Chapter 4
Presumptive Inclusion and Legitimate Exclusion Criteria

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Abstract *This chapter presents an ethics framework for decisions about whether to exclude pregnant women from a clinical research trial. It begins by articulating several background assumptions about the care of pregnant women in the clinical setting and the involvement of pregnant women in clinical research. The uncontroversial truth of these background assumptions supports the idea that pregnant women should be presumed to be included in clinical research, and that their exclusion requires justification. After making the case for the presumptive inclusion of pregnant women, I outline the ethics framework for the legitimate exclusion of pregnant women from clinical research. This framework consists of nine factors that researchers and research ethics committees should consider when deciding whether to exclude pregnant women. Details about research ethics committee review, the nature of risks in pregnancy, the balance between risk and potential benefit, and the context of clinical care are addressed by the framework.*

This chapter outlines an ethics framework for decision-making about the exclusion of pregnant women from clinical research. I provide a brief argument for the inclusion of pregnant women in clinical research as a default position and then articulate criteria that should be considered when departing from this starting presumption. The framework is informed by a series of background assumptions about health care decisions faced by pregnant women, and about their involvement in clinical research. For the most part, I take these assumptions to be uncontroversial, though two of the assumptions require some clarification. This brief review of my starting assumptions is meant to support the claim that there should be a default position in favour of the inclusion of pregnant women in clinical research. The final section of the chapter presents a complex set of criteria that can assist in decisions about when it is justifiable to exclude pregnant women from clinical research.

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4.1 Background Assumptions

Seven background assumptions inform the proposed ethics framework for decision-making about research involving pregnant women. Many of these assumptions are shared by other authors in this book (see Baylis and Ballantyne 2016), and my articulation of these assumptions is inspired by previous work on this issue by these authors. If one holds these assumptions to be true, it is clear that the exclusion of pregnant women from clinical research requires justification. Some of these background assumptions concern pregnant women in the clinical setting; others concern the involvement of pregnant women in research (Baylis 2013).

Assumptions About the Clinical Setting

1. Clinicians should practice evidence-informed decision-making.
2. Pregnant women are capable of making decisions about their health and well-being.
3. Pregnant women are as entitled as any other patient populations to information and professional advice on the basis of which to make decisions about their health.
4. Pregnant women care about their foetuses and future children (Baylis 2012).

Assumptions About Clinical Research

5. By definition clinical research is a potentially risky activity because it involves the unknown.
6. Risks of harm can often be better managed (and potentially diminished) within rather than outside a clinical trial.
7. Some clinical research is too risky to involve pregnant women, or to involve certain classes of pregnant women (i.e., pregnant women at certain gestational stages).

In my view, these background assumptions are non-controversial, though admittedly two claims warrant further explanation. One such claim is that clinicians should practice evidence-informed decision making. Evidence-informed decisions require evidence provided by research. Within the evidence-informed paradigm, the highest quality information is provided by clinical trials (see Healy and Mangin 2016). Because of the fears associated with including pregnant women in clinical trials, clinicians are often forced to rely on lower-quality information when treating pregnant women, such as information from pre-clinical data, case reports, and the retrospective analysis of data. But these sources of information are not the evidence-informed standard for other patient populations and should not be the standard for pregnant patients (see Healy and Mangin 2016).

The second claim requiring further explanation is that risk of harm can often be better managed within a clinical trial than outside a clinical trial. Exclusion from clinical research does not always achieve the goal of protecting the foetus from harm. Exclusion may modify the risk posed to the foetus, but does not eliminate the risk and in some instances may even increase the risk. For instance, exclusion may

expose the foetus to risks associated with non-treatment, or risks associated with treatment in a less-controlled clinical context (see Baylis and MacQuarrie 2016).

4.2 The Default Position

The background assumptions that I have sketched above suggest that, on occasion, there can be scientifically and ethically valid reasons to exclude pregnant women from some clinical research, but that these exclusions should occur *only* when there are good reasons. Insofar as the background assumptions are not idiosyncratic, this conclusion should not be controversial. Nonetheless, pregnant women are under-represented as participants in clinical research. Lyerly, Little, and Faden make the striking claim that "only a dozen medications are approved by the US Food and Drug Administration (FDA) for use during pregnancy" (Lyerly et al. 2008, 7). This under-representation is dangerous for the health of pregnant women, their foetuses, and their future children (Lyerly et al. 2008).

One reason for the problem of under-representation is an overly protectionist mind-set that assumes the involvement of pregnant women in clinical research requires justification. This way of thinking is reflected, for instance, in the US *Common Rule* which places limits on the inclusion of pregnant women in human subjects research (DHHS 2009, 45 CFR 46 Subpart B). Inclusion requires that the research meets ten conditions. This regulatory hurdle can deter researchers from including pregnant women in their studies (Lyerly et al. 2008). A protectionist mind-set is also reflected in work by other authors who specifically address the issue of inclusion and exclusion criteria for pregnant women in research (for example: Chervenak and McCullough 2011; Strong 2011). These authors clearly prioritise the need to protect foetuses and pregnant women from potential research-related harms without recognising the harm done by neglecting research involving this population.

As a remedy to the protectionist mind-set, many authors have recommended that the justificatory burden should be shifted from inclusion to exclusion (Lyerly et al. 2008; Kaposy and Baylis 2011). That is, the default position should be that pregnant women will be included in research unless there is justification for excluding them. The justificatory burden is placed on the exclusion of pregnant women in the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* published by the Council for International Organizations of Medical Sciences (CIOMS). According to this Guideline, "Pregnant women should be presumed to be eligible for participation in biomedical research" (CIOMS 2002, 74).[1]

While Canada's research ethics guidelines have not fully embraced the presumed eligibility of pregnant women, they are nonetheless alert to the dangers of protectionism. Canada's *Tri-Council Policy Statement*, second edition (*TCPS2*) states that

[1] See Macklin (2010) for a discussion of the CIOMS guideline on pregnancy and ambiguities found within this guideline.

pregnant women "shall not be inappropriately excluded from research" (2014, Article 4.3). Exclusion requires "a valid reason" (2014, Article 4.3). *TCPS2* does not articulate any specific exclusion criteria aside from this, but states that ethics review committees should consider foreseeable risks and potential benefits of inclusion and exclusion from research for the pregnant woman, her foetus, and the infant who may result from the pregnancy.

Presented below is a list of criteria that should inform exclusion decisions. This list can be used as a guideline for deciding whether a clinical research study meets the justificatory burden for the exclusion of pregnant women. As Lyerly and her colleagues state, "There are many trials in which that burden may be met" (2008, 18). Some trials are indeed too risky to involve pregnant women. But exclusions should be based on evidence and considered decisions, rather than convenient avoidance of a difficult standard of inclusion. These criteria can guide decisions that result in research that is safe and valuable for pregnant women, which will enable evidence-based care for pregnant women.

Aside from well-founded exclusion criteria, another way to promote safety in clinical research is through trial design. For instance, clinical research trials could build in increased periodic data analysis to detect any early signs of safety failures or lack of efficacy (Kaposy and Lafferty 2012). Another proposal is that Phase I trials involving pregnant women could begin concurrently with Phase III trials of the same intervention that involve the general population (Baylis 2010; Baylis and Halperin 2012). Alternatively, Phase I trials involving pregnant women could be embedded in standard Phase II or Phase III trials with additional safety monitoring for the pregnant research participants (Baylis 2010; Baylis and Halperin 2012). Since this chapter deals only with exclusion criteria, I do not investigate these other elements of trial design. I note, however, that more work needs to be done on research design that promotes the safety of research involving pregnant women.

4.3 Criteria Relevant for Exclusion Decisions

In 2013, Health Canada published a guidance document *Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences*, which supports the *TCPS2* guideline discussed in the previous section. The Health Canada guidance document addresses the inclusion of pregnant women in clinical trials. It states that,

> A decision to enrol pregnant women in a specific trial should be individualized and based on a careful risk/benefit assessment taking into consideration: the nature and severity of the disease; the availability and results of previous nonclinical data on pregnant and non-pregnant animals, and results from clinical data; the availability of alternative therapy/therapies and knowledge about their associated risks; the stage of pregnancy in relation to overall development of the foetus, especially regarding foetal brain development; and the potential for harm to the woman, the foetus or child. (Health Canada 2013)

This guidance document places the burden of justification on the inclusion of pregnant women in clinical trials. It does not adopt the opposite default position of presuming pregnant women eligible for participation in clinical research and requiring justification for their exclusion. Aside from this problem, the document provides a helpful list of factors that should be taken into consideration in decision-making about the exclusion of pregnant women from clinical research. The list is helpful for the formulation of legitimate exclusion criteria since it captures a number of factors that help identify risk, and that account for the nature of risk. Health Canada's list also takes into consideration contextual details about treatment alternatives for pregnant women. Other relevant factors that should be added to this list include: the pregnant woman's choice regarding continuing or terminating the pregnancy (Strong 2012); the risk posed to the individual pregnant woman of *not* participating in the proposed clinical trial; and the likelihood that the drug or intervention under study will be used off-label by pregnant women.

I will elucidate and justify each factor identified on the Health Canada list as well as these additional three factors. These criteria can be used as a frame of reference for identifying instances of legitimate exclusion of pregnant women from clinical research.

Individualised Review

The decision to exclude pregnant women from clinical research should be trial specific. Pregnant women should not be excluded from specific clinical research simply because they are pregnant. Since the uniform exclusion of pregnant women is unjustified, research ethics committees must make decisions about the acceptability of the exclusion of pregnant women based on the harm-benefit profile specific to the proposed clinical trial. Though this sort of review is already common practice within research ethics committees, individualised review entails recognisable challenges. Research ethics committees are faced with multi-dimensional uncertainty about the risks associated with many interventions in pregnancy (see Ells and Lyster 2016).

First of all there is no consensus on the threshold against which different risks in pregnancy can be measured. To give an example of such a threshold in another area of research, in nontherapeutic studies involving children there is the 'minimal risk' standard articulated in a number of research ethics guidelines. For example in Canada's *TCPS2*, children are included among those who may lack capacity to consent for themselves. The participation of this group is generally limited to research entailing only minimal risk (2014, Article 4.6), which is defined as research whose probability and magnitude of possible harms are "no greater than those encountered by participants in those aspects of their everyday life that relate to the research" (Canada 2014, 22). In the United States, the US *Common Rule* (DHHS 2009, 45 CFR 46.102(i)) provides a similar definition of 'minimal risk'. Nontherapeutic paediatric research runs afoul of the *Common Rule* when it exceeds minimal risk, or in some cases a minor increase over minimal risk.

Research ethics committees do not have a similar authoritative threshold to which they can refer when reviewing exclusion decisions in clinical research involving pregnant women. For example, the CIOMS (2002) guideline offers no standard for acceptable risk, and leaves the determination of acceptable risk largely in the hands of pregnant research participants through the informed consent process. In contrast, commentators such as Strong (2011) and Chervenak and McCullough (2011) articulate much stricter standards of acceptable risk.

Secondly, there is a lack of good data about the possible harms of various interventions in pregnancy and the probability of these harms. For example, consider the possible harms associated with an allergy skin test for the purposes of research. Rid et al. (2010) find six potential harms identified in the literature that are associated with allergy skin testing. These potential harms range from skin prick pain to various degrees of allergic reaction and death (Rid et al. 2010). The more catastrophic harms have lower probability. The lack of similar harm data about interventions during pregnancy is caused by the historical avoidance of research in pregnancy (Lyerly et al. 2008). In a study of all drugs approved by the US FDA between 2000 and 2010, researchers found that for 168 of the 172 drugs (97.7 %) teratogenic risk in human pregnancy was 'undetermined' (Adam et al. 2011).

Because of these multiple uncertainties, it would be impossible to develop a formal algorithm for determining whether a research study should exclude pregnant women. Instead, we rely heavily on the judgement of research ethics committees. Because of the uncertainties about the risk threshold and the lack of data about harms in pregnancy, there is legitimate reason to be concerned about the validity of research ethics committee review (Rid et al. 2010). However, the general guidelines provided in this chapter can help diminish the wholesale reliance on the idiosyncratic judgements of research ethics committees.

Nature and Severity of the Disease

The assessment of whether to exclude pregnant women should take the nature and severity of the disease into consideration. If a specific research study concerns an intervention for a disease or condition that commonly affects women, then there is good reason not to exclude pregnant women from participation in the study. Any disease or condition that affects women of reproductive age – such as hypertension, diabetes, and depression – could affect pregnant women. This reason for not excluding pregnant women is weightier if the disease in question has severe effects on pregnant women. Clinicians require evidence on the basis of which pregnant women can be treated. Pregnant women are as entitled to such evidence-based care as any other patients. The exclusion of pregnant women from relevant research studies would deny them and their clinicians the evidence needed for safe and effective treatment. By the same token, if the research concerns an intervention for a disease or condition that typically does not affect pregnant women (like prostate cancer, or

Alzheimer's disease), this may be grounds for excluding this population from participation.

Previous Nonclinical Data on Animals and Results from Clinical Data

The availability and results of previous nonclinical data on pregnant and nonpregnant animals and results from clinical data should factor into the assessment of risk versus potential benefit. Though research is, by definition, a risky activity, there may be ways to diminish risk by attending to the effects of a particular intervention on animals or from other data. National and international research ethics guidelines usually recommend a reliance on previous animal and nonpregnant human studies in order to define the risks associated with research that will likely involve pregnant human participants (CIOMS 2002; DHHS 2009). If these previous studies indicate that the research would be potentially harmful to the pregnant woman, foetus, or future infant, the guidelines typically recommend that pregnant women should be excluded. In particular, if prior studies with pregnant animals or clinical studies with humans indicate a risk of teratogenicity, mutagenicity, or miscarriage of the foetus, or serious health problems for the pregnant woman herself, then this population can typically be excluded from the research.[2]

One possible exception is when the potential research participants who are pregnant are suffering from a very serious or potentially terminal condition. Illness of this nature would typically also imperil the viability of the foetus. In such a scenario, pregnant women need not be excluded from research because of risk to the foetus. It would be unjustified to exclude pregnant women from research because of a pregnancy they would be likely to lose anyway, or if their own life is in danger.

Availability of Alternative Therapy

The availability of an intervention that is the standard of care, and the knowledge about the associated risks of such a standard of care, are relevant for determining whether pregnant women should be excluded. In general, clinical research involving humans is warranted when there is (1) no standard of care for treating the condition in question other than the intervention being studied, or (2) the standard of care is unsatisfactory because of side-effects, access issues, cost, or other reasons,

[2] Note that this dependence on pre-clinical animal studies requires that female animals be used in pre-clinical research. The inclusion of female animals has actually lagged behind the inclusion of female humans in clinical studies (Clayton and Collins 2014). In the US, the NIH is attempting to rectify this harmful deficiency of pre-clinical animal studies through policy changes (Clayton and Collins 2014).

or (3) there is clinical equipoise (defined as honest clinical and stakeholder disagreement about the effectiveness and value of two or more available treatment options) (Freedman 1987).[3] When the condition affects pregnant women, this rationale applies to research that would involve them.

If there is already an acceptable standard of care, and there is good evidence of safety and effectiveness from previous research involving pregnant women to support the standard of care, then this may be justification for excluding pregnant women from a study of an intervention that is not the standard of care.

Stage of Pregnancy in Relation to Overall Development of the Foetus

The risk versus potential benefit assessment should take into account the stage of pregnancy in relation to overall development of the foetus, especially regarding foetal brain development. Some drugs or interventions might pose risks during the development of particular organs or systems but no other risk at later developmental stages. It might be possible to involve pregnant women in such research at later developmental stages in order to minimise risk. The relevant question to pose in the context of some research is not whether pregnant women in general should be excluded, but whether certain sub-groups of pregnant women should be excluded based on factors such as gestational age, while others are included.

Risks to the Pregnant Woman, the Foetus, or Child

Exclusion decisions should consider the risks to the pregnant woman, the foetus, or child. Risks can be short-term or long-term. There may be research-related risks for the pregnant woman herself or the foetus such as miscarriage or premature labour, or longer-term health risks for the child once born. Each of these categories should be taken into account when assessing prior animal and human data for judging whether exclusion is justified (see Kukla 2016).

As I have argued above, there should be an initial presumption in favour of including pregnant women in clinical research absent good reason for excluding them. Data from nonclinical research with pregnant animals and clinical data with pregnant women could provide risk information about health effects on the pregnant woman, foetus, or the future child. Without this kind of data justifying exclusion, pregnant women normally should be included in clinical research subject to their own harm/benefit calculation during the informed consent process.

[3] On the subject of clinical equipoise, Rebecca Kukla (2016) defends a nuanced understanding of equipoise that takes factors other than safety and effectiveness as relevant.

Choice to Continue or Terminate the Pregnancy

The pregnant woman's choice regarding continuing or terminating the pregnancy may be a relevant factor in determining whether they should be excluded. In some cases, pregnant women need not be excluded from research that is risky to the foetus, such as when the pregnant woman has made a firm decision to terminate her pregnancy. Such research is most justified when the foetus has been diagnosed with a condition that is invariably fatal, or in situations in which the research process itself involves the termination of the pregnancy (Strong 2012). Such research is more controversial when there is a possibility that the pregnant woman could change her mind and decide to keep the pregnancy after being involved in clinical research that poses health risks to the foetus or the child if born (Strong 2012; see Harris 2016).

Risks to the Individual Pregnant Woman of Not Participating in Clinical Research

It is important to consider the risks to individual pregnant women of not participating in proposed clinical research. Excluding pregnant women from particular clinical research might deny them the possible benefits of an experimental intervention (Shivakumar et al. 2011). The risks of untreated illness could be great enough to outweigh the risk posed to the foetus by research participation, especially since untreated illness itself poses health risks to the foetus (see Baylis and MacQuarrie 2016).

If we assume that pregnant women are capable of making choices about their own health care, and that pregnant women care about their foetuses, then there should be a strong presumption in favour of allowing pregnant women to give informed consent to research interventions that might benefit them. The routine exclusion of pregnant women from clinical research denies them this opportunity. Furthermore, risks do not disappear when pregnant women are excluded from research. As discussed earlier, such exclusions might drive pregnant women into seeking care that they need in a less-controlled clinical context, or into avoiding care altogether.

It might be difficult to operationalise this consideration in the context of research ethics committee oversight. Such committees might not have information about treatment options outside of the research context. But the presumption of inclusion means that investigators do not have to justify the inclusion of pregnant women – instead, they have to justify exclusion. Investigators should be required to provide written justification for the exclusion of pregnant women on standard research ethics review forms. These justifications should delineate how the potential research harms outweigh the potential research benefits to the pregnant woman, which would force investigators to consider how exclusion would affect these women.

Likelihood That the Intervention Will Be Used by Pregnant Women Even Without Research Evidence

The likelihood that the drug or intervention in the study will be used or needed by the population of pregnant women even without research evidence should affect deliberations about whether to exclude pregnant women. Many classes of drugs are used by pregnant women without research evidence demonstrating safety, and effectiveness (Lyerly et al. 2008; Baylis and Kaposy 2010). If the drug or intervention under study is likely to be used (or is being widely used already) in this population, then there is little justification to exclude pregnant women from studies of the drug or intervention, unless there are reliable prior indications of foetal or maternal risk incommensurate with the likely benefits to the pregnant woman. A similar argument applies if the intervention (such as a vaccine) is already being commonly used among pregnant women to promote the health of the foetus.

An exclusion of pregnant women from studies of interventions needed by pregnant women and likely to be used by them denies clinicians the ability to make evidence-informed decisions and denies pregnant women access to evidence-based care. It is better to expose a small number of pregnant women to the risks of research in a controlled research environment, when more women would otherwise be at risk in a clinical context in which safety and effectiveness are not known.

Some may argue that those who conduct research are not responsible for clinical care standards outside of the research context – that is, that ethical responsibilities in research extend only to research participants. This argument is difficult to accept, however, because the research enterprise is not a closed system. The goal of clinical research is to find cures or improve care in the clinical context. Therefore researchers and their funders are responsible for unjustified exclusions from research that affect the quality of care available to patients, including pregnant women.

4.4 Conclusion

The illegitimate presumptive exclusion of pregnant women from clinical research means that such women are treated off-label and subject to risk in a context where there is limited knowledge directing decision-making in the clinical setting. The inclusion of pregnant women in research is an ethical imperative. As I have argued above, the evidence-informed decision-making standard for pregnant women should be the same as for other patient populations. If the general patient population has access to better evidence for their care than pre-clinical data, case reports, and the retrospective analysis of data, then pregnant women should have access to better evidence as well.

Clinical research takes place in a cultural context in which pregnant women are expected to refrain from all sorts of activities that are perceived as risky. For example, pregnant women are regularly advised to avoid eating sushi and cookie dough,

to refrain from scooping the cat's litter box, sitting in the bathtub too long, sleeping in the wrong position, and so forth (Lyerly et al. 2009). Pregnant women who smoke, use street drugs, or drink alcohol are treated as social pariahs. The foetal protectionist impulse behind excluding pregnant women from clinical research is a symptom of this larger cultural context. At its root, the protective impulse is an expression of the fact that people value the health of pregnant women, their foetuses, and their future infants. The downstream effects of foetal protectionism, however, show this impulse to be a perverse and counter-productive expression of value. If one values the health of pregnant women, foetal health, and child health, then research participation is necessary. The treatment of illnesses in these groups requires medical knowledge generated by clinical research.

In many cases, pregnant women can choose for themselves to participate (or not) in a clinical research study when they weigh the harms and benefits for themselves, their foetuses and their future children, and when they look at their available options. If these options include off-label treatment with less-supervised risks versus participation in a trial with data collection for knowledge production and the oversight of risks, the exercise of autonomous choice may lead pregnant women to consent to trial participation. When there is no scientifically and ethically sound reason to exclude pregnant women from such trials, they should be allowed this choice.

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