3.9 Contraception Requirements

1.0 Purpose

The purpose of this policy and procedure is to describe the contraception requirements for subjects participating in research.

2.0 Policy

It is the policy of the Organization that subjects must utilize appropriate contraception methods while participating in research with potential for reproductive toxicity.

- **2.1.** Contraception requirements should be based on the FDA Pregnancy and Lactation Labeling Rule (for all investigational drug applications submitted after 6/30/2015). Drugs approved prior to 6/30/2015 contraception requirements may be based on FDA Use-in-Pregnancy Category until Pregnancy and Lactation Labelling has been submitted and approved by FDA.
- **2.2.** Female study volunteers who are not of reproductive potential (premenarchal, postmenopausal, or surgically or otherwise sterile) are eligible to participate in research without requiring the use of contraception.
- **2.3.** Male research subjects, including those who have undergone successful vasectomy with resulting azoospermia or have azoospermia for any other reason, should use barrier contraception, or their partners should use appropriate contraception, unless the agent has been shown not to be present in seminal fluid, or the agent has been shown to have no genotoxic, reproductive, or developmental effects in nonclinical or clinical studies.
- **2.4.** It is the responsibility of the investigator with or without the Research Subject Advocate, to discuss the risks and benefits of each form of contraception with potential study participants to ensure that subjects are making an informed choice.

3.0 Categories based on FDA Pregnancy and Lactation Labeling Rule (PLLR)

- **3.1.** ***Group 1:*** No systemic absorption of drug or biologic.
- **3.2.** ***Group 2:*** Review of clinical trials conducted in pregnant women, pregnancy exposure registries, and other large scale epidemiologic studies show no evidence of adverse developmental outcomes.
- **3.3.** ***Group 3:*** In the absence of human data, animal studies show no evidence of adverse developmental outcomes.
- **3.4.** ***Group 4:*** Animal studies show evidence of adverse developmental outcomes, at dose levels higher than those to be used in this study.
- **3.5.** ***Group 5:***
  - **3.5.1.** Review of clinical trials conducted in pregnant women, pregnancy exposure registries, other large scale epidemiologic studies, or well described case-series show evidence of adverse developmental outcomes; OR
  - **3.5.2.** Animal studies show evidence of adverse developmental outcomes, at dose levels similar to those to be used in this study; OR
  - **3.5.3.** The mechanism of action of the drug suggests the possibility of adverse developmental outcomes.

4.0 Definitions of the FDA Use-In-Pregnancy Categories

- **4.1.** ***Category A: Controlled studies show no risk:*** Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.
- **4.2.** ***Category B: No evidence of risk in humans*** Adequate, well-controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals nor, in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility.
- **4.3.** ***Category C: Risk cannot be ruled out:*** Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the potential risk.
- **4.4.** ***Category D: Positive evidence of risk:*** Studies in humans, or investigational or post-marketing data, have demonstrated fetal risk. Nevertheless, potential benefits from the use of the

drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.

- **4.5.** ***Category X: Contraindicated in pregnancy:*** Studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk that clearly outweighs any possible benefit to the patient.

5.0 Procedure

- **5.1.** For drugs or biologics for which there is Pregnancy and Lactation Labelling available (all investigational drug applications submitted after 6/30/2015, and all approved drugs for which Pregnancy and Lactation Labelling has been submitted and approved by FDA), the ICFs must include the appropriate standard contraception language based upon the categories in section 3.0 (see Addendum 1 attached at the end of this policy).
  - **5.1.1.** ***Studies Involving Group 1 Drugs***
    - **5.1.1.1.** Protocol may not require use of contraception. Exceptions to this policy must be approved by the full IRB after adequate justification by the PI.
  - **5.1.2.** ***Studies involving Group 2 Drugs*** (Human data shows no evidence of adverse developmental outcome)
    - **5.1.2.1.** The protocol may require the use of ONE form of contraception, with IRB approval, after justification by the PI.
  - **5.1.3.** ***Studies involving Group 3 Drugs*** (Animal Data shows no evidence of adverse developmental outcome)
    - **5.1.3.1.** The protocol may require the use of ONE form of contraception, with IRB approval, after justification by the PI.
  - **5.1.4.** ***Studies involving Group 4 Drugs*** (Animal studies show evidence of adverse developmental outcomes, at dose levels higher than those to be used in this study)
    - **5.1.4.1.** The protocol must require the use of ONE or TWO form(s) of concurrent contraception.
  - **5.1.5.** ***Studies involving Group 5 Drugs*** (Animal or Human studies show evidence of adverse developmental outcomes, or drug mechanism of action suggests the possibility of adverse developmental outcomes)
    - **5.1.5.1.** The protocol must require the use of TWO forms of concurrent contraception.
  - **5.1.6.** For all groups, the ICF must utilize the appropriate standard language.
  - **5.1.7.** The duration of contraception must be stated in the IRB Application and in the ICF. If contraception is required for longer than the time the drug is being administered, justification must be provided.
- **5.2.** For drugs or biologics for which Pregnancy and Lactation Labeling is not available, the ICFs must include the appropriate standard contraception language based upon the categories in section 4.0 (see Addendum 1 attached at the end of this policy).
  - **5.2.1.** ***Studies Involving Category A Drugs:***
    - **5.2.1.1.** Protocol may not require use of contraception. Exceptions to this policy must be approved by the full IRB after adequate justification by the PI.
  - **5.2.2.** ***Studies Involving Category B Drugs:***
    - **5.2.2.1.** The protocol may require the use of ONE form of contraception, with IRB approval, after justification by the PI.
  - **5.2.3.** ***Studies Involving Category C Drugs:***
    - **5.2.3.1.** The protocol must require the use of ONE or TWO form(s) or concurrent contraception.
  - **5.2.4.** ***Studies Involving Category D Drugs:***
    - **5.2.4.1.** The protocol must require the use of TWO forms of concurrent contraception.
  - **5.2.5.** ***Studies Involving Category X Drugs:***
    - **5.2.5.1.** The protocol must require the use of TWO forms of concurrent contraception.
- **5.3.** For all groups and categories described above, the ICF must use the corresponding standard Contraception language in Addendum 1, except:
  - **5.3.1.** For Group 5 drugs, or category D or X drugs, if the sponsor mandates specific contraception language be included in the ICF this language may be used in lieu of the standard language in Addendum 1, provided the IRB determines that the specified language is as protective of the potential fetus, and does not create undue burden on the mother.
- **5.4.** If PI wishes to list specific forms of birth control in any of the above categories (rather than the generic “appropriate method(s) of birth control” found in the IRB-approved template), the list must include at least (1) condoms (male or female) with or without a spermicidal agent and (2) diaphragm or cervical cap with spermicide, unless the sponsor/PI presents justification that any of these are medically or scientifically inappropriate considering both the nature of the research and the subject population.
- **5.5.** The IRB Executive Chair, on behalf of the IRB Executive Committee, is authorized to negotiate with sponsors and/or PIs to address requests for specific language modifications in the ICF provided the requested modifications are at least as protective as the requirements found in the IRB-approved template.

ADDENDUM #1

ICF Pregnancy Risk Statements

Category A or Group 1 drugs:

PREGNANCY RISKS It is possible that the medicines used in this study could injure a fetus [OR an unborn child] if you, or your partner, become pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions

Category B or Group 2 or Group 3 drugs when contraception is NOT required:

PREGNANCY RISKS It is possible that the medicines used in this study could injure a fetus [OR an unborn child] if you, or your partner, become pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions.

Category B or Group 2 or Group 3 drugs when contraception IS required:

PREGNANCY RISKS It is possible that the medicines used in this study could injure a fetus [OR an unborn child] if you, or your partner, become pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions.

You may want to discuss this with others before you agree to take part in this study. If you wish, we will arrange for a doctor, nurse, or counselor who is not part of this study to discuss the potential risks and benefits with you and anyone else you want to have present.

Because of the potential risks, you, or your partner, must not become pregnant while you are participating in this study. Women must have a negative pregnancy test before entering the study [and before each treatment – as appropriate].

If you are sexually active and can get pregnant, or can get your partner pregnant, you must use ONE appropriate method of birth control every time you have sex, or you must not have sex.

You can get additional information about methods to avoid pregnancy by calling the UNMC Research Subject Advocate's Office at (402) 559-6941.

You will need to continue to use birth control to avoid pregnancy for X months after finishing the research.

By signing this and being in the study, you are agreeing to not get pregnant while you are on the study and for X months after. Should you become pregnant while on this study, you should immediately notify the study personnel. The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can refuse to provide this information.

Category C or Group 4 drugs:

PREGNANCY RISKS It is possible that the medicines used in this study could injure a fetus [OR an unborn child] if you, or your partner, become pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions.

You may want to discuss this with others before you agree to take part in this study. If you wish, we will arrange for a doctor, nurse, or counselor who is not part of this study to discuss the potential risks and benefits with you and anyone else you want to have present.

Because of the potential risks, you, or your partner, must not become pregnant while you are participating in this study. Women must have a negative pregnancy test before entering the study [and before each treatment – as appropriate].

If you are sexually active and can get pregnant, or can get your partner pregnant, you must use ONE [or TWO] appropriate method(s) of birth control every time you have sex, or you must not have sex.

Because of the possible risk to the fetus [OR an unborn child], methods of natural family planning are not, by themselves, reliable enough to avoid pregnancy.

You can get additional information about methods to avoid pregnancy by calling the UNMC Research Subject Advocate's Office at (402) 559-6941.

You will need to continue to use birth control to avoid pregnancy for X months after finishing the research.

By signing this and being in the study, you are agreeing to not get pregnant while you are on the study and for X months after. Should you become pregnant while on this study, you should immediately notify the study personnel. The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can refuse to provide this information.

Category D or Group 5 Drugs:

PREGNANCY RISKS It is possible that the medicines used in this study could injure a fetus [OR an unborn child] if you, or your partner, become pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions.

You may want to discuss this with others before you agree to take part in this study. If you wish, we will arrange for a doctor, nurse, or counselor who is not part of this study to discuss the potential risks and benefits with you and anyone else you want to have present.

Because of the potential risks, you, or your partner, must not become pregnant while you are participating in this study. Women must have a negative pregnancy test before entering the study [and before each treatment – as appropriate].

If you are sexually active and can get pregnant, or can get your partner pregnant, you must use TWO appropriate methods of birth control every time you have sex, or you must not have sex.

Because of the possible risks to a fetus [OR an unborn child], methods of natural family planning are not, by themselves, sufficiently reliable to avoid pregnancy.

You can get additional information about methods to avoid pregnancy by calling the UNMC Research Subject Advocate's Office at (402) 559-6941.

You will need to continue to use birth control to avoid pregnancy for X months after finishing the research.

By signing this and being in the study, you are agreeing to not get pregnant while you are on the study and for X months after. Should you become pregnant while on this study, you should immediately notify the study personnel. The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can refuse to provide this information.

Category X Drugs:

Since studies of the drug in humans, or investigational or post-marketing data, have demonstrated fetal risk, contraception is required and the language must be at least as protective as Category D language above. If the sponsor or FDA require inclusion of specific language relating to fetal risk, monitoring for pregnancy and prevention of pregnancy in the ICF, it may be included, and redundant category D language deleted.

DOCUMENT HISTORY:

Written: 12/28/2015 (Approved: 12/28/2015) - original author not recorded

Revised: 11/21/2017 - revision not documented

Revision #6
Created Thu, Oct 24, 2019 9:32 PM by Autumn M Eberly
Updated Fri, Aug 19, 2022 7:43 PM by Robert A Lewis