



REPRODUCTIVE RISK CONSIDERATIONS IN RESEARCH: CONTRACEPTION, BREASTFEEDING, FERTILITY, UNINTENDED PREGNANCY AND CONSENT PROCESS

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I) 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”.

II) Contraceptive Considerations: Women

- Studies where the purpose of excluding pregnant women is scientific (physiologic changes of pregnancy might affect evaluation of study outcomes) do not necessarily need to mandate specific contraceptive measures.
- Studies of conditions where pregnancy itself is potentially dangerous for both mother and fetus(e.g., most cardiac conditions) may consider reinforcing the need for effective contraception for this rationale alone
- Effectiveness and Choice of Contraceptive Methods
 - Complete abstinence from vaginal intercourse for the study-required duration is acceptable and 100% effective
 - Published annual failure rates are based on outcomes in fertile populations; expected pregnancy rates in populations which are 35 and older, or have chronic illness, will be substantially lower
 - Highly effective (annual failure rate < 1%) with typical use, independent of user
 - Vasectomy
 - Bilateral tubal ligation
 - Intrauterine devices (IUDs)
 - Hormonal implants (Implanon)
 - Highly effective (annual failure rate < 1%) with “perfect use” (allowed by some sponsors, FDA, and International Committee on Harmonization)
 - Above methods, plus
 - Combination oral contraceptives (if no drug-drug interaction)
 - Progestin-only oral contraceptives that inhibit ovulation
 - Progestin-only injections (Depo-Provera)
 - Hormonal patches
 - Vaginal Rings
 - Effective methods (annual failure rate <5% with “perfect use”)
 - Above methods, plus
 - Barrier (condoms, diaphragm, cervical cap) when used consistently with spermicidal gel or foam
 - There is limited documentation on effectiveness of “dual use” methods (e.g., oral contraceptives plus condoms), but predicted effectiveness is <1% based on individual effectiveness of the individual components
 - Studies that require the use of a barrier method plus a highly effective “typical use” method (IUDs or hormonal implants) need to also specifically require use of a barrier with bilateral tubal ligation and vasectomy to be consistent with the implicit required level of effectiveness
 - Sponsors and study teams should consider the impact of age, prognosis, prior or current therapies, and co-morbid conditions on both the probability of pregnancy and the potential burdens of some methods (for example, barrier methods in patient populations where age- or menopause related changes may make use of such methods difficult or painful and adversely impact quality-of-life).

- Methods which meet criteria for effectiveness, but which are contraindicated in a specific study population (e.g., combination hormonal methods in patients at risk of deep venous thrombosis), should not be listed in the ICF.
- The CDC United States Medical Eligibility Criteria for Contraceptive Use provides guidance on specific contraceptive measures for common medical conditions: <https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html>
- For approved drugs, even if being studied for another indication, methods of contraception should be consistent with guidance on the label (for example, drug-drug interactions with oral contraceptives) or with specific REMS for known teratogens
- Any requirement for continued use of contraception after the last exposure to study drug should be justified based on considerations of drug pharmacokinetics and the biology of the female reproductive cycle. Thirty days is a typical minimum (based on average length of the menstrual cycle), but shorter or longer durations may be justified.
 - Avoidance of pregnancy after exposure to study interventions may be justified based on clinical grounds (e.g., the risks of pregnancy in patients with the condition being studied) or scientific grounds (e.g., the effects of pregnancy-related changes on assessment of study outcomes), but the ICF should explicitly state this, rather than imply that there is an ongoing study exposure-related risk
- The ICF should include language discussing the potential need to change contraceptive practices to meet study inclusion criteria.
- If appropriate given the study population, a statement informing women to avoid donating eggs for the same duration as the contraceptive requirement should be considered.
- For known teratogens, a statement informing subjects to avoid donating blood for a period consistent with the pharmacokinetics of the drug should be included.

III) Breastfeeding

- Unless specified in the protocol or label (for a drug approved for at least one indication) based on evidence of no harm, breastfeeding women should be excluded from studies that also require contraception use.

IV) Contraceptive Considerations: Men

- The rationale for requiring contraception in male participants should be explicitly stated in the protocol:
 - The potential for genetic damage to sperm
 - The potential for seminal transmission of study drug(s)
 - If seminal transmission is a concern, the protocol should explicitly state whether the primary concern is potential teratogenicity or the potential for significant exposure of a sexual partner to study drug
 - Both mechanisms
- Studies of approved drugs which (a) do not have advice on male contraception in their label or (b) do not have an existing REMS need to provide a rationale for a male contraception requirement
- If the primary concern is genetic damage,
 - The ICF should specify that contraception is required only if the subject's partner is a woman who could possibly get pregnant

- Any single or dual method meeting required minimal levels of effectiveness should be acceptable.
- A requirement for use of male condoms if the female partner is using a method that meets acceptable levels of effectiveness needs to be justified.
 - Sponsors and study teams should consider the impact of age, prognosis, prior or current therapies, and co-morbid conditions on both the probability of pregnancy and the potential burdens of some methods (for example, barrier methods in patient populations where age- or menopause related changes may make use of such methods difficult or painful and adversely impact quality-of-life).
- Female partners are not research participants and cannot be “required” to use a specific contraceptive method. Choice of contraceptive methods involves consideration of a number of clinical and personal factors, and no contraceptive method is free of some degree of burden in use or risk of side effects. Non-consenting partners cannot be required to take on these burdens as a condition of research participation
- The ICF should include language discussing the potential need to change contraceptive practices to meet study inclusion criteria.
- The protocol and ICF should describe the required duration of contraception, including any time after last exposure to study drug. Ninety days is a common duration, based on the biology of spermatogenesis, but shorter or longer durations may be justified.
- If the primary concern is seminal transmission,
 - Condoms are required for every instance of vaginal intercourse, even if the subject has had a vasectomy
 - The ICF should indicate that condoms are required for all types of intercourse (including anal and oral)
 - If the subject’s partner is pregnant, becomes pregnant, or is breastfeeding
 - If concern is with study drug exposure to partner as well as developing pregnancy
 - In latter case, ICF should be explicit that “partner” includes women who are not capable of getting pregnant and male partners
 - Because condoms alone have a failure rate of approximately 15%, a second method (spermicides, or effective female method) is advised
 - Female partners are not research participants and cannot be “required” to use a specific contraceptive method.
 - The protocol and ICF should describe the required duration of contraception, including any time after last exposure to study drug. This will primarily be based on the pharmacokinetics of the drug (5 terminal half-lives after last dose is a common standard)
 - A statement informing subjects to avoid donating blood for a period consistent with the pharmacokinetics of the drug should be included.
- Studies requiring male contraception should include a statement in the ICF informing subjects not to donate sperm for the same duration as the contraceptive requirement.

V) Study Procedures in the Event of an Unintended Pregnancy

- The protocol and ICF should describe the actions to be taken by the study team in the event an unintended pregnancy occurs in a subject, or, in studies requiring male contraception, a subject's partner. These should include
 - Withdrawal/removal of any study-specific drugs/devices
 - Any changes to study visit schedules
 - Any follow-up by the study team and/or sponsor
 - For male subjects
 - Any additional precautions (e.g., required condom use)
 - A statement about partner consent to be followed and pregnant partner form submitted with application
 - Note that for studies involving minors, a pregnant partner is likely to be a minor as well, and the pregnant partner form should be appropriately revised

VI) Other Reproductive Risks: Fertility

- For studies of drugs or treatments that are known to have effects on long-term fertility, the ICF should include
 - A description of those risks
 - A description of the potential, if any, for fertility preserving options (e.g., sperm or egg storage)

VII) Consent Process

- Every study population will include three categories of potential subjects:
 - No reproductive risk
 - Postmenopausal or surgically sterile women
 - Men who are unable to father children
 - Men who are able to father children but with partners who are unable to become pregnant
 - Reproductive risk, but already using contraceptive methods, or lifestyle, which meet study requirements
 - Reproductive risk, but not currently using a method which meets study requirements
- For subjects with no reproductive risks, inclusion of reproductive risk in the ICF
 - Increases overall cognitive burden of consent
 - Creates potential for emotional burden, especially if most patients with condition are sterile because of treatment (e.g., women with gynecologic cancer)
- For subjects who are at risk but not currently using a method, options may be limited because of condition or co-morbidities, personal/religious preferences, or partner preferences
- For studies where
 - The majority of potential subjects are expected to have no reproductive risk, and
 - Inclusion of reproductive risk language is likely to unnecessarily add to cognitive and/or emotional burden of the informed consent process
 - Study teams may consider the use of a separate Reproductive Risk Consent Addendum

- Examples of study populations where such an addendum would be appropriate include
 - Gynecologic cancer studies where the majority of patients will have undergone hysterectomy and/or bilateral oophorectomy, but some potential subjects may have had conservative treatment
 - Prostate cancer studies where the majority of patients will have undergone therapy affecting sexual function or fertility, particularly men on GnRH agonists or other drugs that significantly lower testosterone and directly inhibit spermatogenesis
 - Breast cancer studies open to men and requiring male contraception, but where potential male subjects are expected to be rare
 - Studies of ocular conditions where the majority of subjects will not be at risk of unintended pregnancy and decreased visual acuity requires the study team to read the ICF to the potential subject
- The potential benefits to subjects of a separate consent addendum should be balanced against the potential impact on operational errors resulting in a potential subject at risk of unintended pregnancy during the study not being informed of required study procedures.