



PREGNANCY TESTING FOR EXCLUSION OF PREGNANT WOMEN FROM CLINICAL STUDIES

7/2/2019

I) Rationale for Exclusion of Pregnant Women

- Because the potential benefits of research participation may extend to pregnant women, the rationale for excluding pregnant women from a specific protocol should be explicitly stated. The rationale should include an assessment of both the risk posed by study interventions above the standard of care for women with the condition being studied, and the potential effects of pregnancy on the scientific validity of the study. Potential rationales include but are not limited to:
 - Studies where there is no increased risk above standard of care, but where the physiological effects of pregnancy may affect important aspects of the study intervention (e.g., drug metabolism) or outcome (e.g., weight change, cardiac output). The potential impact of these physiological changes should be assessed in the context of study duration (e.g., there is minimal clinically relevant change in the early first trimester).
 - Studies where there is a known risk associated with study interventions (e.g., studies of drugs or drug classes that are known to have teratogenic effects in humans)
 - Studies where there is an unknown risk associated with study interventions (e.g., pre-approval studies for drugs that are not approved for another indication and where there is insufficient human data to assess risk)
- The ICF should include a brief statement describing known, suspected, or unknown risks to a developing pregnancy or breastfeeding infant, or, if pregnancy is being excluded for scientific reasons, a brief explanation.

II) Reproductive Risk Review

Before a new study reaches the DUHS IRB, a reviewer from the Dept. of OB/GYN reviews the study for contraceptive use plans, pregnancy testing plans, and reproductive risk language in the ICF. The OB/GYN reviewer will work with study teams as needed to guide pregnancy testing and contraception strategies, on a study by study basis. Study teams are encouraged to contact Dr. Evan Myers, IRB Vice Chair for Reproductive Risks, prior to submission for any issues or questions.

III) Definition of Women of Childbearing Potential

- For research purposes, women are not considered “of childbearing potential” if they
 - Have completed menopause, defined as
 - Age > 55 years old
 - Age 55 years or less and
 - at least 12 months since last menstrual period, OR

- at least 6 months since last menstrual period and FSH > 40 IU
 - More rigorous definitions (e.g., 2 years since last menstrual period, or older age) may be appropriate for specific protocols. The protocol should specifically provide a rationale balancing the potential benefits (lower risk of potential unintended pregnancy exposure) vs harms (burdens of pregnancy testing and contraception in population at extremely low risk of pregnancy, barriers to enrollment and meeting scientific goals, generalizability of results given age and gender distribution of condition being studied) of a more restrictive definition
- Have had a documented “surgical sterilization”, defined as
 - Hysterectomy and/or
 - Bilateral salpingectomy and/or
 - Bilateral oophorectomy
 - Note that the effects of any of these procedures on pregnancy are immediate and sponsor inclusion criteria requiring a “waiting period” should be justified if a potential subject would otherwise be eligible
 - Note that bilateral tubal ligation is a highly effective method of contraception that has a non-zero failure rate—premenopausal women who have had a bilateral tubal ligation are considered capable of becoming pregnant and not “surgically sterilized”
- Do not have (or could not potentially have during the study) a partner who can father children, including
 - Female partners
 - Male partners who are incapable of fathering children because of congenital anomalies, surgery, or medical treatment
 - Note that, as with bilateral tubal ligation, vasectomy is a highly effective method of contraception with a non-zero failure rate. Women who are otherwise capable of having children who have a partner who has had a vasectomy meet criteria for pregnancy testing
- Pregnancy testing in women who do not have a partner who is capable of fathering children should **NOT** be required without a strong scientific rationale
 - Testing of women who do not have a male partner capable of fathering children provides no benefit, and arguably violates the ethical principle of respect
- ICF forms should use the phrase “woman who could possibly become pregnant” rather than “woman of childbearing potential”

IV) Pregnancy Testing for Exclusion of Pregnant Women

- Protocols where study interventions pose no risk to a developing pregnancy but exclude pregnant women for scientific purposes may use clinical criteria (history with pregnancy testing as indicated) for exclusion. The clinical criteria used to exclude pregnant women should be described in the research summary and protocol.
- Protocols where pregnancy testing is done as part of standard of care prior to interventions do not need to include a description of pregnancy testing as part of the informed consent process unless the timing and method of pregnancy testing differs from standard of care

- For protocols where the intervention of greatest potential risk is an imaging study, the Duke Radiology Pregnancy Testing Guidelines should guide the necessity for, and type of, pregnancy test. <https://radiology.duke.edu/wp-content/uploads/2017/02/Complete-Pregnancy-Policy-Revised-10.2016v2.pdf>
- For protocols of drugs approved for another indication, pregnancy testing should reflect the standard of care and any guidance from the label or an FDA Risk Evaluation and Management Strategy (REMS) for use in women of childbearing potential. Any additional testing beyond standard of care should be justified.
- The timing and frequency of pregnancy testing should be based on the need to make decisions based on the results.
 - Inclusion/exclusion
 - Continuation of study interventions with potential risk (e.g., prior to each cycle of a potentially teratogenic drug)
 - Pregnancy tests that occur AFTER study interventions have ended (i.e., they are not informing a decision) need to be justified, since
 - Early detection of pregnancy after study exposure has completed will not affect subsequent risk of adverse outcomes
 - The timing of exposure to study interventions can be accurately estimated by other dating methods after a pregnancy is diagnosed based on symptoms/clinical suspicion
- The choice of serum vs urine pregnancy testing should be based on an assessment of
 - The known or potential risk of study interventions to an early pregnancy
 - The underlying risk of pregnancy in the relevant patient population based on age, prior treatments, etc.
 - The size of the incremental gain in negative predictive value of serum over urine, which is a function of underlying risk of pregnancy (primarily driven by age)
 - The risk of a false positive or indeterminate result in some populations, such as women 40 years old and older (2-5%), or women with chronic renal failure
 - Detailed Considerations, as well as a calculator for estimating the effectiveness of different pregnancy testing protocols in different populations, are available at <https://www.ctti-clinicaltrials.org/projects/pregnancy-testing>
 - In general, the increase in the negative predictive value of a serum test over a urine test is greatest in situations where
 - The risk of pregnancy is highest (healthy populations, populations where most women are under the age of 35)
 - Documentation of pregnancy risk and/or contraceptive method is not available, or has not been established for study purposes (e.g., initial screening pregnancy test)
 - Additional pregnancy testing to confirm ongoing eligibility to continue study interventions is not planned and the exposure is planned for 2 weeks or longer
- Pregnancy tests must either be performed in a CLIA certified laboratory and/or be FDA-approved for point-of-care testing.
 - The Duke Office of Clinical Research (DOCR) is responsible for overseeing the specific types of allowed test, procedure, training, and quality assurance for point-of-care testing performed by Duke research staff.

- Home pregnancy tests are **NOT** acceptable as part of research protocols for determining study eligibility, or making decisions about continuing study exposures that may have reproductive risks, because
 - The high degree of observer variability in interpreting home pregnancy tests among intended users
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4119102/#R808-36>
 - <https://www.tandfonline.com/doi/abs/10.1517/17530059.2013.830103>
 - Note that sensitivity (false negative) rates for patients in the second study were 30-40% (absolute difference) higher compared to study coordinators. When false negative rates approach 50%, having subjects flip a coin would be equally effective.
 - Ethical issues, including
 - Burden on subject in event of falsely interpreting positive test as negative with resulting ongoing exposure during early pregnancy
 - Burden on subject who does not want to discontinue study drug in interpreting ambiguous result
 - In theory, an exception could be made if home pregnancy test acceptability is documented as part of an FDA REMS for an approved drug. Currently, such tests are not acceptable for high risk exposures in populations at risk of pregnancy (e.g., isotretinoin for acne in adolescents and young adults—<https://www.verywellhealth.com/accutane-ipledge-requirements-for-women-15675>)
 - The unacceptability of home pregnancy testing in clinical trials was also endorsed in the CTTI recommendations: <https://www.ctti-clinicaltrials.org/projects/pregnancy-testing>
 - For protocols where (a) pregnancy testing is required in between study visits, and (b) travel to Duke for testing is a burden on the subject, arrangements can be made to have the testing performed at an outside facility, either a CLIA-approved laboratory or health care facility using FDA-approved point-of-care systems (e.g., local physician's office).
 - Costs of such tests should be borne by the sponsor, not the subject
- Informed consent forms should describe the type and timing of all pregnancy tests. If serum testing is used, the risk of a false positive/indeterminate result in women 40 years old and older, and women with certain conditions such as chronic renal failure, should be described, along with the potential need for additional testing. If testing is performed throughout the study, the ICF should also indicate the potential for false negative results in the setting of very early pregnancy and the need to notify study staff for any suspicion about potential pregnancy, even in the setting of a recent negative pregnancy test.

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