

New Guidance for Industry on Pregnant Women and Risk Communication Advisory Committee Meeting on the Pregnancy and Lactation Labeling Rule

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Disclosure and Acknowledgement

- I have no financial relationships to disclose relating to this presentation
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA
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Brief History

- 1974: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
 - Concern has also been expressed that the poor and minority groups may bear an inequitable burden as research subjects. The Commission believes that those groups which are most “vulnerable to inequitable treatment should receive special protection.”

Recommendations

2. Research directed toward the pregnant woman may be conducted or supported, and should be encouraged, by the Secretary, DHEW, provided such research (a) has been evaluated for possible impact on the fetus, (b) will place the fetus at risk to the minimum extent consistent with meeting the health needs of the pregnant woman, (c) has been approved by existing review procedures with adequate provision for the monitoring of the consent process, and (d) the pregnant woman has given her informed consent. (Adopted unanimously.)

1. Therapeutic research directed toward the fetus may be conducted or supported, and should be encouraged, by the Secretary, DHEW, provided such research (a) conforms to appropriate medical standards, (b) has received the informed consent of the mother, the father not dissenting, and (c) has been approved by existing review procedures with adequate provision for the monitoring of the consent process. (Adopted unanimously.)

3. Nontherapeutic research directed toward the pregnant woman may be conducted or supported by the Secretary, DHEW, provided such research (a) has been evaluated for possible impact on the fetus, (b) will impose minimal or no risk to the well-being of the fetus, (c) has been approved by existing review procedures with adequate provision for the monitoring of the consent process, (d) special care has been taken to assure that the woman has been fully informed regarding possible impact on the fetus, and (e) the woman has given informed consent. (Adopted unanimously).

It is further provided that nontherapeutic research directed at the pregnant woman may be conducted or supported (f) only if the father has not objected, both where abortion is not at issue (adopted by a vote of 8 to 1) and where an abortion is anticipated (adopted by a vote of 5 to 1).

Brief History: 1977-1994

- FDA Guidance “General Considerations for the Clinical Evaluation of Drugs”
 - Specifically stated that women with childbearing potential should be excluded from phase 1 and early phase 2 studies
 - Once some information about relative safety and effectiveness had been amassed in early phase 2 trials, and once preclinical data on teratogenicity and female fertility in animals had been obtained, women with childbearing potential could participate in later phase 2 and phase 3 studies
- FDA Guidance revised in 1993
 - Ban of women of childbearing potential removed
 - Still a presumption of exclusion of pregnant women in clinical trials

Women and Health Research: IOM Report 1994



- Goals of Report
 - Consider the ethical and legal implications of including women, particularly pregnant women and women of childbearing potential, in clinical studies
 - Examine known instances of litigation regarding injuries to research subjects and describe existing legal liabilities and protections
 - Provide practical advice on these issues for consideration by NIH, institutional review boards (IRBs), and clinical investigators

1994 IOM Report: Conclusions

- Scientific Considerations
 - Agreed that gender and demographic groups should be included in clinical trials whenever possible; but disagreed that all clinical trials should be designed to permit subgroup analyses
- Social and Ethical Considerations:
 - Educational efforts to avoid unconscious gender biases in clinical trial designs, recruitment strategies, and informed consent.
 - Also advocated to encourage women to be scientific researchers and assume positions of authority within the scientific hierarchy
- Legal Considerations: Unable to quantify liability risk.
 - The law is not yet clear on whether a woman's informed consent to participate in a clinical study is adequate to protect a study sponsor from liability for injured offspring.
 - Urged increased attention in health care reform and tort reform for issues of research-related injury as well as a review of compensation schemes for research injury, including attention to prenatal and preconceptual injuries to offspring.
 - Liability concerns should not represent an impediment to implementation of policies that favor the broader inclusion of women in clinical studies.

1994 IOM Report: Conclusions

- Considerations of Risks to Reproduction and Offspring
 - Drugs should be tested in men and women of reproductive age, including pregnant and lactating women who are or become ill, prior to marketing, rather than awaiting the results of releasing the drug to the general public.
 - Adequate measures should be taken to provide participation including adequate informed consent process. Informed consent should include measures to prevent pregnancy during the clinical trial, and pregnancy termination options.
 - Change DHHS regulations' presumption of exclusion (i.e., that no pregnant woman may be a research subject except under certain conditions (45 CFR 46.207)) to one of inclusion
 - Deletion of pregnant women as a “vulnerable” population deserving of special protection under 45 CFR 46.111

45 CFR Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research



- Originally promulgated on August 8, 1975 and revised several times
- Pertains to research involving fetuses, pregnant women, and human *in vitro* fertilization. Pregnant women or fetuses may be involved in research if all of the following conditions are met:
 - (a) 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;
 - (b) 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; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
 - (c) Any risk is the least possible for achieving the objectives of the research;
 - (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;

45 CFR Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research



- (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.
- (f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- (g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
- (h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- (i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- (j) Individuals engaged in the research will have no part in determining the viability of a neonate.



Ethical Considerations for Including Women as Research Participants

- American College of Obstetricians and Gynecologists Ethics Committee Opinion published November 2015
- Recommendations
 - Potential for pregnancy should not automatically women for participation in clinical studies
 - Address obstacles to participation (e.g., lack of adequate child care)
 - Representation of all potentially affect individuals, including diverse and underserved populations
 - Pregnant women should be defined as “scientifically complex” rather than “vulnerable”
 - Contraception requirements should be tailored the actual risks of pregnancy in an individual study for an individual study participant
 - Requiring participation consent from a woman’s intimate partner is neither warranted nor ethically justified
 - Consideration of enrolling pregnant women in research requires balance of risk of fetal harm with potential for benefit and the importance of information to be gained on the health of women and fetuses

Recent Changes to 45 CFR 46

- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, **pregnant women, mentally disabled persons**, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.
- Changed January 19, 2017 and takes effect July 19, 2018
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, **individuals with impaired decision-making capacity**, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.



Draft Guidance for Industry

“Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials”

- Published April 9, 2018
- There is need for data to inform safe and effective treatment during pregnancy, such that clinicians and patients do not have to undertake a risk-benefit analysis for the use of drugs and biological products in pregnant women with limited human safety information
- In certain situations, it is ethically and scientifically appropriate to collect data in pregnant women in clinical trials conducted during drug development
- Ethical Considerations
 - FDA regulations do not contain a section similar to 45 CFR part 46, subpart B; however, FDA recommends that these requirements be satisfied for FDA-regulated clinical research.
 - Mirror the same 10 requirements under 45 CFR 46 Subpart B

Other Guidance Highlights

- General guidelines for research conducted premarketing setting:
 - Adequate nonclinical studies (including studies on pregnant animals) have been completed and the clinical trial holds out the prospect of direct benefit to the pregnant woman
 - **And/or** fetus that is not otherwise available outside the research setting or cannot be obtained by any other means (e.g., the pregnant woman may not have responded to other approved treatments or there may not be any treatment options)
- General guidelines for research conducted Postmarketing setting:
 - Adequate nonclinical studies (including studies on pregnant animals) have been completed
 - **And** there is an established safety database in nonpregnant women from clinical trials or preliminary safety data from the medical literature and/or other sources regarding use in pregnant women
 - **And** one of the following:
 - Efficacy cannot be extrapolated **and/or** Safety cannot be assessed by other study methods
- Women who become pregnant during a clinical trial
 - Unblinding should occur so that additional counseling can be given
 - Additional considerations are discussed

Other Clinical Trial Considerations



- Minimizing Risk to the Pregnant Woman
 - Obtain adequate reproductive and developmental toxicology data in relevant nonclinical models
 - Identify the trial population that will derive the most benefit while trying to minimize risk
 - Considering the gestational timing of exposure to the investigational drug in relation to fetal development
 - Choosing appropriate control populations
- Disease Type and Availability of Therapeutic Options in the Pregnant Population
- Timing of Enrollment
- Pharmacokinetic Data
- Safety Data Collection and Monitoring
- Stopping a Clinical Trial That Enrolls Pregnant Women

Useful Links



- Guidance available at:
 - <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM603873.pdf>
- Comment period closes on June 8, 2018
 - Information on submitting comments can be found at:
 - <https://www.federalregister.gov/documents/2018/04/09/2018-07151/pregnant-women-scientific-and-ethical-considerations-for-inclusion-in-clinical-trials-draft-guidance>

Risk Communication Advisory Committee



- Held on March 5-6, 2018
- Discussed the impact of pregnancy and lactation labeling information in prescription drug and biological products as modified under the Pregnancy and Lactation Labeling Rule
 - How information in PLLR labeling is being perceived and used by health care providers and other stakeholders
 - Factors that are critical to health care providers' interpretation of the data and counseling of pregnant women on the risks and benefits of a medication, and
 - How to convey risk information to health care providers to accurately and adequately inform risk-benefit considerations for medication use during pregnancy.
- Recordings and other materials available at:
 - <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/ucm594576.htm>

Discussion Questions to the Committee

- Discuss how factors impact healthcare provider decision-making and patient counseling
- Discuss how effective PLLR has been in conveying safety evidence in pregnancy that is useful in benefit-risk decision making
- Discuss your interpretation of certain phrases currently used in PLLR
- When there is limited evidence suggesting a safety signal in pregnancy, discuss criteria that should prompt FDA to communicate this information

Highlights of RCAC Recommendations

- Ensure that the benefit is stated clearly, including the potential risks of NOT taking the drug
- Presentation/format of information should allow for quick review
- Use plain language and consistent terminology
- Improve on organization and presentation of information
- Consider a tabular summary of the evidence, including the strength and quality of the evidence Animal data; strength of evidence of human data; time on market
- Improve on information provided about relationship of animal data to human data
- Improve on certain terminology and phrases that are confusing (e.g., adverse developmental outcomes)
- Test messaging for comprehension

Questions