

# GUIDELINE FOR INCLUSION/EXCLUSION OF PREGNANT INDIVIDUALS IN NIH IRP ROTOCOLS AND INFORMATION ABOUT PREGNANCY TESTING

## 1 Rationale for the Inclusion of Pregnant Women

If the research enrolls pregnant women, fetuses or neonates then the study must satisfy all of the requirements of 45 CR 46 subpart B. Refer to NIH HRPP [Policy 400](#) to ensure sufficient information is provided to allow this study meets Subpart B determination criteria.

If the study does not intentionally enroll pregnant women, but it is possible for a participant to become pregnant while on study (i.e., child-bearing potential), and the researcher intends to keep the participant on the study (because pregnancy is not an off-study criterion), then the protocol must provide sufficient justification and information for the IRB to determine that all of the requirements of [subpart B](#) are met.

Otherwise, it is best to exclude pregnant women. In studies that explicitly exclude pregnant women, if a participant becomes pregnant while on study and the researcher wishes to keep the participant on-study, then an amendment must be submitted to provide the justification for continued participation of the pregnant woman on the research.

## 2 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 (i.e., provide the justification for exclusion). The rationale should include an assessment of both the potential risks 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 exclusionary rationale include but are not limited to:

- The protocol does not meet the requirements for inclusion of pregnant women under 45 CFR 46 Subpart B.
- 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 or animals)
- 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 to a pregnant woman or fetus.)

The informed consent form (ICF) should include a brief statement describing known, suspected, or unknown risks to a developing fetus or breastfeeding infant, or, if pregnancy is being excluded for scientific reasons, a brief explanation should be provided.

## 3 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
    - at least 12 months since last menstrual period, OR
  - 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 for persons.

Informed consent forms should use the phrase such as “woman who could possibly become pregnant” rather than “woman of childbearing potential.”

Note that it is acceptable for a protocol to specify a different definition of “childbearing potential”, and if so, the definition in the protocol should be followed. If the protocol does not explicitly define this, the guideline above should be followed in the Intramural Research Program.

#### **4 Pregnancy Testing for Exclusion of Pregnant Women**

Protocols where study interventions pose no risk to a developing fetus, but exclude pregnant women for scientific reasons, may use clinical criteria (history, with pregnancy testing as indicated) for exclusion. The investigator should describe the clinical criteria used to exclude pregnant women in the research protocol.

- NOTE an exception to this: The majority of data to date has failed to show that exposure to Magnetic Resonance (MR) has deleterious effects on the developing fetus. Nonetheless, if pregnancy is established, in clinical practice the decision to proceed with a *non-contrast* MR study at 1.5 Tesla (T) or greater is based on the medical benefits weighed against the unknown risk. The safety of

MR at fields strengths higher than 1.5 T (i.e. 3T, 7T) during pregnancy has not been thoroughly assessed. Thus, while MRI without contrast is generally considered a minimal risk procedure, when this imaging is performed for the purposes of research, a pregnancy test is required to rule out pregnancy prior to performing the test. (See <https://www.acr.org/-/media/ACR/Files/Radiology-Safety/MR-Safety/Manual-on-MR-Safety.pdf> for more information.)

Protocols where pregnancy testing is done as part of routine practice prior to interventions (e.g., CT scan) do not need to include an additional description of pregnancy testing as part of the informed consent process unless the timing and method of pregnancy testing differs from the standard of care at the NIH.

For protocols using drugs or biologics, including approved agents (whether used on or off label), pregnancy testing should reflect the standard of care and be consistent with guidance in the package insert, and if applicable, FDA labeling for use in women of childbearing potential.

The timing and frequency of pregnancy testing should be based on the need to make decisions based on the results of testing, such as:

- 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.

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 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 a subject in event of falsely interpreting positive test as negative with resulting ongoing exposure during early pregnancy.
  - Burden on a subject who does not want to discontinue study drug based on ambiguous results.
- 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-iplodge-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 NIH 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).

Informed consent forms should describe the type and timing of all pregnancy tests.