Line 2050 Guideline 19: Pregnant and lactating women as research participants

Grouping pregnant women and lactating women into one category is problematic. There is no logical or principled reason to cluster these populations.

The medical, health, social and legal issues are discrete, as are the research risks and the barriers to research participation. Moreover, there is an important difference between pregnant and lactating women insofar as there are different options for managing the risks to others. For example, lactating women who elect to participate in research can purchase breast milk or use infant formula and thereby protect the interests of their newborns. No such option exists for pregnant women. Because we don't yet have artificial wombs, pregnant women who consent to participate in research do not have an option for moving their developing fetuses out of harms way.

What do pregnant and lactating women have in common that warrants them being lumped together? The answer to this question can't be that their participation in research introduces a potential research risk to another, as this is true with other participants in research (e.g., participants in radiation research), and as noted above, this need not be true for lactating women.

Also, Guideline 19 ends-up including an erroneous statement by virtue of clustering these discrete populations. See **Lines 2094-2101**. The introductory sentence makes clear reference to "the health needs to pregnant and lactating women" and yet the three bullets below this statement have nothing to do with lactating women. One way to correct this problem is to amend the introductory sentence so that it only applies to pregnant women. Doing so, however, further increases the percentage of the Commentary on Guidelines 19 that only applies to pregnant women (e.g., **Lines 2079-2081; Lines 2085-2092; Lines 2123-2157**). Already, close to 50% of the commentary only applies to pregnant women.

Lines 2056-2057 In no case must the permission of another person replace the requirement of individual informed consent by the pregnant or lactating woman.

This statement appropriately confirms that the consent of another **cannot replace** the consent the pregnant or lactating woman. This statement does not, however, preclude the possibility that the consent of another could be **required in addition** to the consent of the pregnant or lactating woman. This statement should be amended with respect to pregnant women and should state unequivocally that pregnant women are independently capable of consenting or refusing research participation. Conversely, it may be reasonable to require consent from two parties in the case of lactating women (as when both parents are actively involved in the care of their newborn). This is another reason not to lump these two discrete populations together.

Lines 2058-2060 For research interventions or procedures that have the potential to benefit either pregnant or lactating women or their fetus or infant, risks must be minimized and outweighed by the prospect of individual benefit.

From one perspective, this statement is poorly worded and moreover adds nothing substantive to Guideline 4 according to which "the research ethics committee must ensure that risks to participants are minimized and appropriately balanced in relation to the prospect of individual benefit or the social value of the research" (**Lines 278-280**). From another perspective, this statement is important insofar as it makes clear that the research participants are not just the pregnant women and the lactating women. The research participants whose interests must be considered include **the developing fetus, the newborn, and possibly the older offspring who will have long-term follow-up** (for research involving pregnant women) and possibly **the newborn** (for research involving lactating women).

Line 2061 For research interventions or procedures that have no potential benefits for participants.

There are those who maintain that there are all kinds of potential "indirect" benefits associated with research participation (e.g., benefits of altruism, benefits of closer monitoring that come with being in a

trial). Elsewhere in Guideline 19 there is a reference to “direct” benefit, to “health” benefit and to “individual” benefit. It would suggest the early introduction and consistent use of clear wording – there can be research of "potential medical benefit" where medical benefit includes the ability to ameliorate, alleviate, or prevent a physical or psychological problem, and there can be research of “no potential medical benefit” where there is no ability to ameliorate, alleviate, or prevent a physical or psychological problem. This second category of “no potential medical benefit” might nonetheless include other benefits such as social, emotional, moral or spiritual benefits (some refers to these as “health” benefits).

Does “participants” (in **Line 2061**) include the pregnant woman, the lactating woman, the developing fetus, the newborn and the older offspring who will have long-term follow-up? If so, what kind of research intervention is contemplated that would have no potential “benefit” [not sure what kind of “benefit”] for any of these participants and yet would satisfy the requirement on **Lines 2063-2064** “**the purpose of the research must be to obtain knowledge relevant to the particular health needs of pregnant or lactating women or their fetuses or infants.”**

Lines 2062-2068

There is a problem with the ordering of these three bullets. The first bullet is about “no more than minimal risk” and the last bullet is about “minor increase over minimal risk”. The second bullet is an interruption. It should be moved above bullet #1.

Line 2062 and Lines 2067-2068

The language of “minimal risk” and “minor increase over minimal risk” doesn’t really have traction with this population and reads as boilerplate language taken from research involving children. For example, as concerns pregnant women, what is a ‘minimal risk’ or ‘minor increase over minimal risk’ in any drug or vaccine trial where there is uncertainty about whether the drug or vaccine will cross the placenta and where this may be a desired or a non-desired feature of the trial? What would have been a ‘minimal risk’ or ‘minor increase over minimal risk’ trial of the adjuvanted H1N1 vaccine in pregnant women (known to be an at risk population)? On a go forward basis, how would the ‘minimal risk’ or ‘minor increase over minimal risk’ standard be applied in a trial of Zika vaccine?

This all gets very messy with the discussion **on Lines 2135 ff “Risks in research must be compared to risks that an average, normal, healthy pregnant or lactating woman experiences in daily life or during routine examinations”** This might well encourage researchers to target pregnant and lactating women in developing countries where the risks of daily living are considerably higher.

The committee should do away with the language of ‘minimal risk’ and ‘minor increase over minimal risk’. Instead, the committee should provide concrete helpful guidance as to what factors should be considered in determining whether there is a favourable or proportionate harm-benefit ratio. This would include:

- Nature and severity of the disease;
- Previous nonclinical data on pregnant and non-pregnant animals, and results from clinical data;
- The availability of alternative therapies and knowledge about their associated risks;
- The stage of pregnancy in relation to overall development of the foetus

See, 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

Lines 2069-2071 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 occur immediately.

Is there a reason not to have an equivalent (but separate) statement about research involving lactating women as there might be adverse events that do not occur immediately?

Line 2072 As a general rule, health related research involving pregnant women …

This is the only place that specifies "health related research". Is this intentional? For example, shouldn't **Line 2061** also specify health related research? It would appear so, given the point made in bullet #2.

Line 2079 acknowledges the problem of **routine exclusion** of pregnant women from clinical trials, but does not make a strong statement about the need to ensure **appropriate inclusion** of pregnant women in clinical trials. It is common place in discussions of trial design to review inclusion/exclusion criteria. Failure to use the term "inclusion" anywhere in Guideline 19 is a serious error of omission.

Line 2083 …currently unknown risks and benefits to them, as well as to the fetus or nursing infant.

It is important to be clear and consistent about the fact 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. The word "potential" should be included before "benefit".

Lines 2094-2095 Research designed to obtain knowledge relevant to the health needs of pregnant and lactating women should be promoted in the following areas:

As noted above, the bullets that follow this opening statement only apply to pregnant women. There is nothing that applies to lactating women.

What about including "research designed to obtain knowledge relevant to the health needs of developing fetus, the nursing newborn, the child exposed to a research intervention while a fetus," etc…? Not all research in pregnant or lactating women aims to address the health needs of pregnant or lactating women.

Line 2111 Researchers and research ethics committees must ensure that potential research participants…

In a discussion of consent, the research participants are the pregnant women or the lactating women. And yet, in a discussion of research risks (e.g., **Line 2061**) it appears that the research participants also include the developing fetus, the newborn, and the child who will require long-term follow-up. It will be important to use the term "participants" accurately and consistently through the CIOMS research guidelines.

Line 2120 "individual benefit"

Presumably "individual benefit" is to be distinguished from "benefit to the class of persons to which the individuals belong – pregnant or lactating women", but is "individual benefit" only an individual medical benefit or does it include an individual health benefit. Note the suggestion above re: use of terms "potential medical benefit", "no potential medical benefit", and "potential health benefit"

It is also important to note that **Line 2130** makes reference to a "direct benefit". Is this the same thing as an "individual benefit"? Is this meant to be a reference to a "medical benefit" or a "health benefit"? What about "indirect" benefits?

Line 2152 fetal abnormality may occur as a consequence of participation in research

It is important that Guideline 19 addresses access to abortion in the event of fetal harm that results from research participation. But what about cases where there is a fetal abnormality that has nothing to do with research participation, the pregnant woman has chosen a termination of pregnancy, and prior to doing so would like to consent to participate in research to help with knowledge production (perhaps this is

research to determine whether a drug crosses the placenta). Guideline 19 is silent on this important matter. This should be addressed.