<p>For research interventions or procedures that have the potential to benefit either the pregnant or the lactating woman or their fetus or infant risks are acceptable if they are minimized and outweighed by the prospect of the individual benefit.</p> <p>For research interventions or procedures that have no prospect of benefit, the researcher must ensure that</p> <ul style="list-style-type: none"> <li>• These research interventions or procedures that pose no more than minimal risk; and</li> <li>• The purpose of the research is to obtain knowledge relevant to the particular health needs of pregnant or lactating women or their fetuses or infants.</li> </ul>	<p>The distinction between research “with the prospect of individual benefit” and research “with no prospect of benefit” is deeply problematic. If the research has no prospect of benefit, it should not be done.</p> <p>The distinction you may be looking for is between “research of potential health benefit” and “research of no potential health benefit” where the potential benefit is collective knowledge production. In both cases what matters is the possibility of a favourable or proportionate harm/benefit ratio taking into consideration both the nature and the probability of occurrence of the potential harms and benefits, on a broad understanding of both of these terms. Potential harms and benefits may be physical, psychological, social, emotional, moral or</p>	<p>All research involving humans (including pregnant women) should have a favourable or proportionate harm-benefit ratio. The threshold concept of minimal risk is not applicable to research involving pregnant women.</p> <p>What matters for both “research of potential health benefit” and “research of no potential health benefit” (where the potential benefit is knowledge production) is whether there is the prospect of a favourable or proportionate harm-benefit ratio for the pregnant woman, her fetus and her future children, taking into consideration both the nature and the probability of</p>

		spiritual. They may also be social, emotional, moral or spiritual.	occurrence of the potential harms and benefits.
		If the potential benefits are seen to be insignificant and unlikely, then clearly only equivalent or lesser harms with a similar or lower probability of occurrence should be tolerated. Alternatively, if the potential benefits are seen to be significant and likely, then it is reasonable to tolerate more substantial and likely potential harms.	Potential harms and benefits to health may be physical, psychological, social, emotional, moral or spiritual. All efforts should be made in the design of research to maximize potential benefits and minimize potential harms.
		In the case of research with no prospect of individual health benefit to the woman, her fetus or subsequent children, less risk is tolerable in order to generate a favourable harm to benefit ratio. Research with no potential health benefit to the woman, her fetus or future children still has the potential for population health benefit.	
<b>Missing from Guideline 15</b>		While the Commentary addresses the importance of long-term follow up as part of the research protocol, this is not included in Guideline 15.	All research involving pregnant women must include short-term and long-term follow up of future children, as adverse events associated with research in pregnancy may not be exposed immediately.
<b>Last sentence of Guideline 15</b>	As a general rule, health related research involving pregnant women that has the potential for serious harm to the fetus involving pregnant women should be conducted only in settings	Access to safe and timely termination of pregnancy should be available to all women. As referenced in this document, however, this point is in tension with the obligation to only	Access to safe and timely termination of pregnancy, in the event of an unexpected adverse outcome, should be

	<p>where they can be guaranteed access to a safe, legal abortion in the event that the participation in the research makes the pregnancy unwanted.</p>	<p>proceed with research where there is the prospect of a favourable harm/benefit ratio.</p> <p>In the context of research, unforeseen adverse outcomes that negatively affect a pregnancy are possible and as a result of this women may want to terminate their pregnancy. In these circumstances, safe timely access to a termination of a pregnancy should be available.</p>	<p>available to pregnant research participants.</p>
<b>Commentary</b>	<p>Some research involving pregnant women may be directed at the health of the fetus. In such cases, the role of the woman remains the same: she is the decision maker for any interventions that affect her, although it is desirable to obtain the father's opinion also.</p>	<p>This comment is deeply problematic. First, the putative father may be no more than a sperm donor. He may be a violent person who abused the mother, etc... Second, the statement that his opinion should be solicited is unhelpful as there is no indication that his opinion should be heeded. This idea, borrowed from 45CFR46 (US Common Rule), should be eliminated. Instead, there should be a clear statement to the effect that the pregnant woman is the sole person who may consent to research involving herself (and of necessity her fetus). This is particularly important for international guidelines that will be applicable in different political jurisdictions and cultural contexts.</p> <p>A statement to this effect should follow sentence #4 of the Guideline and not be</p>	<p>Pregnant women are independently capable of consenting or refusing research participation</p>

### General Themes That Require Incorporation

- It would be helpful if the commentary following the Guideline included a strong rationale for the responsible inclusion of pregnant women in biomedical research. Elsewhere, we have written “A direct consequence of the routine exclusion of pregnant women from clinical trials is pregnant women using over-the-counter and prescriptions medications in the absence of population-specific clinical trial data about the potential benefits and harms of these medications for themselves, their fetuses and their future children. In our view, pregnant women are as entitled as other patient populations to robust clinical trial data about safety and dosing on the basis of which to make evidence-informed decisions. To this end, we maintain that pregnant women should be presumed eligible to participate in clinical trials.” This kind of statement would help to better contextualize the information about the tragedy with the drug thalidomide.
- It would be helpful to include a clear statement about the *sine qua non* of a favourable or proportionate harm-benefit ratio for all research involving humans, including pregnant women. The notion of minimal risk borrowed from 45 CFR 46 (US Common Rule) is in tension with the rest of the document. In the US, pregnant women are identified as a “vulnerable” group, hence the reference to minimal risk. The CIOMS Guidelines do not identify pregnant women as a vulnerable group and so should not import the notion of minimal risk.
- It may be helpful to consult: Health Canada. 2013. 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](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/womct_femec-eng.php).