# Evidence-Based Guidance for Contraceptive Use in Phase I and Clinical Pharmacology Trials Including Women of Child-Bearing Potential

Jeanelle Kam, Rogelio Mosqueda-Garcia and Matthew Medlock
Med-Sci Clinical Pharmacology, Covance Inc., Dallas, Texas

## Introduction

For multiple decades, there was a presumption that women of child-bearing age should automatically be excluded from any clinical study. The 1977 FDA guideline, "General Consideration for the Clinical Evaluation of "Drugs," recommended excluding women of child-bearing potential from Phase I and Phase II clinical study participation until reproductive toxicity studies and evidence of efficacy was available. The automatic exclusion of an entire segment of our population has led to large gaps in our pharmaceutical knowledge, with the majority of it pertaining to women and fetuses. Important information pertaining to the metabolic activity, potential drug-drug interaction, overall safety and/or efficacy in women of child-bearing potential is missing.[1]

In 1993 the FDA reversed the 1977 recommendation when it published, "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of "Drugs."[1]

The FDA confirmed its decision in 1996 in recognition of the notable ethical principle of justice with regard to who receives the benefits of clinical research and in assuring an individual's right to participate in research. As a result, investigators are now encouraged to engage women of child-bearing potential (WOCBP) earlier in clinical trials. The inclusion of WOCBP may help detect clinically significant safety signals such as sex differences in drug metabolism and earlier indications of response in the study investigational product developmental program.[2]

## Rationale for Utilizing Current Acceptable Birth Control Method (BCM) in WOCBP

The pregnancy rates in the United States still remain high, with approximately 50% of all pregnancies being unintentional.[3] *The unintended pregnancies increase the risk for adverse maternal and child health outcomes due to delayed prenatal care, premature birth and negative physical and mental health effects among the children.*[4] According to the Guttmacher Institute, two-thirds of U.S. women at risk of unintended pregnancy who practice contraception consistently and correctly (i.e. of ***a Perfect user*** in a given year) account for only 5% of unintended pregnancies. In contrast, 18% of women at risk who use contraception inconsistently or incorrectly (i.e. of ***a Typical user*** in a given year) account for 41% of all unintended pregnancies.[4]

In addition to the high rate of unintentional pregnancies in the general population, pregnancies discovered during clinical trials are also a contributor to the high rates. Despite the protocol-specific BCM recommendations, pregnancy testing and Principal Investigator (PI) education, WOCBP have demonstrated the ability to become pregnant while on a clinical trial. One such example is from a Phase III HPV vaccine trial in which there was ~10% pregnancy rate even with mandated BCM use and pregnancy testing prior to each dose.[5] This was deemed predictable based on the study population of WOCBP between the ages of 18-24 (having high ability to get pregnant), sexually active (at risk for pregnancy), and effectiveness of BCM being ~90%.[5]

Given the statistics and variables as noted above, it would be prudent to err on the side of caution with the BCM recommendations for healthy WOBCP enrolled in early clinical trials conducted at US Covance Clinical Research units. For Covance guidance purposes, the general *recommendation is to consider all WOCBP as those practicing "typical use" for a given BCM.*

## Definitions

**Women of Child-Bearing Potential (WOCBP):** premenopausal female that is anatomically and physiologically capable of becoming pregnant following menarche.[1,6-7] For typical Covance early Phase I/ Phase Ib clinical trials, WOCBP will include healthy women at least 18 years old.

**Women of Non-Child-Bearing Potential (WONCBP):** female that is either 6 months post-surgical sterilization via hysterectomy, bilateral oophorectomy[6] or is confirmed as a postmenopausal state.

**Postmenopausal Female:** female with amenorrhea for 12 months without an alternative medical reason with confirmatory FSH levels of ≥40 IU/L).[1,6] The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin releasing hormones, anti-estrogens, selective estrogen receptor modulators or chemotherapy.

**Men of Child-Bearing Potential (MCBP):** a male that is considered fertile after puberty.[6]

**Men of Non-Child-Bearing Potential (MONCBP):** a permanently sterile male via bilateral orchiectomy[6] or at least 3 months post-vasectomy.

**Effectiveness of Birth Control:** each contraceptive method has a typically expressed "failure rate," or percentage of women who can be expected to become pregnant within the first year that she will use a chosen method. Effectiveness rates are defined in two ways[8-9]:

1. Perfect use (Theoretical effectiveness): how well a given contraceptive method will work when used correctly and consistently with every act of intercourse
2. Typical use (Use effectiveness): how well a given contraceptive method will work in typical or actual use situations including occasional, inconsistent or incorrect use based on human error and non-ideal factors

Because WOCBP are more likely typical birth control users rather than perfect users, to ensure the safety of the subject and to prevent unintentional pregnancies, one should consider requiring two forms of acceptable birth control such as a hormonal method (OCP) plus a barrier method (male condom with spermicide). Of note, female condoms and male condoms are not advised to be used simultaneously because they can adhere to each other and cause slippage or breakage of one or both devices therefore decreasing the effectiveness.[9]

**Highly Effective Birth Control Method:** defined by ICH M3 (R2) Guideline[10-11] as a method of birth control resulting in a low failure rate (e.g. <1% per year) when used consistently and correctly (Perfect use). Such examples of highly effective or "most effective" with <1% per year as defined by the American College of Obstetrics & Gynecology and CDC are reversible: hormonal implants, intrauterine devices (hormonal or non-hormonal), OCP (progestin only, estrogen/progesterone), hormonal patch, hormonal ring and permanent sterilization: female (abdominal, laparoscopic and hysteroscopic sterilization), and male (vasectomy).[12-13] In these cases, Covance investigators may need to suggest additional birth control method restrictions. Examples of highly effective birth control will include 2 forms of acceptable methods based on "typical use."

**Effective Birth Control Method:** birth control methods that have higher annual failure rates based on *typical use* rather than *perfect use.* For the purposes of this document we have chosen to further delineate effective/acceptable birth control methods into two main categories; *6-9% annual failure rates* **and** *12-25% annual failure rates.* It is our recommendation that WOCBP who use birth control methods with a ***6-9% failure rate/year,*** and thus lower effectiveness based on typical use, utilize at least 2 forms of acceptable methods while on study and for 30 days after study completion.[12-13] WOCBP that choose methods with an even higher failure rate, those with ***12-25% failure rate/year***[12-13] require at least 2 forms of acceptable methods.

**Combined Hormonal Contraception (CHC)[9]:** contraceptive methods that include both an estrogen (typically ethinyl estradiol) and a progestin (several are available). Some common examples are most oral contraceptives, vaginal rings or transdermal patches.

**Embryo:** a fertilized egg in earliest stage of development from time of fertilization until approximately eight weeks.

**Fetus:** a developing and transforming embryo beginning at the ninth week after fertilization, (eleventh week in gestational age).

**Reproductive Toxicity[14]:** "The occurrence of biologically adverse effects on the reproductive systems of females or males that may result from exposure to environmental agents. The toxicity may be expressed as alterations to the female or male reproductive organs, the related endocrine system, or pregnancy outcomes. The manifestation of such toxicity may include, but is not limited to, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, lactation, developmental toxicity, premature reproductive senescence or modifications in other functions that are dependent on the integrity of the reproductive systems."

**Developmental Toxicity:** The occurrence of adverse effects on the developing organism (conceptus) that may result from exposure prior to conception (either parent), during prenatal development or post-natally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth and (4) functional deficiency.[14-15]

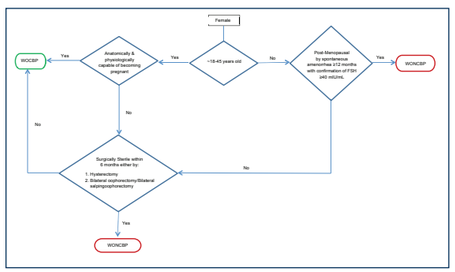


**Figure 1. Recommended definitions for a healthy WOCBP vs. a WONCBP in early Phase I/Phase Ib clinical trials.**

The ICH M3 (R2) has defined "highly effective" BCM as those alone or in combination resulting in a "low failure rate" (<1% per year) when used as correctly and consistently (known as "Perfect User"[10]). Though it is ideal that all WOCBP enrolling in clinical trials practice "perfect use" of BCM, the reality is that 18% of women at risk who use BCM "inconsistently" (known as "Typical User") account for 41% of unintentional pregnancies.[18] The general recommendation is to consider healthy WOCBP as a "typical user" of BCMs, and when enrolling this population, the acceptable BCMs would be recognized based on the effectiveness of the methods (failure rates). The following BCMs are considered "highly effective" with "perfect use" and defined as a "primary method."

***A primary method/non-barrier would include:***

1. Hormonal or Non-Hormonal Intrauterine Device (IUD)
2. Hormonal Implants
3. Surgical Sterility (Bilateral tubal ligation or Essure-hysteroscopic sterilization)
4. Hormonal Injections (e.g. Depo-Provera)
5. Oral combined OCP/Progestin-only pill
6. Combined hormonal patch
7. Combined hormonal vaginal ring

***A secondary method/barrier would include:***

1. Male condom with spermicide
2. Female condom with spermicide
3. Over-the-counter sponge with spermicide
4. Cervical cap with spermicide
5. Diaphragm with spermicide

To account for "typical users," a secondary method must be used for WOCBP enrolled in early studies involved with study IPs that have known (high risk) or unknown (medium risk) developmental and reproductive toxicology (DART) data. Therefore, "highly effective" BCMs would include two forms (1 primary and 1 secondary) of acceptable BCMs to increase the efficacy of these methods for WOCBP on clinical trials practicing "typical use."

Typically, all new drug applications (NDA) filed with the FDA will include data from the DART studies.[16] The decision to include healthy WOCBP in early clinical trials will depend on several key elements including the type of study investigational product (new chemical entity [NCE] or large molecule), review of DART studies if available, and the mitigation of unintentional pregnancies through appropriate BCM requirements along with intensive pregnancy monitoring.[10,17]

Per the ICH M3 (R2) guidance, in all ICH regions, WOCBP may be included in early clinical trials *without preclinical embryo-fetal toxicity studies* in special circumstances. These include intensive control of pregnancy risk in short (e.g. 2 weeks) clinical trials or if there is a high incidence of a disease/condition in women and not including this population would not meet the objectives of the trial, and if including WOCBP would also have sufficient pregnancy precautions.[10] In all ICH regions, WOCBP can be included in Phase I and II clinical trials before conduct of the *female fertility studies*. For Covance purposes, consider this as a "special circumstance" as noted below.

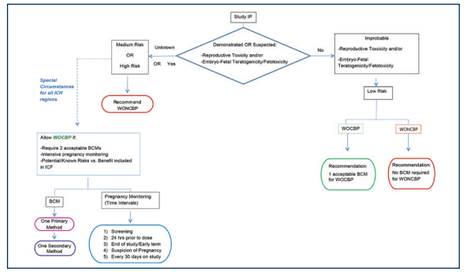


**Figure 2. Algorithm for inclusion of WOCBP vs. WONCBP and recommendations for BCM for early Phase I/Phase Ib clinical trials.**

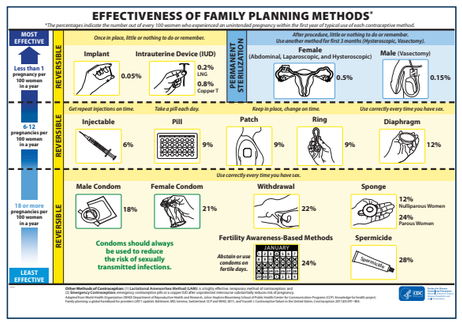


**Figure 3. Effectiveness of family planning methods (13).**

The figure provides the effectiveness of each BCM based on "typical use." This figure has been used as a reference to create Covance BCM recommendations.

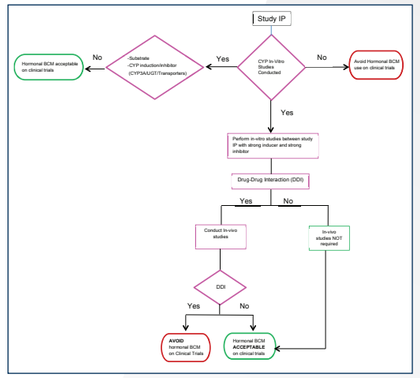


**Figure 4. Algorithm for use of hormonal BCM among WOCBP during early Phase I/Phase Ib based on drug-drug interaction (DDI) studies.**

Most times, hormonal contraceptive agents could be deemed viable options for WOCBP during early Phase I/Phase Ib trials. However, study IPs may potentially interact with estrogen and/or progesterone specifically through the hepatic cytochrome (CYP) P450 metabolic enzyme system that may either increase or decrease the efficacy of hormonal contraceptives.[19-20] Therefore, prior to recommending hormonal contraceptives on clinical trials, a thorough analysis of preclinical *in vitro and in vivo* studies such as the evaluation of a study IPs characteristics on whether it is a CYP substrate, inducer or inhibitor would be prudent to avoid decreased hormonal BCM efficacies and unintentional pregnancies. Of note, there are several other metabolic enzymes (e.g. uridine disphosphate [UDP] and glucouronyl transferases [UGT]), or transporter enzymes (e.g. P-glycoprotein [P-gp]), hepatic uptake transporters (e.g. organic anion transporting polypeptide [OATP1B1, OATP1B3]) that may cause a DDI with a study IP (small NCE, or biologic molecule) and should also be evaluated via *in vitro and in vivo* studies.[21]

It is also important to note that study IPs may cause gastrointestinal (GI) adverse events such as nausea/ vomiting and therefore, the general recommendation is to avoid hormonal oral contraceptive pills (OCP) as this may also decrease the efficacy of this method. In this circumstance, the recommendation is to avoid oral contraceptives on a trial or if a WOCBP is already on this method and desires to continue her OCPs, an additional acceptable BCM will be required.

## Discussion

- The aim of this guidance is to harmonize definition terms for what constitutes a WOCBP vs. WONCBP and highly effective BCMs among healthy women participating in early clinical studies.
- Using evidence-based algorithms to determine the safety of the inclusion of women in early clinical trials and providing general recommendations for appropriate BCMs, along with intensive pregnancy testing, will help mitigate unintentional pregnancies among healthy WOCBP in Phase I clinical studies.
- It is important to note that protocols will define the requirements of BCMs such as Acceptable BCM, Highly effective BCM, Effective BCM, etc., as it is likely recommended based on nonclinical studies if completed on such studies as pharmacokinetics (PK), and DDI with the study IP.

## References

1. Guidance for Industry: General Considerations for the clinical evaluation of drugs. In the FDA GCP Good Guidance Practices Feb 1997; 1-11.
2. Committee on Research, Women as subjects in research 2015; Retrieved from: https://doresearch.stanford.edu/policies/research-policy-handbook/human-subjects-and-stem-cells-research/women-subjects-research.
3. U.S. Selected Practice Recommendations for Contraceptive Use, 2013: Adapted from the World Health Organization Selected Practice Recommendations for Contraceptive Use, 2nd Edition, Recommendations and Reports June 2013 (RR05); 1-46; Retrieved from http://www.cdc.gov/mmwr/preview.
4. Unintended pregnancy in the United States (Fact Sheet) Jul 2015; Retrieved from: http://www.guttmacher.org/pubs/FB-UnintendedPregnancy-US.html, Jul 2015.
5. Pregnancy Testing in Clinical Trials, Summary of an Expert Meeting held July 15 & 16, 2013; Retrieved from: http://www.ctticlinicaltrials.org/files/Pregnancy_Testing/CTTI_PregnancyTesting_Meeting_HighLevelSummary_Final.pdf.
6. Recommendations related to contraception and pregnancy testing in clinical trial; Advisory non-binding guidance supported by national competent authorities represented at the CTFG-meeting in Rome 2014-09-15; Retrieved from: http://www.mhra.gov.uk/home/groups/lunit1/documents/websiteresources/con2033037.pdf.
7. Policy Statement Regarding Pregnancy Testing: Duke University Health System Human Research Protection Program, 25 Oct 2011; Retrieved from: http://irb.duhs.duke.edu/wysiwyg/downloads/Pregnancy_Testing_Policy_01-14-2013.pdf.
8. Trussell, J. Contraceptive failure in the United States. Contraception 2011; 83: 397-404.
9. A Quick Reference Guide for Clinicians: Choosing a Birth Control Method, Association of Reproductive Health Professionals, Sept 2011.
10. Guidance for Industry: M3 (R2) Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals," Jan 2010 ICH Revision 1.
11. Clarification of contraceptive wording in clinical trials conducted in the UK. Version 2-amended 21 May 2010.
12. The American College of Obstetrics and Gynecologist, Handout on the Effectiveness of Birth Control Methods, 2011.
13. The U. S. Department of Health and Human Services, Centers for Disease Control (CDC), Handout on the Effectiveness of Family Planning Methods, 2011.
14. Guidelines for Reproductive Toxicity Risk Assessment, Published on October 31, 1996, Federal Register 61(212):56274-56322.
15. ICH Harmonised Tripartite Guideline: Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5 (R2), November 2005.
16. Atkinson, A.J., Shiew-Mei, H., Lertora, J.J.L., and Markey, S.P., Chapter 24: Drug Therapy in Pregnant and Nursing Women in Principles of Clinical Pharmacology, 3rd Edition. (Elsvier Inc., San Diego 2012), pp. 395-416.
17. Pharmacology/Toxicology in the Investigator Brochure," Saber, H., PhD, Office of New Drugs/CDER/FDA, from the FDA's Clinical Investigator Course, Nov 2011.
18. Contraceptive Use in the United States, Fact Sheet. Guttmacher Institute, July 2015. Retrieved from: http://www.guttmacher.org/pubs/fb_contr_use.html.
19. Faculty of Sexual & Reproductive Healthcare Clinical Guidance: Drug Interactions with Hormonal Contraception, Clinical Effectiveness Unit, Updated January 2012.
20. Guidance Document: Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences, Retrieved from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-id/clini/womct_femec-eng.php, May 29, 2013.
21. Guidance for Industry: Drug interaction studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, Draft Guidance, U.S. Department of Health and Human Services, FDA, and Center for Drug Evaluation and Human Services, Feb 2012.

***Presented at ACCP 2015***

COVANCE
SOLUTIONS MADE REAL®