Therapeutics Research Program Guidance for the Development of Protocol Procedures to Address Reproductive Risk

Brief Overview

This guidance is for investigators and network protocol teams to consider when developing clinical trials that will potentially include females and males of reproductive potential, in which there may be reproductive risks from the study product(s), strategies, or procedures. This document provides guidance on protocol inclusion/exclusion criteria, pregnancy testing and contraception requirements, follow-up for unintended pregnancy, pregnancy registries, and informed consent.

Introduction

Previously, the Therapeutics Research Program (TRP) issued a document entitled **"Guidance on Use of Contraception for Protocol Eligibility Criteria."** This guidance was based, in part, on FDA guidance regarding product labeling for use in pregnancy and specifically used the FDA pregnancy categories A, B C, D and X. In June 2015, the FDA began phasing out pregnancy categories and replaced them with a new package insert (PI) format for FDA drug labels to provide the information needed by clinicians to assess the potential of a drug to harm a fetus or alter reproductive potential. The new PI format has specific sections in which potential risks, such as structural abnormalities, embryo/fetal/infant mortality, functional impairments or growth problems potentially caused by a drug are described.

The **2015 FDA labeling** provides for a consistent format for presentation of information about pregnancy, lactation, reproductive risk in the PI to facilitate clinicians' ability to make decisions about use of products and in counseling participants. The new sections include:

- A **Pregnancy** subsection (8.1) which contains information for a **pregnancy exposure registry** for the drug when one is available. Information in the Pregnancy sub-section includes a Risk Summary, Clinical considerations, and Data.
- A **Lactation** subsection (8.2) which provides information about using the drug while breastfeeding, such as the amount of drug in breast milk and potential effects on the breastfed infant.
- A **Females and Males of Reproductive Potential** subsection (8.3), new to the labeling, which includes information, when necessary, about the need for pregnancy testing, contraception recommendations, and information about infertility as it relates to the drug.

(Above adapted from **this FDA webpage**)

TRP Definitions

Please note: Definitions used here apply to this guidance document and may differ from definitions found in other reference materials.

Reproductive Potential:

Women and men are generally considered to be of "reproductive potential" if a non-menopausal female has not had a hysterectomy, bilateral oophorectomy, or medically-documented ovarian

failure or a male can produce sperm. See "Age and Reproductive Potential" below, and Appendix 1, Section A for further details and details on documentation.

Heterosexually active men and women:
Female and male participants are considered "heterosexually active," if they are, or could possibly be engaging in behaviors that could lead to pregnancy, including heterosexual activity, sperm donation or participation in in vitro fertilization or other methods that could result in pregnancy. As this is by self-report, providers are cautioned to assess the reliability of the response—e.g., interview in front of a parent, or guardian. Men or women who do not engage in behaviors that could lead to pregnancy are not considered to be "heterosexually active," for the purpose of this guidance document.

Low to very low reproductive Potential:
Tubal ligation/cauterization or vasectomy of the male partner (unless there is documented azoospermia), while highly effective in preventing pregnancy, may not prevent all pregnancies.

- Women who are using assisted reproductive technology in the attempt to conceive and men who donate sperm are of "reproductive potential."
- Transgender men (including those using testosterone) with internal female organs are still at risk for pregnancy, if having vaginal sex without use of contraception with fertile males.
- A history of, a diagnosis of, or treatment for, infertility is not in itself sufficient to exclude a participant from the need for pregnancy testing and contraception.

Age and Reproductive Potential:
For girls, reproductive potential occurs when ovulatory menstrual cycles are established. Although the timing of ovulation relative to menarche is variable, there are reports of ovulatory cycles prior to menarche. Girls can be of reproductive potential as early as Tanner breast development stage B3.

- Boys are of reproductive potential once they mature to Tanner genitalia development stage G3 or higher.
- Women are considered post-menopausal or not of reproductive potential, if they have not menstruated for at least 12 consecutive months (in the absence of medications known to induce amenorrhea), and have a documented Follicle-Stimulating Hormone (FSH) level of greater than 40 mIU/mL or a result in the testing laboratory's menopausal range. If an FSH level is not available, then women are considered not of reproductive potential if they have had 24 consecutive months of amenorrhea (in the absence of medications known to induce amenorrhea).

Types of contraception

1) **Highly effective contraception** is defined as:

- A tubal ligation: for many teratogenic (and mutagenic) products, tubal ligation is considered a form of contraception, not a form of surgical sterilization (e.g., hysterectomy, bilateral oophorectomy). For products with low to moderate reproductive risk, tubal ligation is usually considered a form of surgical sterilization;
- An approved hormonal contraceptive such as oral contraceptives, emergency contraception used as directed, patches, implants, injections, rings or hormonally-impregnated intrauterine device (IUD), or
- An IUD.

2) **Less effective contraception** is defined as:

- Barrier methods (such as a condom used with or without a spermicide or a diaphragm or cervical cap used with a spermicide) used alone are not highly effective contraception.

Depending on the study population or design, some contraceptive methods may not be appropriate. For example, protocol-specified medications (e.g., Protease Inhibitors, Non-nucleoside Reverse Transcriptase Inhibitors) may alter the metabolism of hormone-based methods. This interaction may make hormone-based methods less effective and no longer considered effective contraception. Therefore, alternative or an additional contraception method may be required.

Standard contraceptive language should be modified to reflect medically acceptable contraceptives for the study population and the study product, based on either consultation with an obstetrician-gynecologist or review of standard guidelines, such as:

- http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a1.htm?s_cid=rr5904a1_w,
- http://www.fda.gov/ForConsumers/ByAudience/ForWomen/FreePublications/ucm313215.htm

See Appendix 1, Section B for details on documentation.

Considerations for Protocol Development

The study investigator and the protocol team should consider the following factors when determining the inclusion and exclusion criteria and contraception requirements to include in the protocol (or research proposal) to address avoidance of pregnancy and minimize reproductive risks to study participants: 1) Characteristics of the population being studied, such as fertility; reproductive potential, including age, Tanner stage or menopausal status; 2) A determination of the reproductive risk of the study product based on available data, including data from the PI or Investigator's Brochure (IB), such as human, animal, in vitro data; and 3) Assessment of risk should consider the quality and amount of evidence, as well as the limitations of these data as presented.

- For female study participants, the risk period for fetal and infant harm during and after female exposure to a potentially mutagenic and/or teratogenic product, as described in the PI and/or IB.
- For male study participants, the risk of fathering an abnormal fetus/child or the inability to father a child due to exposure to mutagenic products in semen or which may impact sperm quality or quantity.
- The study participants should be assessed periodically during the conduct of the study as reproductive potential may change over time and contraception needs may change while the participant is on study.

If the PI or IB specifies pregnancy testing requirements, contraception requirements or other limitations for use in men or women of reproductive potential, these stipulations must be used by the investigator in the design of the clinical trial and the protocol document. If data are lacking in the PI or IB, the investigator should use clinical and scientific judgment to appropriately manage reproductive risk in the clinical trial. Recommendations are included in **Table 1**.

Table 1. Suggested Contraception Requirements Based on Study Population and Study Product Risk of Potential Fetal and Reproductive Risk.

Reproductive Risk / Population	Most potentially mutagenic products	Most potentially teratogenic products[a]	Most products with low risk for fetal and reproductive risk	Products with unknown fetal and reproductive risk
Pregnant women	Exclude	Exclude	Consider inclusion if sufficiently safe, feasible, and scientifically appropriate	Exclude
Participants of reproductive potential, who are hetero-sexually active	Barrier methods may be required. Consider use of 2 forms of contraceptives for all participants, as described in table in cell directly to the right.	A Combination of **TWO** of the following[b]: • Barrier method of contraception: condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide • IUD • Hormone-based contraceptive[c] • Tubal ligation[d] Consider if use in females only or both male and female participants	Consider not requiring, or for female participants of **ONE** of the following[b]: •Barrier method of contraception: condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide •IUD •Hormone-based contraceptive[c]	Barrier methods may be required. A Combination of **TWO** of the following[b]: • Barrier method of contraception: condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide • IUD • Hormone-based contraceptive[c]
Participants of reproductive potential, who are NOT hetero-sexually active	Consider requiring methods as described above.	Contraception may be required as described above in all women of reproductive potential.	Consider enrollment without contraception requirements.	Consider requiring methods as described above.
Participants with very low or NO reproductive potential	Barriers methods may be required.	Contraception usually not required.	Contraception usually not required.	Barrier methods may be required. Define contraceptive requirements of this population using scientific and clinical judgement.

[a]Additional or specific requirements may be found in the PI, medical alert, or IB, e.g. the labeling for efavirenz specifies that only the female study participant (not all study participants) must use two reliable contraceptive methods, one of which must be a barrier method. In such cases, all the relevant instructions must be included in the protocol.

[b]Investigators should note, and providers and participants should be advised that not all contraceptive choices listed above can prevent HIV transmission and that some may increase the risk of HIV acquisition and transmission. Study participants who are sexually active with HIV negative or unknown HIV serostatus partners should be advised that they need to consider effective strategies for reducing the risk of HIV transmission, as well as meeting the requirement for effective contraception during their participation in the study.

- Consider adding language like this to the consent: "Some of the methods listed above may not prevent the spread of HIV to other people. You should discuss your contraceptive choices with your health care provider to choose the best way for you to both prevent pregnancy as required by this study and to prevent the spread of HIV to your partner(s)."

[c]Drug-drug interactions with some ARVs will make hormonal contraception a less reliable method.

[d]Tubal Ligation is considered a form of sterilization for lower risk products. For most potentially mutagenic (and most potentially teratogenic) products, if not otherwise specified in the PI or IB, it is considered a form of contraception.

Once the investigator or protocol team determines that the study product(s) or procedures pose some level of reproductive risk, then the study design must reflect appropriate management of risk, and the protocol document must contain a justification for the chosen criteria and procedures to address the following points:

1) For exclusion of pregnant women, the protocol should address:

- Rationale for exclusion of pregnant women who may otherwise qualify for study enrollment.
- If pregnancy at entry is exclusionary, then a method for excluding pregnancy prior to the start of study products should be defined.
- How pregnancy will be detected and managed on study should be specified (as described directly below in 2).

2) For inclusion of women of low or high reproductive potential, protocol should address:

- Rationale for and methods used for avoiding pregnancy, or limiting participation in behaviors that could lead to pregnancy (e.g., types of contraception required, or limitations in egg or sperm donation).
    - Note that the time of risk may also include a period after study activities have ended where the protocol specifies the use of contraception or requires participants not to participate in behaviors that could lead to pregnancy.
- The timing of pregnancy testing at screening, during and perhaps after the conduct of the study; the frequency of testing; and method of pregnancy testing.
- Modifications to study procedures, such as product holds, and follow-up procedures if a woman does become pregnant while on study.
- Whether study product can be restarted after the pregnancy is over, and if breast-feeding while on study product is allowed.
- How pregnancy outcome data will be collected, especially if women are taken off or chose to come off study, and whether infant outcome data are also needed.
- If the sponsor or FDA or regulatory authority requires any pregnancy outcome information be submitted to a pregnancy exposure registry, this should be noted in the protocol document.

3) Clinical trials using products of low risk for fetal and reproductive risk

- If the protocol team decides to require use of contraceptives for participants of reproductive potential enrolled in the clinical trial, explain why in the protocol.
- Consider allowing individuals who do not engage in behaviors that could lead to pregnancy, to enroll without use of contraception.
- Reproductive potential of the study participants should be reassessed periodically during the conduct of the study as reproductive potential may change over time and contraception needs may change while the participant is on study.

4) Clinical trials using products of high-risk for fetal and reproductive risk (potentially mutagenic and/or teratogenic)

- Barrier methods of contraception are insufficient when used alone and must be used with another highly effective method of contraception. See Appendix 1, Section A for details on documentation.

- For some study products at very high risk of fetal harm, girls who have reached Tanner breast development stage B2 may be required to use some form of contraception.
- In some instances, if there is high risk of mutagenicity with use of the product, requiring use of a condom by boys at Tanner genitalia development stage G2 or higher, might be considered.
- Women who have undergone tubal ligation/cauterization and men who have undergone vasectomy will usually be required to use some form of contraception.
- Some high-risk products (mutagenic agents, most often) might require men and women of reproductive potential, even if not participating in behaviors that could lead to pregnancy, to use barrier methods or other forms of contraception.
    - This is usually due to a concern that seminal or vaginal/cervical fluid may contain a mutagenic agent; exposing the partner to a potential reproductive risk. May require vasectomized men to use condoms to prevent exposure. In these cases, all study participants of reproductive potential, will have to agree to use barrier methods or other forms of contraception as defined by the risk potential of the product.
    - High-risk products may also require participants not to engage in behaviors that could lead to pregnancy (e.g., sperm donation, *in vitro* fertilization).

5) Informed consent considerations

The consent form should clearly describe, at a minimum:

- The risks of the study product to reproductive potential, and risks of exposure to the developing fetus.
- The appropriate methods to avoid pregnancy that are required by the study.
- Timing of pregnancy testing that is required for study inclusion; frequency of pregnancy testing during the study; any post-study testing requirements.
- Study procedures and follow-up that will take place if a female participant becomes pregnant while on study.

Appendix 1: Acceptable Documentation of Sterilization, Menopause and Child's or Adolescent's Reproductive Potential

A) Acceptable documentation of hysterectomy and bilateral oophorectomy, tubal ligation, tubal micro-inserts, vasectomy and menopause

1) For participants receiving protocol-specified low risk medications:

- Patient-reported history

2) Confirmation of the lack of reproductive potential is **REQUIRED** for participants receiving protocol-specified mutagenic or teratogenic medications:

- Written documentation or oral communication from a clinician or clinician's staff documented in source documents of one of the following:
- Physician report/letter
- Operative report or another source documentation in the patient record
- Discharge summary
- Laboratory report of azoospermia (is required to document successful vasectomy)
- FSH measurement elevated into the menopausal range as established by the reporting laboratory.
    - Note 1: The female study participant may not be able to provide written proof of a male partner's vasectomy status since he is not usually enrolled in the same study to provide consent for release of this information. **The verbal report from the female study participant of her partner's status should be written into the source documents, in most instances.**
    - Note 2: In studies of study products that are potentially mutagenic or teratogenic, if the female study participant reports a history of infertility based on one of the above categories, but written documentation is not obtainable, or she states that her partner has had a vasectomy, the female study participant must agree to use at least one barrier method with a possible second method required at the discretion of the site study physician. **Documentation of the study participant's statement should be entered the source document.**

B) Acceptable Documentation of a child's or adolescent's reproductive potential:

1) Assess the child's reproductive potential:

- Participant /caregiver-reported history
    - In males: the onset of puberty, or in females: onset of menarche.
- Physical exam: Tanner stage assessment.

2) If the participant is pre-pubescent:

- Document the assessment that the participant has not reached reproductive potential (e.g., Tanner B2 in girls or G2 for boys for some mutagenic drugs).
- Protocol-directed contraception and pregnancy testing are not necessary.
    - Study site staff should continuously reassess reproductive potential during the study as a participant's contraception needs may change over time.

3) If the onset of puberty has occurred or physical exam shows evidence of reproductive potential:
   - Document the assessment that the participant has reached reproductive potential.
   - Contraceptive counseling, contraception and pregnancy testing are required as specified by the protocol, if the participant is participating in behaviors that could lead to pregnancy.

Appendix 2: Previous FDA Pregnancy Categories:

The previous FDA pregnancy used discrete letter categories to express the balance between the potential benefit of use with the potential reproductive risk. They are defined briefly below:

Category A- Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B- Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

Category C- Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D- There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X- Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Regulations & References

- The Federal Register for the FDA Label: https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for
- 21 CFR, Part 201, Labeling: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57
- 45 CFR 46, Subpart B, Additional Protections for Pregnant Women, Fetuses or Neonates Involved in Research: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46
- Pediatric Endocrinology (Fourth Edition) ISBN: 978-1-4557-4858-7
- Pediatric Endocrinology, A Clinical Handbook ISBN: 978-3-319-18370-1