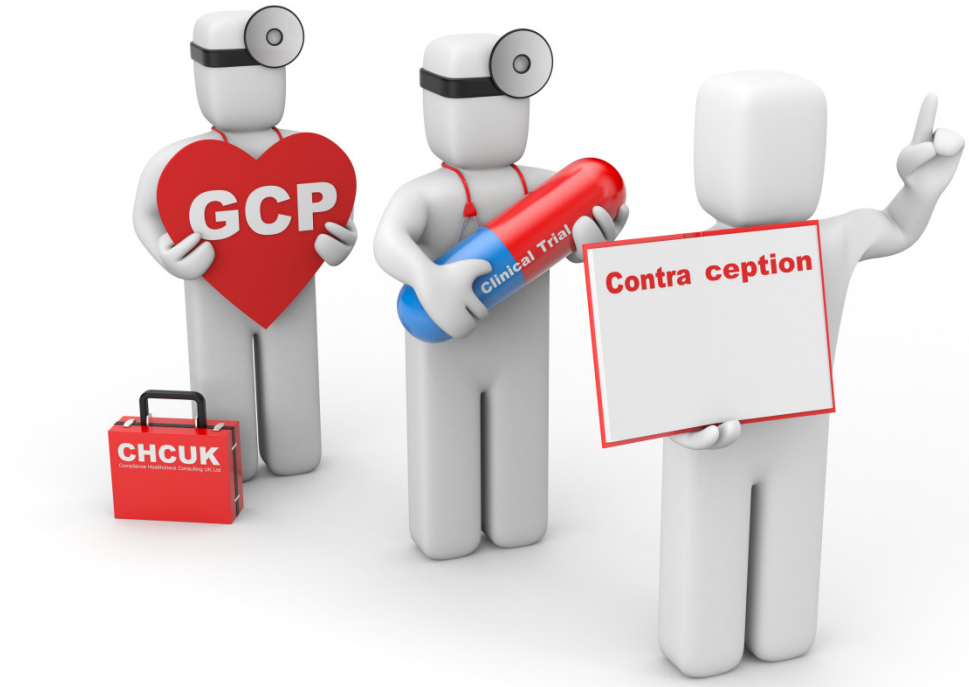
GCP Considerations: Contraception

Guidance on the recommended precautions when including men and women of child bearing potential in clinical trials, as well as, a consideration of the recommended birth control methods



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Document History

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Introduction

We routinely include statements in the clinical trial protocol and patient information leaflet/subject information sheet about potential harm to the unborn child and the need for use of a 'reliable form of contraception' during the clinical trial (see below for examples), but what do we mean by a 'reliable form of contraception'?

For Women:

Please share this information with your partner if it's appropriate.

The treatment might harm an unborn child; therefore you should not take part in this study if you are pregnant, breast-feeding or you may become pregnant during the study period. If you could become pregnant, we will ask you to have a pregnancy test (urine or blood) before taking part. ***You must agree to use a reliable form of contraception during the trial, e.g. oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom****. This should be continued for at least X months after the treatment has finished.*

If you do become pregnant during the course of the study, we would ask you to tell your study doctor immediately so we can help decide appropriate action. We would discuss referral for specialist counselling on the possible risks to your unborn baby and arrangements will be offered to monitor the health of both yourself and your unborn baby. The pharmaceutical company may also request your consent to collect information about your health and that of the baby.

Source: Annex 23 of the NRES Guidance on Information Sheets and Consent Forms. Version 3.5, May 2009

For Men:

Please share this information with your partner if it's appropriate.

It is (or is not) known if the study medicine will affect sperm or semen and therefore you should not father a child during this study or for a safety period of X months after treatment. ***If your partner might become pregnant you must use reliable forms of contraception during the trial and for X months afterwards, e.g. oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom.***

If your partner becomes pregnant during the study or within months of stopping treatment, you should inform your study doctor immediately.

As the risk to your partner and baby is unknown, it is desirable for your partner to agree to medical supervision during her pregnancy and for the baby after it is born. Your study doctor will work with the sponsoring company to organise this. Your partner will be invited to sign a consent form to allow medical supervision. The pharmaceutical company may also request you and your partner's consent to collect confidential information about her health and that of the baby.

Source: Annex 23 of the NRES Guidance on Information Sheets and Consent Forms. Version 3.5, May 2009

The following short report walks you through the recommended precautions when including men and women of child bearing potential in clinical trials, as well as, a consideration of the recommended birth control methods.

This report is intended to be a generic 'considerations' tool and therefore the reader should always abide by, and comply with, their applicable national regulations and guidelines and local policies and procedures.

Recommended Precautions when Including Men and Women of Child Bearing Potential in Clinical Trials

Reproduction Toxicity Study Requirements

It is important to characterize and minimize the risk of unintentional exposure of the embryo or foetus when including women of child-bearing potential (WOCBP) in clinical trials. One approach to achieve this objective is to conduct reproduction toxicity studies to characterize the inherent risk of a drug and take appropriate precautions during exposure of WOCBP in clinical trials (Refer to Table 1). A second approach is to limit the risk by taking precautions to prevent pregnancy during clinical trials (as per Section 11.3 of ICH M3).

Consideration of the Recommended Birth Control Methods

Precautions to prevent pregnancy include pregnancy testing (e.g., based on the β-subunit of HCG), use of highly effective methods of birth control, and study entry only after a confirmed menstrual period (Refer to Table 2). Testing for pregnancy during the trial and subject education should be sufficient to ensure compliance with the measures designed to prevent pregnancy during the period of drug exposure (which could exceed the length of study). To support these approaches, informed consent should be based on any known pertinent information related to reproduction toxicity, such as a general assessment of potential toxicity of pharmaceuticals with related structures or pharmacological effects. If no relevant reproductive information is available, the potential for unidentified risks to the embryo or foetus should be communicated (as per Section 11.3 of ICH M3).

Comparison of the Effectiveness of the Recommended Birth Control Methods

Table 3 provides a comparison of the effectiveness of the birth control methods recommended either through ICH M3 or by the MHRA in the guidance document entitled 'Clarification of Contraceptive wording in clinical trials conducted in the UK'.

Useful Links

Global Guidelines

- ICH E8 - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: General Considerations for Clinical Trials

- ICH M3 - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (R2)

    - Approved by CHMP June 2009, issued as CPMP/ICH/286/95. Date for coming into operation: December 2009.

UK Competent Authority

- Medicines and Healthcare products Regulatory Agency (MHRA)

    - MHRA's Good Clinical Practice (GCP) Inspectorate

    - MHRA - Clarification of contraceptive wording in clinical trials conducted in the UK

UK Guidance

- NHS Website - How effective is contraception?

- National Research Ethics Service Guidance on Information Sheets and Consent Forms v3.5 May 09

USA Guidance

- FDA Guidance – FDA Birth Control Guide

Table 1 – Recommendations on Timing of Reproductive Toxicity Studies to Support Inclusion of Men and Women of Child Bearing Potential in Clinical Trials

Country	Clinical Trial	Required Reproduction Toxicity Study Information	Reference
MEN			
EU, Japan & USA	Phase 1 & 2	▪ Repeated Dose Toxicity Study Men can be included in Phase 1 & 2 trials prior to the conduct of the male fertility study since an evaluation of the male reproductive organs is performed in the repeated dose toxicity studies	ICH M3(R2) *(Section 11.1)* *(Note 2)*
	Prior to Inclusion in Phase 3	▪ Male Fertility Study Men can be included in Phase 1 & 2 trials prior to the conduct of the male fertility study since an evaluation of the male reproductive organs is performed in the repeated dose toxicity studies	ICH M3(R2) *(Section 11.1)* *(Note 2)*
Pregnant Women			
EU, Japan & USA	Prior to inclusion in any Clinical Trial	▪ All reproduction toxicity studies ▪ Standard battery of genotoxicity tests Prior to the inclusion of pregnant women in clinical trials, all reproduction toxicity studies and the standard battery of genotoxicity tests should be conducted. In addition, safety data from previous human exposure should be evaluated	ICH M3(R2) *(Section 11.4)*
Women of Childbearing Potential			
EU, Japan & USA	Prior to inclusion in any Clinical Trial	▪ All reproduction toxicity studies ▪ Standard battery of genotoxicity tests all female reproduction toxicity studies and the standard battery of genotoxicity tests should be	ICH M3(R2) *(Section 11.3)*

Country	Clinical Trial	Required Reproduction Toxicity Study Information	Reference
		completed prior to the inclusion, in any clinical trial, of women of child bearing potential not using highly effective birth control or whose pregnancy status is unknown	
	Phase 1 & 2	▪ Preliminary Reproduction Toxicity Data from two species Inclusion of up to 150 WOCBP receiving IMP for a relatively short duration (up to 3 months) can occur prior to completion of definitive reproduction toxicity testing, assuming adequate birth control methods are used*	ICH M3(R2) *(Section 11.3)* *(Note 3)* *(Note 4)*
	Short Duration Clinical Trial	▪ None WOCBP can be included in clinical trials without non-clinical development toxicity studies (e.g., embryo-foetal studies) when there is intensive control of pregnancy risk over short duration clinical trials (such as 2 weeks)	ICH M3(R2) *(Section 11.3)*
	Predominance of the disease in Women	▪ None WOCBP can be included in clinical trials without non-clinical development toxicity studies (e.g., embryo-foetal studies) when there is a predominance of the disease in women, the objectives of the clinical trial cannot be effectively met without inclusion of WOCBP, and there is sufficient control over pregnancy risk.	ICH M3(R2) *(Section 11.3)*
EU & Japan	Prior to inclusion in any Clinical Trial	▪ Definitive nonclinical developmental toxicity studies In the EU and Japan, other than the above described situations, definitive nonclinical developmental toxicity studies should be completed prior to exposure to WOCBP	ICH M3(R2) *(Section 11.3)*

* A highly effective method of birth control is defined as one which results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner. For subjects using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed (ICH M3(R2), Note 4).

Country	Clinical Trial	Required Reproduction Toxicity Study Information	Reference
USA	Prior to inclusion in Phase 3	▪ Embryo-foetal development In the US, assessment of embryo-foetal development can be deferred until prior to Phase 3 for WOCBP using highly effective contraceptive methods	ICH M3(R2) *(Section 11.3)* *(Note 4)*
UK	Prior to inclusion in any Clinical Trial	The decision to include WOCBP in any study should be based upon relevant and up-to-date regulatory guidelines (e.g., ICH M3). In the event that the guidelines are not followed, applicants should ensure a clear rationale for this is provided, preferably in the body of the protocol or in the "Overall risk and benefit assessment" document	MHRA Guidance Document†

† MHRA - Clarification of contraceptive wording in clinical trials conducted in the UK

Table 2 - Consideration of the Recommended Birth Control Methods

Country	Clinical Trial	Recommended Birth Control Method(s)	Reference
Women of Childbearing Potential			
EU, Japan & USA	When Participating in any Clinical Trial	▪ Highly Effective Contraception In general, women of childbearing potential should be using highly effective contraception to participate in clinical trials	ICH E8 *(Section 3.2.2.1)* ICH M3(R2) *(Section 11.3)*
UK		▪ Reliable Form of Contraceptive, for example: ➢ Oral contraceptive and condom ➢ IUD and condom ➢ Diaphragm with spermicide and condom	NRES‡ *(Annex 23)*
UK		▪ Acceptable Forms of Effective Contraceptive, which include: ➢ Oral, injected or implanted hormonal methods of contraception ➢ Placement of an IUS or IUD ➢ Barrier methods of contraception i. Condom or Occlusive cap with spermicide ➢ Male sterilization ➢ True abstinence	MHRA Guidance Document§
Men			
EU, Japan & USA	When Indicated	▪ An Appropriate Contraceptive	ICH E8 *(Section 3.2.2.1)*

‡ National Research Ethics Service Guidance on Information Sheets and Consent Forms v3.5 May 09
§ MHRA - Clarification of contraceptive wording in clinical trials conducted in the UK

Country	Clinical Trial	Recommended Birth Control Method(s)	Reference
		For male subjects, potential hazards of drug exposure in the trial to their sexual partners or resulting progeny should be considered. When indicated (e.g., trials involving drugs which are potentially mutagenic, or toxic to the reproductive system), an appropriate contraceptive provision should be included in the trial	
UK	If Risk of Partner becoming Pregnant	▪ Reliable Forms of Contraceptive, for example: ➢ Oral contraceptive and condom ➢ IUD and condom ➢ Diaphragm with spermicide and condom If your partner might become pregnant you must use reliable forms of contraception during the trial and for X months afterwards.	NRES[**] *(Annex 23)*
	Contraceptive Requirements to be Included as Needed	Contraceptive requirements for male subjects with partners of childbearing potential should be included in the protocol where needed. These requirements should also extend to a suitable period after the last dose of study medication (e.g. a whole spermatogenic cycle or five half-lives) and should be based upon the availability and results of reproductive toxicity data.	MHRA Guidance Document
	If there is a Risk of Exposure to Ejaculate	If it has been determined that there is a significant risk of drug exposure through the ejaculate (including that of men who have had vasectomies) that might be harmful to partners (male and/or female) of male subjects on the study, the protocol should stipulate the use of condoms for the duration of the study and a suitable time period after the last dose of study medication.	MHRA Guidance Document

[**] National Research Ethics Service Guidance on Information Sheets and Consent Forms v3.5 May 09

According to ICH M3 and ICH E8, in general, women of childbearing potential should be using highly effective contraception to participate in clinical trials. Where "highly effective methods of contraception" are defined as:

- Methods of birth control which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomised partner.

Table 3 - Comparison of the Effectiveness of the ICH M3 and MHRA Recommended Birth Control methods

Highly effective methods of contraception	Recommended By	Failure Rate (Per year)			
		ICH M3 Requirement	Pearl Index	FDA Guidance	UK National Health Service
Implant	ICH M3, MHRA	<1%	0.05%	<1%	<1%
Injectable (Single hormone)	ICH M3, MHRA	<1%	0.3 – 3.0%	<1%	<1%
Injectable (Combined hormone)	ICH M3, MHRA	<1%	0.2%	<1%	<1%
Combined Oral	ICH M3, MHRA	<1%	0.3 – 8.0%	5%	<1 %
Progesterone Only	MHRA	<1%	0.3 – 8.0%	5%	1%
IUD	ICH M3	<1%	0.2%	<1%	<1%
IUS	MHRA	<1%	0.6 – 0.8%	<1%	<1%
Male Condom (+ spermicide)	MHRA	<1%	2.0 – 15%	11 - 16%	2%
Occlusive Cap (+ spermicide)	MHRA	<1%	6.0 – 16%	17 – 23%	4 - 8%
Male Sterilisation	ICH M3, MHRA	<1%	0.10 – 0.15%	<1%	<1%
Sexual Abstinence	ICH M3, MHRA	<1%	Not Listed	Not Listed	Not Listed

KEY

	No additional contraceptive needed - Meets ICH M3 definition of highly effective method of contraception
	Additional contraceptive needed – When used by itself, does not meet ICH M3 definition of highly effective method of contraception

REFERENCES

FDA Guidance – FDA Birth Control Guide

ICH E8 - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: General Considerations for Clinical Trials

ICH M3 - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (R2)

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MHRA Guidance Document - MHRA - Clarification of contraceptive wording in clinical trials conducted in the UK

NRES - National Research Ethics Service Guidance on Information Sheets and Consent Forms v3.5 May 09

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