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CHAPTER 9-4

Subpart B Research: Additional Protections for Pregnant Women, Human Fetuses, and Neonates

Maggie Little

Anne Drapkin Lyerly

Abstract

It is now widely agreed that research with pregnant women is critically important and that such research must be responsibly conducted. Because research with pregnant women involves implications for potential offspring, this means added specifications for it to proceed. This chapter describes the background and key components for research with pregnant women, including an overview of the regulatory approach to such research and a discussion of the eligibility criteria for including pregnant women in research. The final section provides a brief summary of the two other, less commonly encountered, topics addressed by subpart B of the Common Rule: research on neonates born of uncertain or nonviability and research with the post-delivery placenta or a deceased fetus.

Introduction

Research with pregnant women is critically important. Pregnant women often face serious illness, ranging from immune disorders to infectious diseases to cancer and need access to effective, safe, and appropriately dosed therapeutics (Task Force on Research Specific to Pregnant Women and Lactating Women, 2018). Indeed, pregnant women are often one of the populations most in need of safe and effective therapeutics, given the increased susceptibility to illness that pregnancy can bring, as well as heightened risks when disease and pregnancy co-occur (Lyerly et al., 2008). Without pregnancy-specific research, decisions about therapeutic choice and dosing are based on assumption rather than evidence. Furthermore, evidence gaps can lead to reticence to use medications that are in fact safe and critical to preventing or managing diseases during pregnancy, leaving both pregnant women and the children they bear in harm's way. Key organizations now endorse the importance of research with pregnant women, including the American College of Obstetricians and Gynecologists (2015), the Society for Maternal-Fetal Medicine (n.d.), the Office of Women's Health of the National Institutes of Health (Foulkes et al., 2011), and a recent presidential Task Force on Research Specific to Pregnant Women and Lactating Women (2018).

Overview

Until recently, pregnant women were categorized as a "vulnerable population" in regulations governing human subjects research. Though the term did not appear in subpart B, the pre-2018 version of subpart A of the U.S. Code of Federal Regulations for the Protection of Human Subjects (the Common Rule) designated at several points pregnant women as vulnerable alongside "prisoners, children, individuals with mental disabilities, and individuals at economic or educational disadvantage"—populations that either by capacity or by context are compromised in their ability to provide valid consent to participate in research or who are at special risk of exploitation.

It was increasingly recognized that such a designation was problematic (Council for International Organizations of Medical Sciences, 2016). The term tacitly suggests that pregnancy renders women incapable of offering valid consent or that they are by nature susceptible to exploitation. Yet pregnancy does not itself limit the ability to reason, and although there are some cultures in which pregnancy meaningfully constrains women's free decision-making around matters such as research participation, the factors that lead to such constraints are highly contextual and do not redound to the category of pregnancy in its own right. Furthermore, it had become clear that the designation of pregnant women as a "vulnerable population" unintentionally had a profoundly chilling effect on the pursuit of research—even highly responsible research—into the health needs of pregnant women and the children they bear, leaving pregnant women a "therapeutic orphan" (Little et al., 2019).

The 2018 revisions to the Common Rule confirmed that "the final rule no longer includes pregnant women … as examples of populations that are potentially vulnerable to coercion or undue influence" (Federal Register, 2017, Preamble p. 7204). Although various factors can make specific pregnant women vulnerable (e.g., being incarcerated), pregnant women as a group should not be characterized as a vulnerable population for purposes of human subjects research review.

Instead, the bioethics literature and professional guidance now frame pregnant women as a "special" or "complex" population, by virtue of both physiological differences and ethical complexities that pregnancy entails, such as the need to consider the interests of both the woman and fetus (Blehar et al., 2013; Foulkes et al., 2011). The American College of Obstetricians and Gynecologists (ACOG) has endorsed the term "scientifically complex" (encompassing both biological and ethical complexities) as a way to indicate both that pregnant women and the children they will bear need to be protected individually from research risks and also that they are protected as a population *through* the conduct of responsible research (ACOG, 2015).

Like any research involving human subjects, research with pregnant women must meet all standard research protections as defined in the Common Rule; for instance, risk must be the least needed for scientific purposes, and appropriate informed consent must be obtained before research proceeds. Subpart B explicitly incorporates those general protections by reference. Subpart B then adds an overlay of additional requirements, on top of those specified more generally for human subjects research, laid out in **45 CFR 46.204**. These additional requirements centrally fall into three categories: (1) requirements about preliminary evidence needed before pregnant women are eligible for inclusion; (2) parameters for allowable research-related risk, especially for the fetus; and (3) questions of paternal (and, for research with pregnant adolescents, parental) consent.

It should be noted that subpart B also allows for exceptions to its requirements if the research presents an opportunity to "understand, prevent, or alleviate a serious problem" affecting pregnant women, fetuses, or neonates. Under this provision, special approval must be granted by the Secretary of the Department of Health and Human Services in consultation with an expert panel and with public commentary **[45 CFR 46.207]**. To our knowledge, this pathway has never been invoked.

Preliminary Evidence [45 CFR 46.204(a)]

Subpart B's first specific requirement for including pregnant women in research concerns the availability of preliminary evidence to inform judgments of potential research-related risks to the fetus or pregnant woman. Specifically, subpart B states: "Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses" **[45 CFR 46.204(a)]**.

The qualification "where scientifically appropriate" is not explained but is presumably meant to acknowledge that some research involves no potential for physiological risks (e.g., cohort studies) and that research that does carry such potential may have access to sufficiently rich data, apart from preclinical studies specified to inform assessment of that potential. For instance, there may be useful data from safety databases about the use of the therapeutic in nonpregnant women, observational reports on use during pregnancy, or data from unintended exposures of pregnant women in the context of research that can serve the function of providing adequate preliminary evidence even in the absence of preclinical studies involving animals or prospective studies involving nonpregnant women (Food and Drug Administration, 2018).

While subpart B itself does not provide details about which preclinical animal studies assessing risks to the fetus are adequate, it should be noted that the Food and Drug Administration (FDA) provides detailed guidance on the topic for research taking place in the investigational new drug (IND) space. Any research done with pregnant women in the IND space will need to conform to FDA's specific preclinical animal requirements (including female reproduction toxicity studies and the standard battery of genotoxicity tests; FDA, 2010). Furthermore, because FDA requires detailed reproductive toxicity studies (specific animal studies looking at potential fetal risks, among other things) for all applications for drug approval, any research on approved therapeutics will perforce meet subpart B's requirement regarding preliminary animal studies.

FETAL RISK CONSIDERATIONS

In establishing standards limiting allowable fetal risk, the regulations should not be seen as opining on the moral status of the fetus (Little et al., 2019). Instead, the permissible fetal risk standard is designed on the presupposition that the pregnancy will be continued. This is both because such a presupposition is empirically true of the vast majority of such research and because it serves to ensure that trials do not burden women's options around pregnancy continuation by assumption or design. This latter principle is further underscored by subpart B's direction that researchers cannot be involved in any decision making around pregnancy termination (whether, timing, method) and that no inducements, monetary or other, to terminate can be offered by researchers.

Allowable Research-Related Risk [45 CFR 46.204(b and c)]

A critical issue in conducting research with pregnant women is determining the specific standards for what research-related risk is acceptable to the fetus, which cannot consent to that risk. Allowable risk for the pregnant woman is left implicit and is hence presumably subsumed under subpart A's parameters for allowable risk in the general population.

Disjunctive Fetal Risk Standard

The standard of acceptable research-related risk depends on whether the trial in question offers the "prospect of direct benefit." Trials involving the prospect of direct benefit—sometimes called "therapeutic research"—are those in which the study intervention may provide direct individual benefit from research participation if the intervention proves successful. That is, although the overarching purpose of the research is to gather further evidence for future patient populations, the trial is at a mature enough stage that it may also carry the prospect of comparative health benefits to research subjects.

Trials with no prospect of direct benefit, in contrast, are those in which the possibility of benefit cannot reasonably be expected. For studies that have no prospect of direct benefit, enrollment is purely for the value of advancing biomedical knowledge that will potentially benefit future patients or populations. These studies include early phase trials in which researchers have intentionally minimized the study intervention dose as a strategy to answer specific questions about safety; trials marked by too little evidence to reach a threshold of any reasonable prospect of benefit (even if benefits do accrue during the study); and studies whose focus is to better understand a point of biology or physiology rather than to test a potential preventive or therapeutic intervention.

Trials Involving Prospect of Direct Benefit

For trials offering the prospect of direct benefit to the pregnant woman, the fetus, or both, subpart B is quite permissive of inclusion in research. According to subpart B, research involving the prospect of direct benefit is allowable if the risk to the fetus is "caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus" **[45 CFR 46.204(b)]** and the risk to fetus is the "least possible" **[45 CFR 46.204(c)]**. Taken literally, this provides remarkably little constraint on allowable fetal risk, because the risk to the fetus could in principle be both extremely high and disproportionate to any benefits potential to the study. However, consensus in the clinical research ethics literature finds that acceptable risk is determined by the reasonability of the relation of risk to the potential benefits offered by participation: The likelihood and importance of the potential benefits must be reasonably judged to outweigh the potential risks, and the potential risk/benefit comparison must not be worse than available alternatives.

Importantly, subpart B is silent about whether the prospect of direct benefit to the pregnant woman can justify an increment of research-related risk to the fetus. The "prospect of benefit" category is simply described as a category of potential benefit to *either* woman *or* fetus, and the standard indicates only that risks should be justified by benefits, without specificity about to whom (woman or fetus/future child) such risks and benefits apply. It is generally assumed that pregnant women may altruistically consent to some personal research-related risk for the sake of fetal/future child benefit; there is also an assumption that some degree of fetal risk can be justified by adequate potential for maternal benefit, as is true in the practice of clinical obstetric care (Little et al., 2016; Little et al., 2017). Furthermore, fetal health is often deeply linked to maternal health: If participation

in a trial offers the prospect of direct medical benefit to pregnant women, very often that intervention entails specific and quantifiable medical benefits to the fetus by virtue of reducing the effects of maternal disease on neonatal health outcomes. Indeed, where pregnant women are involved in research to treat maternal illness (e.g., HIV, thyroid disease, diabetes), net benefit to the fetus/future child can often be anticipated. That said, maternal and fetal risks and benefits are not always aligned with each other, and presumably there are limits (on both sides) about when benefit to one can justify risk to the other, potentially resulting in some difficult cases for individual IRBs.

Trials Involving No Prospect of Direct Benefit

For trials that involve no prospect of direct benefit to *either* the woman *or* the fetus, research-related risks to the fetus are capped at a very low threshold. Such trials can pose no more than "minimal risk" to the fetus **[45 CFR 46.204(b)]**. "Minimal risk" is defined in the Common Rule as "the probability and magnitude of anticipated harms with those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" **[45 CFR 46.102(j)]**. The "minimal risk" standard (which is also used in other arenas of the regulations), although often difficult to apply and subject to widely varying interpretations by IRBs (Shah et al., 2004; Wendler, 2005), is intended to provide a category of negligible risk. Of note, subpart B also states that the purpose of the research must be the development of important biomedical knowledge that "cannot be obtained by any other means" **[45 CFR 46.204(b)]**.

Some have raised concerns that these requirements are problematic. The language creates an extremely low ceiling, as it may be interpreted to exclude pregnant, women from studies with negligible risk simply because they are pregnant, and to preclude gathering data in studies that may be judged to entail a very low risk that exceeds the minimal risk threshold—such as some pharmacokinetic studies—that would critically inform dosing of a drug in research or clinical contexts. Furthermore, the fetal protections outlined here are more restrictive than those outlined in the corresponding regulations for research with children. Children are allowed to participate in minimal risk studies without the added stipulations that the knowledge sought "cannot be obtained by any other means." Regulations governing research with children also allow for a "minor increase over minimal risk" for research likely to contribute generalizable knowledge of vital importance for the understanding or amelioration of the child's disorder or condition. Some, including the president's Task Force, have recommended that a revision of subpart B should include the category of "minor increase over minimal risk" parallel to what is allowed in pediatric research, so further developments on this issue are possible (Task Force on Research Specific to Pregnant Women and Lactating Women, 2018).

PATERNAL CONSENT REQUIREMENTS

In the vast majority of cases, consent of the woman alone fulfills the regulatory requirement. Maternal and fetal interests are often intertwined, and so in most research with pregnant women—even research aimed fairly narrowly at improving fetal health—a prospect of benefit to the woman can be expected. Still, serious concerns have been raised about the enduring requirement for paternal consent in cases of prospect of direct benefit to the fetus alone. Here, too, the regulation exceeds what is required in pediatric research. According to subpart D, where there is a prospect of direct benefit to a child alone, the consent of *one parent* only is sufficient. Yet before birth, the same circumstance requires the consent of *two* parents. Other concerns include that giving the father veto power does not respect a pregnant woman's autonomy; is inconsistent with standards of clinical care, in which a pregnant woman's consent for interventions to benefit the fetus alone is sufficient; may compromise the privacy or safety of a pregnant woman who may be subject to intimate partner violence; and fails to account for the range of relationships, such as same-sex partnerships and arrangements involving gamete donation. Finally,

anecdotal evidence indicates that the requirement continues to operate as a barrier to inclusion of pregnant women in biomedical research. Considering these objections, the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) and others have urged full removal of a paternal consent requirement from the U.S. regulations.

Additional Consent [45 CFR 46.204(d-g)]

Subpart B is clear that for most research, informed consent of the pregnant woman alone, in accordance with parameters outlined in the Common Rule, is sufficient. Identifying the rare case in which paternal consent might be required again depends on the previously noted disjunct between research with and without prospect of direct benefit. If the study holds out the prospect of direct benefit for the woman, her consent alone is sufficient, even if there is also benefit to the fetus. If the study does not hold out the prospect of direct benefit for either the woman or the fetus, then the consent of the woman alone is again sufficient, given the negligible fetal risk such research permits. Only in cases where there is the prospect of direct benefit to the fetus but not to the woman is consent of the father required, with exceptions for cases in which the pregnancy resulted from rape or incest, or the father is unavailable, incompetent, or incapacitated.

The content of consent is defined in the Common Rule **[45 CFR 46.116]**; subpart B also sets out the additional requirement that "each individual providing consent … is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate" **[45 CFR 46.204(f)]**.

Finally, children and adolescents represent a considerable proportion of the pregnant population, and their physiologies or social contexts may make them an important population for research participation (for instance, research on HIV in some communities). Subpart B specifically states that "For children … who are pregnant, assent and permission are obtained in accord with the provisions of subpart D" **[45 CFR 46.204(g)]**.

Research Involving Neonates and Post-Delivery Research of the Placenta or a Deceased Fetus

Subpart B addresses two additional topics beyond research with pregnant women: research on neonates born of uncertain viability and nonviable neonates **[45 CFR 46.205]** and research involving the post-delivery placenta or a dead fetus or fetal material **[45 CFR 46.206]**. The latter section is very brief, centrally handing off guidance to any applicable federal, state, or local laws and regulations regarding such activities; we therefore do not discuss it in any detail here.

The section on research with neonates sets the following parameters:

1. Those conducting research may play no role in assessing or determining the neonate's viability.
2. If the neonate is determined to be nonviable, research may take place only under extremely limited conditions. The research can neither artificially maintain the neonate's vital functions nor terminate its heartbeat or respiration; the research can add *no* additional risk to the neonate; and even then can be pursued only if in service to "important biomedical knowledge that cannot be obtained by other means."
3. If the neonate is of uncertain viability, there are two different conditions under which research may be undertaken: research that carries the prospect of enhancing the probability of survival of the neonate to viability or research in service to important biomedical knowledge not otherwise obtainable and that carries *no* additional risk to the neonate.
4. Finally, if or once the neonate is determined to be viable, any proposed research is to be evaluated under subpart D.

NEONATES OF UNCERTAIN VIABILITY

The inclusion of discussion regarding neonates born of uncertain viability and nonviable neonates in subpart B is in one sense surprising, because research with newborns would generally be covered under subpart D. That said, subpart D does not consider or reflect the spectrum of scenarios encountered in how and when pregnancies may end, including, for instance, a highly premature but liveborn neonate that is clearly nonviable or whose viability is profoundly unclear. At the time of the 2001 revisions to subpart B, these scenarios were a topic of extensive focus and debate, perhaps in part because they intersect with questions about the moral status of early human life (McCullough et al., 2008). Whatever the impetus, **45 CFR 46.205** encompasses extensive commentary, including detailed specifications of when one parent, both parents, or their legal representatives must be involved.

Conclusion

Overall, subpart B is permissive of research with pregnant women. Although it presents some barriers to its conduct that could be resolved through regulatory guidance, much important research can be done now, ethically and in accordance with subpart B as it currently stands. Such research is necessary and important to developing a robust evidence base that is critical to the health of women during and after pregnancy, as well as the children they bear.

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CHAPTER 9-5

Subpart C Research: Additional Protections for Prisoners

Paul P. Christopher
Julia G. Gorey
Josiah Rich