Clarification of contraceptive wording in clinical trials conducted in the UK

Scope:

The decision to recruit a subject to any study should always be at the discretion of the investigator and should be based upon:

- The minimum contraceptive requirements in the protocol.
- The investigator's knowledge of that subject's medical history and lifestyle.
- The risk and/or benefit to the subject and any progeny.

This document provides clarification of acceptable contraceptive requirements and protocol wording in clinical trials conducted in the UK with respect to:

- Contraceptive requirements to prevent conception.
- Reproductive Status.
- Use of barrier methods of contraception to limit drug exposure via semen to sexual partners and any progeny.

Clarification of Wording and Requirements:

Highly effective method of contraception / birth control as defined in ICH (M3)

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.

Barrier Contraceptive

A contraceptive device that physically prevents sperm from entering the endometrial cavity and fallopian tubes (e.g. male condom, female condom or diaphragm).

Women Not of Childbearing Potential

Women who are postmenopausal or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy).

Women of Childbearing Potential (WOCBP)

Any female who has experienced menarche and does not meet the criteria for "Women **Not** of Childbearing Potential".

Inclusion of WOCBP onto studies and contraceptive requirements.

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 that a clear rationale for this is provided, preferably in the body of the protocol or in the "*Overall risk and benefit assessment"* document.

Where WOCBP are included in studies, the protocol should contain clear criteria for contraceptive requirements. Applicants should note that it is not acceptable to refer to the Informed Consent Form as the sole document containing these requirements. The requirements should be based on the extent of reproductive toxicity studies conducted and the results of these studies.

Acceptable forms of effective contraception include:

1. Established use of oral, injected or implanted hormonal methods of contraception. *[The decision to allow use of hormonal contraceptives should be based on the Investigational Medicinal Product's (IMP's) metabolism and potential for interactions, pharmacology and the adverse event profile (e.g. vomiting)]*.

2. Placement of an intrauterine device (IUD) or intrauterine system (IUS). *[Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g. steel or copper wire]*

3. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. *[The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:*

    - *Failure rates indicate that, when used alone, the diaphragm and condom are **not** highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.*
    - *However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. **Therefore, spermicides are not a barrier method of contraception and should not be used alone.***

4. Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). *[For female subjects on the study, the vasectomised male partner should be the sole partner for that subject]*.

5. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. *[Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]*.

Two forms of highly effective contraception

For certain studies, e.g. in the event of teratogenicity or lack of adequate reproductive toxicity data, there is a requirement for two forms of highly effective contraception. In this situation, subjects should be instructed to use two different forms of effective contraception (e.g. from the list above).

Double barrier methods of contraception

It is accepted that only in rare circumstances the protocol might require double-barrier methods of contraception **(caution should be exercised to not confuse this terminology with the requirement for two effective forms of contraception, see above).**

It should also be noted that in studies where two forms of effective contraception are required a subject may choose to use a double-barrier method of contraception, in which case the following definition is acceptable:

Condom* and Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

* A female condom and a male condom should not be used together as friction between the two can result in either product failing.

Contraceptive requirements for male subjects on studies

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.

Male subjects whose partners are pregnant

Where there is a risk of drug secretion through the ejaculate, male subjects (including men who have had vasectomies) whose partners are pregnant should use condoms for the duration of the study and for a suitable time afterwards (e.g. five half-lives). This is to ensure that the fetus is not exposed to the IMP through vaginal absorption.

Exposure to partners during the study

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.

Sperm Donation

Recommendations for sperm donation for a suitable period during the study and after the last dose of study medication might need to be considered in line with the availability and results of reproductive toxicity studies.

Marketed Products

For any product marketed in any EU member state or ICH country, the contraceptive requirements should comply with the Summary of Product Characteristics (SmPC) or equivalent. This assumes that the product is being used broadly within its licensed indication and route of administration.

Paediatric Studies

Studies in paediatric populations where it is possible that there might be an expectation that subjects both male and female are sexually active and have reached puberty, should contain guidance on contraception.