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WOMEN'S HEALTH CARE PHYSICIANS

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Committee on Ethics

The American Academy of Pediatrics, American Society for Reproductive Medicine, and Society for Maternal–Fetal Medicine endorse this document. This Committee Opinion was developed by the Committee on Ethics of the American College of Obstetricians and Gynecologists as a service to its members and other practicing clinicians. While this document reflects the current viewpoint of the College, it is not intended to dictate an exclusive course of action in all cases. This Committee Opinion was approved by the Committee on Ethics and the Executive Board of the American College of Obstetricians and Gynecologists.

Ethical Considerations for Including Women as Research Participants

ABSTRACT: Inclusion of women in research studies is necessary for valid inferences about health and disease in women. The generalization of results from trials conducted in men may yield erroneous conclusions that fail to account for the biologic differences between men and women. Although significant changes in research design and practice have led to an increase in the proportion of women included in research trials, knowledge gaps remain because of a continued lack of inclusion of women, especially those who are pregnant, in premarketing research trials. This document provides a historical overview of issues surrounding women as participants in research trials, followed by an ethical framework and discussion of the issues of informed consent, contraception requirements, intimate partner consent, and the appropriate inclusion of pregnant women in research studies.

Attitudes concerning inclusion of women in research trials have changed dramatically over the past several decades. Although changes have been made to encourage and recruit more women into research studies, a gap still exists in the available data on health and disease in women, including those who are pregnant. In addition, concerns about the potential for pregnancy in research trial participants have led to practices involving overly burdensome contraception requirements. This document provides a historical overview of issues surrounding women as participants in research trials, followed by an ethical framework and discussion of the issues of informed consent, contraception requirements, intimate partner consent, and the appropriate inclusion of pregnant women in research studies.

On the basis of the principles outlined in this Committee Opinion, the American College of Obstetricians and Gynecologists offers the following recommendations and conclusions:

- Although significant changes in research design and practice have led to an increase in the proportion of women included in research trials, knowledge
- gaps remain because of a continued lack of inclusion of women, especially those who are pregnant, in premarketing research trials. Continued emphasis on recruitment of women into research must be encouraged. The potential for pregnancy should not automatically exclude a woman from participating in a clinical study, although the use of contraception may be required for participation in specific circumstances.
- In order to aid in the recruitment of women, researchers should specifically address obstacles to participation that may be experienced disproportionately by women, such as the lack of adequate child care during time spent as a research participant.
- Further efforts are needed to ensure that research is designed to include representation of all potentially affected individuals, including those in diverse and underserved populations who often are not fully represented in current study designs.
- Pregnant women in research trials should be defined as a “scientifically complex” rather than a “vulnerable” population.

- Contraception requirements for research participants of reproductive capacity often are out of proportion to the actual risks of study drugs or interventions. Instead, the requirement for contraception in a given research trial should be tailored to the individual study design and should be determined based on the actual risks to the pregnancy of an individual research participant.
- In the absence of a few specific scenarios, requiring participation consent from a woman's intimate partner is neither warranted nor ethically justified.
- Maternal and fetal risks are deeply interconnected, and consideration of enrolling pregnant women in research requires balancing the risk of fetal harm with the potential for benefit and the importance of the information to be gained on the health of women and fetuses.

Historical Context

Significant efforts by the National Institutes of Health (NIH) in the early 1990s led to a meaningful increase in the proportion of women participating in research trials (1). As a result, a great deal of important information was obtained detailing diseases and their treatment as they pertain to women—information that was previously unavailable. Although significant changes in research design and practice have led to an increase in the proportion of women included in research trials, knowledge gaps remain because of a continued lack of inclusion of women, especially those who are pregnant, in premarketing research trials. Continued emphasis on recruitment of women into research must be encouraged. The potential for pregnancy should not automatically exclude a woman from participating in a clinical study, although the use of contraception may be required for participation in specific circumstances. In addition, the ways in which the possibility and implications of fertility are addressed in the design and conduct of trials remains suboptimal.

Because disease processes may have different characteristics in women and men, and because women and men may respond differently to treatments and interventions, women need to be included as participants in research. Arguments previously advanced to defend the exclusion of women from research cited the possibility of harms to the fetuses of women who are, or may become, pregnant. However, the risk of such harm can be minimized and, in itself, does not always justify the exclusion of women from research. Exclusion of women from medical research trials will only perpetuate the paucity of applicable data and the suboptimal practice of applying male-derived research results to women's health.

Ethical Considerations

Because of a history of systematic exclusion of women from research, in 1993 Congress directed that women

were to be included in all federally funded clinical investigations, unless inappropriate (2). Consequently, the NIH now requires that women and members of minority groups and their subpopulations be included in all NIH-funded research “unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant institute/center director that inclusion is inappropriate with respect to the health of the participants or the purpose of the research” (1). This strategy appears to have been effective, with data from 2011 through 2012 indicating that 57% of the approximately 17.7 million NIH-funded trial participants were women (3). Similar data, however, are not available from non-NIH-funded research, for which collection of demographic information can be limited.

Despite this advance, participation in important areas of research continues to lag among women. If the medical treatment of women is based on studies from which women were excluded as research participants, then a concern for generalizability must be raised, and women are at risk of not receiving the same level of evidence-based care available to men. Justice requires that women be included in studies in sufficient numbers to determine whether their responses to treatment are different from those of men and whether treatment options derived from research are equivalently applicable to women and men (4). In order to aid in the recruitment of women, researchers should specifically address obstacles to participation that may be experienced disproportionately by women, such as the lack of adequate child care during time spent as a research participant.

Women may be motivated to participate in research trials by altruism to further the care of women, by the ability to receive novel and state-of-the-art medical care, or by the benefits of highly supervised medical monitoring of treatment. Sometimes individuals without health insurance choose to participate in these trials because such trials may provide enhanced access to care, cost-free care, or reimbursement for time and travel. Involvement in research protocols should not diminish a woman's expectation that she will receive appropriate medical care during the study and in the future. In general, however, enrollment of participants from racial and ethnic minorities, including minority women, in research trials remains low (5–7). Further efforts are needed to ensure that research is designed to include representation of all potentially affected individuals, including those in diverse and underserved populations who often are not fully represented in current study designs.

Pregnant Women as “Scientifically Complex”

One of the reasons that pregnant women have been systematically excluded from research is their perceived status as “vulnerable.” In 2010, the NIH Office of Research on Women's Health supported a workshop to address ethical, regulatory, and scientific issues raised by the enrollment of pregnant women in research studies (8).

One of the recommendations from the workshop was that pregnant women in research trials should be defined as a “scientifically complex” rather than a “vulnerable” population (8). Participants in the workshop argued that a vulnerable population is one that has a compromised ability to protect its interests and provide informed consent. Pregnant women do not, as a group, meet this definition. Pregnant women have the same capacity for autonomous decision making as their nonpregnant counterparts, including decisions regarding whether or not to participate in appropriate research studies.

Pregnant women are scientifically complex, reflecting a combination of physiologic and ethical complexity. The ethical complexity is reflected in the need to balance the interests of the pregnant woman and the fetus. Maternal and fetal interests usually align, as appropriate care of the woman is necessary for the health of the fetus, but these interests may diverge in the setting of research, especially research that is not focused on concerns of pregnancy, labor, or fetal health.

Just Inclusion of Women in Research Trials

Improved medical management of conditions that previously may have precluded pregnancy, such as cystic fibrosis or organ transplantation, has expanded the population of women able to achieve pregnancy. Women who have significant medical conditions often will require pharmacologic management, and many of these conditions and disease processes (eg, diabetes mellitus, inflammatory bowel disease, depression, and epilepsy) are known to have negative effects on the fetus, the pregnant woman, or both if poorly controlled. Yet pregnant women often are not permitted to enroll in studies of novel treatments for complex or chronic medical conditions. Such broad exclusion without assessing potential benefits against the potential risks of the pharmacologic agent is short sighted. For example, if an agent being studied would allow pregnant women to gain better control of their disease than current treatment regimens and potentially lead to better maternal and fetal outcomes, enrollment in studies of such agents should be considered. Along these lines, consider the case of a woman participating in a research study who subsequently becomes pregnant, an outcome that could be related to her improved health status after enrollment. Should she be removed from the trial because of her pregnancy, despite the possibility of achieving improved health by use of the study agent? The decision should include consideration of the principles of autonomy, justice, beneficence, and nonmaleficence (4).

Informed Consent

Appropriate and adequately informed consent by the potential participant or another authorized person and an independent review of the risks and benefits of research by appropriate institutions, agencies, or both are fundamental to the formulation of any research protocol (9). The researcher has an obligation to disclose to the woman

and discuss with her all material risks affecting her; in the case of a pregnant woman, this includes all material risks to the woman and her fetus (10). Disclosure should include risks that are likely to affect the patient’s decision to participate or not to participate in the research.

Anything beyond minimal risk must be weighed carefully against the potential benefits to the woman (and the fetus, in the case of a pregnant woman) when the advisability of participation is considered. According to applicable federal regulations, “minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” (11). It has been questioned whether the “daily life” used for comparison should be that of the general population or that of the participant. Using the participant’s daily life as the standard might make a higher level of risk acceptable; therefore, the general population standard is advised (9).

Because the process of informed consent cannot anticipate all conceivable risks, women who develop unanticipated complications should be instructed to contact the researcher or a representative of the institutional review board (IRB) immediately. Pregnant women who enroll in a research trial and experience a research-related injury should be informed about their therapeutic options, including those related to the pregnancy. When a pregnancy has been exposed to more than minimal risk in the conduct of research, the woman should be encouraged to participate in any available follow-up evaluations to assess the effect on her and her fetus or child.

Contraception Requirements and Research Trials

Many research trials, regardless of the nature of the study or the potential for harm in pregnancy, require all female participants to use at least one reliable form of contraception. Although it is reasonable for investigators and research sponsors, with the IRB’s approval, to require the use of effective birth control measures for women of reproductive capacity as an inclusion criterion for participation in research that may entail more than minimal risk to a fetus, consultation with an obstetrician–gynecologist or other gynecologic care provider is encouraged regarding the efficacy and risk of contraceptive measures. Standard contraception mandates by investigators generally fail to consider what exactly constitutes “reliable”; the required methods often are prescriptive and potentially coercive, have their own inherent risks, and may not match the woman’s preference. In addition, this practice could introduce confounding variables through the intake of exogenous hormones by study participants. Finally, contraceptive requirements often do not apply to men. The particular study and its specific risks with respect to either a real or potential pregnancy should be considered appropriately for male and female

participants, and inclusion and exclusion criteria should be based on scientific data.

Contraception requirements for research participants of reproductive capacity often are out of proportion to the actual risks of study drugs or interventions. Instead, the requirement for contraception in a given research trial should be tailored to the individual study design and should be determined based on the actual risks to the pregnancy of an individual research participant. If a pharmaceutical agent under study has been shown to be a teratogen in an animal study or early-phase trial, it is important and appropriate to advise participants of the need to avoid becoming pregnant during the study. Similarly, it is appropriate for investigators and sponsors, with the approval of the IRB, to require a negative pregnancy test result as a criterion for participation in research when the research may pose more than minimal risk to a fetus.

If it is anticipated that the research may pose more than minimal risk to a fetus, the informed consent process should involve a review of contraception options and their efficacy. Some study protocols mandate use of a specific contraceptive method, such as oral contraceptives or an intrauterine device. These mandates are inappropriate based on the principles of respect for autonomy, beneficence, and justice. A woman should be allowed to choose a birth control method, including abstinence, according to her needs and values (12). Requiring birth control use by a woman who is not sexually active violates a commitment to respect her as a person. Hormonal contraceptive methods that could interfere with study results may be excluded on scientific grounds, but additional restrictions are inappropriate.

Intimate Partner Consent

Research that involves female or male reproductive health can raise questions about the potential effect of the research on the participant's intimate partner, and some investigators and IRBs have required consent from the research participant as well as his or her intimate partner. In the absence of a few specific scenarios, requiring participation consent from a woman's intimate partner is neither warranted nor ethically justified. Such consent is not required for general medical care or even in care related to continuing or terminating a pregnancy. Intimate partner consent is appropriate if there is a risk of the partner's exposure to an investigational agent and exposure to that agent carries more than minimal risk; data will be collected regarding an intimate partner's impression of the investigational agent; or inclusion or exclusion criteria directly relate to an intimate partner, such as if testing of a partner is required for a woman to enroll in the trial (eg, semen analysis or testing for a sexually transmitted infection).

If, after careful consideration, it is determined that none of the aforementioned conditions apply, intimate partner consent is not warranted. Otherwise, intimate partner consent could impose a barrier to participation

for a woman, interfere with a woman's choice of reproductive options, or interfere with a woman's right to make independent decisions about her health care.

Pregnant Women as Research Participants

Lessons in Excluding Women From Research Trials

It is helpful to reflect on the reproduction-related history of medication studies in the 1950s and 1960s and on the resulting real and perceived risks of adverse pregnancy outcomes. The most devastating of these cases (and the case most often cited to justify contraception requirements and pregnancy exclusions) involved the use of thalidomide during pregnancy. A more careful examination of that and other studies, however, points to the need for evidence-based consideration of pregnancy exposures in research rather than broad exclusion of all pregnant women. Although fetal safety most commonly is seen as a reason to exclude pregnant women from research, this experience also speaks to the need to include pregnant women in research. Anything beyond a minimal risk, however, must be weighed carefully against the potential benefits to the woman and fetus when the advisability of participation is considered. The pursuit of zero fetal risk is not attainable and will come at a real risk to maternal health, and potentially to the health of a wider population of fetuses, outside the research setting. There is an ethical obligation to confront the challenges of including pregnant women in research to address maternal health and fetal safety.

Although there is concern that including pregnant women in the study of new drugs potentially could cause fetal harm, it is critical to recognize that excluding pregnant women from research also can lead to harm. This was observed when thalidomide was approved in Europe and used by pregnant women, who had not been studied, leading to widespread birth defects. Had appropriate studies of thalidomide been conducted in pregnant women before its endorsement, it is likely that far fewer than the more than 10,000 adverse pregnancy outcomes would have occurred (13). Notably, none of the early trials considered harms to fetuses that might accrue from thalidomide ingestion by potential fathers; more recent research has shown that thalidomide is present in semen (14). Men who take thalidomide for clinical purposes are now cautioned to use synthetic or latex condoms or to avoid sexual contact (even in the context of vasectomy) with a woman who is pregnant or could become pregnant, at least through the first trimester.

The introduction of Bendectin (pyridoxine [vitamin B₆]/doxylamine) into the U.S. market is an example of undue caution that may be a response to the history of thalidomide. In 1956, the combination of doxylamine, dicyclomine (an antispasmodic agent), and vitamin B₆ was approved by the U.S. Food and Drug Administration

(FDA) and introduced into the U.S. market as Bendectin, an effective agent for the treatment of nausea and vomiting of pregnancy (15). In the years that followed, numerous lawsuits alleging association with birth defects were filed, ultimately resulting in the voluntary withdrawal of Bendectin from the market in 1983. This occurred despite the publication of research before and after the withdrawal of Bendectin that failed to detect evidence that the medication was linked to specific birth defects (16–19). A large meta-analysis, including 170,000 exposures, further demonstrated the doxylamine–pyridoxine combination to be safe in pregnancy and to cause no increase in adverse fetal effects (20). It was not until 2013, after ongoing proof of a lack of credible evidence of an association between Bendectin and birth defects, that the drug was reintroduced for clinical use (with FDA approval) for nausea and vomiting of pregnancy (21). In this case, premature and unfounded withdrawal of a medication for lack of pregnancy-specific investigation was followed by the development of a large body of appropriate pregnancy-specific research that ultimately disproved decades of concern.

Research Interventions Specific to Pregnancy

Interventions That May Potentially Benefit the Pregnant Woman and Her Fetus

Although pregnancy is a time for caution when considering research trials, it also is the only opportunity to study interventions aimed at treating pregnant women. For example, trials aimed at determining appropriate tocolysis for prevention of preterm birth or interventions for treatment of gestational diabetes can be conducted only during pregnancy.

In addition, research during the process of labor and delivery is vital to improving care for women and their newborns. The fact that a pregnant woman is entering labor or in labor does not preclude her from consenting to participate in research. A pregnant woman in labor may be able to undergo the appropriate informed consent process for research, similar to individuals with conditions that may have parallel connotations to labor, including life-threatening, emotionally distressing, or emergency situations (eg, appendicitis, cancer diagnosis, and myocardial infarction).

Non-Pregnancy-Related Interventions That May Benefit a Woman During Pregnancy

A significant proportion of pregnant women undergo therapies aimed at managing nonobstetric medical conditions. Studies have estimated that more than 60% of pregnant women use at least one prescription medication during their pregnancies (22). Most of these medications have not specifically been studied in pregnancy. The unknown risk status of the vast majority of FDA-approved medications puts fetuses at risk. Had these drugs been studied in pregnancy early in their use, data on risk may have provided an opportunity to better

balance the risks and benefits of their use. Because pregnancies are increasingly occurring in older women and in those with complex medical problems, the use of prescription medications by pregnant women is likewise increasing. Physicians who care for pregnant women with complex medical problems, and the pregnant women themselves, are faced with making health care decisions based on insufficient clinical evidence in an era when evidence-based medicine is standard practice.

The challenge of caring for pregnant women on the basis of insufficient evidence is similar to the treatment of children before reforms in responsible pediatric research. In 1994, the NIH publicly recognized a need for increased research in the pediatric population because of a significant gap in knowledge regarding safe and effective treatments (23, 24). Guidance required the default inclusion of children in clinical, social, and behavioral research unless the investigator produced a cogent reason for their exclusion. As a result, current therapeutic information exists for some, though certainly not all, medications with respect to pediatric dosing, safety, and pharmacology.

Broad exclusion of pregnant women from research trials actually may place fetuses at risk because of a resulting lack of applicable knowledge regarding how best to treat pregnant women with concomitant medical conditions. However, inclusion of a token number of pregnant women in a study would not provide meaningful information regarding the maternal and fetal effects of the intervention. Alternatively, requiring inclusion of an adequate number of pregnant women to meet power requirements for the primary outcome (or to exclude uncommon fetal morbidities) could raise prohibitive obstacles to research. Thus, thoughtful, responsible study design aimed at appropriate inclusion of pregnant women in research trials, when possible, while maintaining fetal safety as a key corollary consideration, is an important goal.

Complexities of Performing Research During Pregnancy

Research in pregnant women presents specific scientific, ethical, and legal complexities. The physiology of pregnancy changes dramatically across weeks, months, and trimesters, with complex feedback loops within and between the maternal body, placenta, and fetus. Although trade-offs between maternal and fetal risks and benefits can introduce difficult challenges in study design, these are not in themselves a reason to exclude pregnant women. Several factors must be considered before pregnant women are excluded, including whether extrapolated knowledge from trials with pregnant animals and nonpregnant humans is available; whether the study offers the potential for direct benefit to the woman, her fetus, or both; and whether risks of inclusion already have been clearly established and minimized.

A significant concern in moving forward with enrolling pregnant women in research is that an intervention

could cause harm to the fetus, and especially that the intervention or medication under study could cause a birth defect or other harms. Although there is a cognitive bias toward considering the risks of intervention, including the risk of inclusion in research, there also is a risk associated with failing to intervene and exclusion from research. Pursuit of zero risk to the fetus may come at a cost to the woman and the fetus and sets a standard that we do not expect from parents enrolling infants and children in research. Maternal and fetal risks are deeply interconnected, and consideration of enrolling pregnant women in research requires balancing the risk of fetal harm with the potential for benefit and the importance of the information to be gained on the health of women and fetuses.

Research in pregnant women requires thoughtful study design. In 2009, the National Institute of Allergy and Infectious Diseases conducted a tiered research trial of the H1N1 vaccine (25). This study was conducted after initial safety and efficacy information for the general population was available, and it specifically evaluated women in the second trimester and third trimester to minimize inadvertent teratogenicity and to target the population most at risk of severe disease from H1N1 infection. Studies of this nature allow an incremental increase in risk as the chance of likely benefit increases.

The results of the H1N1 study involving pregnant women support the idea that it is possible to responsibly reform human research protection guidelines to enable pregnant women to have greater access to participation in research and its benefits. This represents a shift from protecting populations *from* research toward protecting populations *through* research. Women who were interviewed after participation in research trials that studied the efficacy of the H1N1 vaccine reported feeling that exclusion from trials such as these precluded them from potential research-related benefits (26). Similarly, many of the participants in the H1N1 vaccine studies viewed research participation as “safer” than care in the clinical setting (26). If pregnant women view care during a research study as potentially superior to, or at least as good as, the clinical care they are receiving, they may begin to demand access.

The Fetus as the Focus of Research Trials

Treatments aimed specifically at the fetus also may be the focus of research trials. The overarching goal of fetal interventions is clear: to improve the health of children by intervening before birth to correct or treat prenatally diagnosed abnormalities (27). Any fetal intervention, however, has implications for the pregnant woman’s health and bodily integrity and, therefore, cannot be performed without consideration of her well-being and without her explicit informed consent (27, 28). It is impossible to enroll the fetus in a research trial without affecting the pregnant woman either physically (in the

case of surgical treatments) or pharmacologically (as in the case of medications given to the woman that then cross the placenta to treat the fetus). Because the pregnant woman who chooses to undergo these research procedures and treatments must assume some of the risk, respect for her autonomy requires a thorough discussion and evaluation of the maternal risks and harms of any of these therapies and her informed consent (29). A pregnant woman’s right to informed refusal must be respected fully. The potential benefit to the fetus should not be overstated in an effort to ensure maternal participation. Similarly, it is essential that undue risks to a woman’s health not be undertaken if the likely benefit to the fetus is minimal.

Safeguards should be in place to protect women considering fetal research (27). One possible safeguard would be to involve a research participant advocate with no direct ties to the experimental protocol who can act as an independent advocate for the pregnant woman, especially when the proposed fetal intervention poses significant maternal risks (30). Such advocates should be nondirective in their support of the woman’s decision and should focus on meeting the woman’s decision-making needs. Involving someone who has an understanding of the culture of research but maintains separation from the research team can provide an ethical safeguard to support the pregnant woman (31).

Consent of the Nongestational Intended Parent During Pregnancy

Consent of the pregnant woman alone is sufficient for most research involving pregnant women. When research has a significant chance of benefit or harm to the fetus, consent of a father also may be required by federal regulations (32) (see Table 1). It may be difficult, however, to discern whether research is intended for the benefit of the pregnant woman, the fetus, or both (33). These regulations regarding paternal consent are controversial and not consistent with the wide variety of family structures that may be encountered, and they have generated vigorous debate.

Proponents of coparent consent endorse this requirement because they believe it is consistent with recognition of and respect for the rights of the nongestational intended parent in protecting the welfare of the fetus. They believe this represents a reasonable compromise between acknowledging parental rights and reducing barriers to participation in research by pregnant women.

The American College of Obstetricians and Gynecologists supports a woman’s autonomy in making decisions during her pregnancy. Recognition of the rights of the nongestational intended parent during pregnancy may infringe upon and weaken maternal autonomy. As in other clinical situations, the pregnant woman’s consent should be sufficient for research interventions that affect her or her fetus.

Table 1. Selected Federal Regulations on Informed Consent for Participants in Human Research* ↵

Issue	Citation	Regulation
Maternal consent	45 C.F.R. §46.204(d)	If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A [†] of this part;
Paternal consent	45 C.F.R. §46.204(e)	If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A [†] of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

*Federal regulations on protection of human research participants are found in Protection of human subjects. 45 C.F.R. part 46 (2014). Selected sections of the regulations dealing with informed consent are reprinted here; the complete, current version may be found at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>.

[†]Basic HHS policy for protection of human research subjects. 45 C.F.R. §46.101–124 (2014).

Conclusion

All women, regardless of race, ethnicity, sexual orientation, or socioeconomic status, should be presumed eligible for participation in research studies. The potential for pregnancy should not automatically exclude a woman from participating in a study, although the use of contraception may be required for participation. Inclusion of women in research studies is necessary for valid inferences about health and disease in women. The generalization of results from trials conducted in men may yield erroneous conclusions that fail to account for the biologic differences between men and women. Although many improvements have occurred since the time of systematic exclusion of women from research trials, more work needs to be done on the design of research trials so that they do not inappropriately constrain the reproductive choices of study participants or unnecessarily exclude pregnant women. It is important that researchers and funding organizations recognize the ways in which fertility, in the context of research trials, has been managed historically in a manner that is not evidence based and that is overly burdensome for female participants in research and that they make the necessary changes to remedy this situation.

References

1. National Institutes of Health. NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research – amended, October 2001. Bethesda (MD): NIH; 2001. Available at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. Retrieved April 28, 2015. ↵
2. NIH Revitalization Act of 1993, Pub. L. No. 103-43 (1993). ↵
3. National Institutes of Health. Monitoring adherence to the NIH policy on the inclusion of women and minorities as subjects in clinical research. Comprehensive report: tracking of clinical research as reported in fiscal year 2011 and fiscal year 2012. Bethesda (MD): NIH; 2013. Available at: <http://orwh.od.nih.gov/research/inclusion/pdf/Inclusion-ComprehensiveReport-FY-2011-2012.pdf>. Retrieved April 28, 2015. ↵
4. Beauchamp TL, Childress JF. Principles of biomedical ethics. 7th ed. New York (NY): Oxford University Press; 2013. ↵
5. Chen MS Jr, Lara PN, Dang JH, Paterniti DA, Kelly K. Twenty years post-NIH Revitalization Act: enhancing minority participation in clinical trials (EMPaCT): laying the groundwork for improving minority clinical trial accrual: renewing the case for enhancing minority partici-

- pation in cancer clinical trials. *Cancer* 2014;120(suppl 7):1091–6. [PubMed] [Full Text] ↵
6. Dickerson DL, Leeman RF, Mazure CM, O'Malley SS. The inclusion of women and minorities in smoking cessation clinical trials: a systematic review. *Am J Addict* 2009;18:21–8. [PubMed] [Full Text] ↵
 7. Geller SE, Koch A, Pellettieri B, Carnes M. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? *J Womens Health (Larchmt)* 2011;20:315–20. [PubMed] [Full Text] ↵
 8. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling pregnant women: issues in clinical research. *Womens Health Issues* 2013;23:e39–45. [PubMed] [Full Text] ↵
 9. National Bioethics Advisory Commission. Ethical and policy issues in research involving human participants. Bethesda (MD): NBAC; 2001. Available at: <https://bioethicsarchive.georgetown.edu/nbac/human/overvol1.pdf>. Retrieved April 28, 2015. [PubMed] [Full Text] ↵
 10. General requirements for informed consent. 45 C.F.R. §46.116 (2014). ↵
 11. Definitions. 45 C.F.R. §46.102 (2014). ↵
 12. Anderson JR, Schonfeld TL, Kelso TK, Prentice ED. Women in early phase trials: an IRB's deliberations. *IRB* 2003;25(4):7–11. [PubMed] ↵
 13. Kim JH, Scialli AR. Thalidomide: the tragedy of birth defects and the effective treatment of disease [published erratum appears in *Toxicol Sci* 2012;125:613]. *Toxicol Sci* 2011;122:1–6. [PubMed] [Full Text] ↵
 14. Teo SK, Harden JL, Burke AB, Noormohamed FH, Youle M, Johnson MA, et al. Thalidomide is distributed into human semen after oral dosing. *Drug Metab Dispos* 2001;29:1355–7. [PubMed] [Full Text] ↵
 15. Geiger CJ, Fahrenbach DM, Healey FJ. Bendectin in the treatment of nausea and vomiting in pregnancy. *Obstet Gynecol* 1959;14:688–90. [PubMed] [*Obstetrics & Gynecology*] ↵
 16. Mitchell AA, Rosenberg L, Shapiro S, Slone D. Birth defects related to bendectin use in pregnancy. I. Oral clefts and cardiac defects. *JAMA* 1981;245:2311–4. [PubMed] ↵
 17. Zierler S, Rothman KJ. Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy. *N Engl J Med* 1985;313:347–52. [PubMed] ↵
 18. Holmes LB. Teratogen update: bendectin. *Teratology* 1983;27:277–81. [PubMed] ↵
 19. Sanders J. From science to evidence: the testimony on causation in the Bendectin cases. *Stanford Law Rev* 1993;46:1–86. [PubMed] ↵
 20. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. *Teratology* 1994;50:27–37. [PubMed] ↵
 21. Gee RE, Wood SF, Schubert KG. Women's health, pregnancy, and the U.S. Food and Drug Administration. *Obstet Gynecol* 2014;123:161–5. [PubMed] [*Obstetrics & Gynecology*] ↵
 22. Daw JR, Mintzes B, Law MR, Hanley GE, Morgan SG. Prescription drug use in pregnancy: a retrospective, population-based study in British Columbia, Canada (2001–2006). *Clin Ther* 2012;34:239–249.e2. [PubMed] ↵
 23. National Institutes of Health. NIH policy and guidelines on the inclusion of children as participants in research involving human subjects. Bethesda (MD): NIH; 1998. Available at: <http://grants.nih.gov/grants/guide/notice-files/not98-024.html>. Retrieved April 28, 2015. ↵
 24. Shaddy RE, Denne SC. Clinical report—guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Committee on Drugs and Committee on Pediatric Research. *Pediatrics* 2010;125:850–60. [PubMed] [Full Text] ↵
 25. Sperling RS, Engel SM, Wallenstein S, Kraus TA, Garrido J, Singh T, et al. Immunogenicity of trivalent inactivated influenza vaccination received during pregnancy or postpartum. *Obstet Gynecol* 2012;119:631–9. [PubMed] [*Obstetrics & Gynecology*] ↵
 26. Lyerly AD, Namey EE, Gray B, Swamy G, Faden RR. Women's views about participating in research while pregnant. *IRB* 2012;34:1–8. [PubMed] ↵
 27. Maternal-fetal intervention and fetal care centers. Committee Opinion No. 501. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2011;118:405–10. [PubMed] [*Obstetrics & Gynecology*] ↵
 28. Informed consent. ACOG Committee Opinion No. 439. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2009;114:401–8. [PubMed] [*Obstetrics & Gynecology*] ↵
 29. Lyerly AD, Mitchell LM, Armstrong EM, Harris LH, Kukla R, Kuppermann M, et al. Risk and the pregnant body. *Hastings Cent Rep* 2009;39:34–42. [PubMed] [Full Text] ↵
 30. Neill KM. Research subject advocate: a new protector of research participants. *Account Res* 2003;10:159–74. [PubMed] ↵
 31. Silber TJ. Human gene therapy, consent, and the realities of clinical research: is it time for a research subject advocate? *Hum Gene Ther* 2008;19:11–4. [PubMed] ↵
 32. Protection of human subjects. 45 C.F.R. part 46 (2014). ↵
 33. National Human Research Protections Advisory Committee. Comment letter to HHS on 45 CFR 46 Subpart B—September 2001. Washington, DC: NHRPAC; 2001. Available at: <http://www.hhs.gov/ohrp/archive/nhrpac/documents/oct01c.pdf>. Retrieved April 28, 2015. ↵

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Ethical considerations for including women as research participants. Committee Opinion No. 646. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;126:e100–7.