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Condoms — Guidance on clinical studies —

Part 1: Male condoms, clinical function studies based on self-reports

Préservatifs — Directives relatives aux études cliniques —

Partie 1: Préservatifs masculins — Études fonctionnelles cliniques basées sur des auto-déclarations

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 157, *Non-systemic contraceptives and STI barrier prophylactics*.

A list of all the parts of ISO 29943 can be found on the ISO website.

Introduction

Male condoms made from natural rubber latex (NRL) have a long history of safety and effectiveness and their performance during use is well established. However, male condoms made from new materials require clinical validation to ensure that their performance during actual use is not inferior to that of NRL condoms. Such clinical validation studies, called clinical function studies, are designed to compare the rates of acute failure event, i.e. breakage or complete slippage. Statistical analysis based on a non-inferiority comparison is employed to help ensure that the difference is not excessive.

This clinical study guidance is intended to help in the design, execution, analysis and interpretation of clinical function studies conducted in accordance with requirements of the ISO 23409 for synthetic male condoms. However, it can also be used with appropriate modifications to evaluate other male condoms with additional claims for improved efficacy or safety (see ISO 4074:2015, Clause 8). In addition to information regarding the clinical validation study, this document provides recommendations on pilot studies and statistical analysis plans. Annexes include previously used case report forms and protocols that can be modified or adapted.

NOTE Based on the normative clinical requirement of relevant standards, these studies are designed to recruit participating couples who agree to use the test and control condoms for vaginal intercourse. Such studies can also collect incidental data on condom use during anal sex; however, that is not the primary objective. To satisfy study power requirements, it is critical that sufficient reports are collected on condom use during vaginal intercourse. Study sponsors typically take preventive measures, such as initial screening and consenting of study couples, and obtain agreement that study couples will use condoms this way.

These clinical function studies are not typically designed to directly evaluate condom protection against pregnancy or sexually transmitted infections (STIs).

Finally, it is important to recognize that clinical function studies of condoms are human research studies. Therefore, all persons designing, running and analysing clinical studies of new condoms should be familiar with all relevant standards for research involving human subjects, including ethical considerations. For additional information, refer to ISO 14155.

Condoms — Guidance on clinical studies —

Part 1: Male condoms, clinical function studies based on self-reports

1 Scope

This document is intended to help in the design, execution, analysis and interpretation of clinical function studies conducted in accordance with the requirements of ISO 23409 for male synthetic condoms.

These clinical studies compare the performance of a new male condom to an established male condom during vaginal intercourse (not anal intercourse). In particular, these studies are designed to assess acute failure events during use (i.e. clinical slippage and clinical breakage).

This document also provides direction on the analysis of data when the study is completed, as well as interpretation of these results by manufacturers and regulatory bodies.

Certain clinical trial elements are not addressed in this document, including compensation, confidentiality of individuals and their records, use of local ethics committees, etc. These and many other clinical trial design issues are covered in greater detail in ISO 14155.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at http://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

NOTE All of the clinical failure events defined below represents potential vaginal exposure to semen and other penile discharge. Non-clinical failure events do not risk exposure.

3.1
clinical breakage
breakage or tearing of the condom during intercourse or withdrawal from the vagina

Note 1 to entry: This might not be noticed until after inspection of the condom following intercourse.

Note 2 to entry: Any breakages that do not meet the definition of clinical breakage are considered “non-clinical breakage” (e.g. tearing the condom when opening the package).

3.2
clinical breakage rate
number of condoms broken or torn during intercourse or withdrawal divided by the number of condoms used during intercourse

Note 1 to entry: The clinical breakage rate is typically reported as a percentage.

3.3
clinical slippage
condom slipping off completely during intercourse or during withdrawal from the vagina

Note 1 to entry: Sometimes slippage occurs because the user failed to hold onto the condom at the base of the penis during withdrawal and/or because the user delayed withdrawal after sex. These events are considered user failures; record such events as "non-clinical slippage." Do not count such user failures as clinical slippage events.

Note 2 to entry: If a condom slips off primarily as a result of breakage, do not count that as a slippage event.

3.4
clinical slippage rate
number of condoms that slipped completely off the penis during intercourse or withdrawal divided by the number of condoms used during intercourse

Note 1 to entry: The clinical slippage rate is typically reported as a percentage.

3.5
clinical failure event
clinical breakage (3.1) or *clinical slippage* (3.3)

3.6
non-inferiority margin
δ
statistical term used to identify clinically meaningful differences between products

Note 1 to entry: Differences between product means which are less than δ are interpreted as noise inherent in the study while differences between product means which are greater than δ are attributed to a meaningful difference between products.

3.7
bias
systematic error caused by a variable not considered in the calculation of results

Note 1 to entry: Three common causes of bias in this type of clinical study are 1) selection bias, where certain types of study subjects are not representative for the outcome being assessed, 2) recall bias, where poor questionnaire design or lengthy time between when condom is used and when the use events are recorded and 3) misclassification, where the outcome of interest (e.g. breakage or slippage) is recorded or assigned erroneously.

Note 2 to entry: The term bias is used in statistics to refer to how far the expected value of a statistic lies from the parameter it is estimating.

4 Pilot clinical studies

Validation of a new condom to generally accepted standards requires considerable time, effort and money. Therefore, pilot studies should be done to characterize and quantify the risk in undertaking the necessary larger scale investigation of clinical breakage and slippage. Typically, these pilot studies enrol 35 to 50 couples who use three to five condoms of each type (test and control). Pilot studies are intended to help determine whether the larger clinical validation study is warranted (i.e. are study results promising). Pilot studies can also be used to test questionnaires and other study instruments. Such studies also provide information for assumptions on clinical failure rates in the intended study population as these will influence the calculations of study power and sample size of the larger study. Annex B contains a sample outline for a pilot clinical study.

5 Clinical validation investigation

5.1 Objectives of clinical validation investigation

The clinical protocol should contain a concise statement on the purpose of the clinical breakage and slippage study, e.g. to evaluate the performance of a new test condom during vaginal intercourse compared with a control condom. The protocol should clearly state the hypothesis being tested (i.e. whether the non-inferiority margin of total clinical failure rates for synthetic and control condoms complies with the requirements specified in ISO 23409:2011, Clause 10).

Another possible study objective would be meeting the requirement of ISO 4074:2015, Clause 8 for a clinical study to support claims of improved efficacy or safety.

5.2 Outcome measures

The protocol should prospectively state and define the outcome measures to be evaluated when the study is completed, as well as the means by which such data will be collected.

a) The primary outcome measures are the total clinical failure rates for the test and control condoms.

b) Secondary outcome measures are

   1) clinical slippage rates, and

   2) clinical breakage rates.

c) Adverse events. The protocol should contain provisions for collecting data on safety outcomes, e.g. pain, discomfort, bleeding, penile or vaginal irritation, etc.

d) Other outcome measures (optional) are

   1) non-clinical breakage,

   2) non-clinical slippage, and

   3) user acceptability.

5.3 Study subjects

5.3.1 General

The protocol should describe the exact method(s) of recruiting subjects. Recruitment should attempt to draw from a representative target population that includes various socio-economic, ethnic, cultural and condom user experience backgrounds. The study should include multiple investigational sites and the number of study subjects enrolled should be evenly distributed across sites.

The various stages and elements of the study are described below. Annex C provides a sample timetable of events for the individual study subject. It may be configured to the specifics of a given study.

NOTE Selection bias can be introduced into a study by recruiting or oversampling couples who do not represent the target population. For example, highly experienced condom users (such as commercial sex workers) might not challenge the condom as much as inexperienced users and so targeting these couples for recruitment can result in artificially low failure rates.

5.3.2 Enrolment of study subjects

The following inclusion and exclusion criteria are suggested as an example for a low risk study. However, other entry criteria can be used depending on the study context.

5.3.2.1 Inclusion criteria

The following is a list of recommended criteria for selection of study couples.

a) mutually monogamous, current relationship ≥ 3 months;

b) already protected from pregnancy, e.g. oral contraceptive, intrauterine device, injectable, patch, male or female sterilization;

c) 18 years to 45 years of age;

d) sexually active, sufficient to meet protocol requirements; agree to have penile-vaginal intercourse with frequency sufficient to meet protocol requirements;

e) agree to use only study condoms during time of participation;

f) agree not to use drugs or non-study devices that can affect sexual performance;

g) able to understand instructions for correct use of condoms;

h) no known sexually transmitted infections including HIV/AIDS;

i) agree to use only lubricant(s) provided by the study;

j) agree not to wear any genital piercing jewellery while using study condoms;

k) willing and capable of following requirements of protocol, including willingness to respond to questions about reproductive and contraceptive history and use of condoms during interviews and on self-administered questionnaires;

l) available for follow-up.

If self-administered questionnaires are used in the study, the study subjects should have an adequate level of literacy commensurate with the questionnaires.

5.3.2.2 Exclusion criteria

The following is a list of recommended criteria for excluding a couple from the study at the time of entry or at any time during the study.

If either partner is (or becomes) aware that

a) he/she is allergic or sensitive to the material(s) of the test or control condoms,

b) female partner is pregnant or desires to become so while participating in study,

c) subject knowingly has a sexually transmitted infection,

d) commercial sex workers,

e) itinerant persons who cannot be able to complete the study, e.g. migrant farm workers,

f) male partner has known erectile or ejaculatory dysfunction,

g) either partner is using any medications or preparation applied topically or intravaginally to the genitalia other than that supplied for the study,

h) either partner is an employee of study sponsor or affiliated with clinical research centre,

it is possible to conduct a condom breakage and slippage study in a population at risk of pregnancy, i.e. not using a back-up contraceptive. In fact, this can be more representative of the target population in the commercial market. However, the risk of pregnancy during the study should be considered, as well as any measures in the protocol to manage that risk. Such a study can be subject to additional requirements from the local regulatory body.

5.4 Informed consent

The purpose and requirements of the study should be explained before prospective couples are presented with informed consent forms. Subjects should also be advised that more detailed information about sexual activity will be collected than is typical of most family planning visits. Subjects should be given an opportunity to ask questions about the study and/or the content of the informed consent. Couples should be informed that both partners should agree to participate in the study in order for them to join. If both members of the couple agree to participate, they should each be given a separate informed consent form to sign. All volunteers should provide written informed consent before they are enrolled in the study. All participants should receive a copy of their signed informed consent forms.

Subjects should be informed about the potential for condom failure and the availability of emergency contraception in the event of condom failure (if not otherwise using a highly effective alternate method of contraception).

NOTE Useful information regarding informed consent is available in Reference [11]. Also see Reference [12].

5.5 Test and control condoms

5.5.1 General

Both control and test condoms should be evaluated according to ISO 16037. This is important because these results are used to establish the specifications of the new condom and to verify that the control condom represents a typical condom already approved for market. When the test condom is synthetic, then sufficient sample sizes should be used to establish baseline properties as specified in ISO 23409.

NOTE ISO 16037 is a test method and not restricted to rubber products.

The protocol for the clinical function study should provide physical description of both test and control condoms, including material, length, lay-flat width, thickness, lubricant formulation and appearance.

5.5.2 Test condom

The test condom should meet performance specifications throughout the study.

a) Test condoms used in the clinical study should be manufactured using the same manufacturing process(es), equipment, specifications and quality assurance procedures as the product to be commercially marketed. Test condoms for the clinical study should be selected from a normal production run.

b) Test condoms should be selected from a single lot. As stated above, when the test condom is synthetic, the compliance of the lot with the specification should be assessed using the sample plans specified in ISO 23409:2011, Annex B.

   If test condoms for the clinical study are selected from more than one lot, then precautions should be taken to ensure that the individual lots comply with the specification and are of a similar age and from a similar period of production, e.g. within 3 months. It is not acceptable to mix samples from lots produced using significantly different processes or equipment.

c) As specified in ISO 23409:2011, Clause 11, when the test condom is synthetic the airburst properties of test condoms from all lots (preferably only a single lot) should be determined using a sample size of at least 2 000 condoms. Other properties of the condom should be determined and recorded using the principles underlying ISO 16037.

d) For the purposes of the trial, the test condoms can be packed in non-standard packaging, i.e. showing sequence and randomization allocation without typical brand. However, the packaging should provide the same level of protection to the condom as normal production packaging. If non-standard packaging is used, the manufacturer or the organization responsible for the trial should ensure that the proper labelling information (such as that specified in ISO 23409:2011, 16.2 for synthetic condoms) is made available to the study participants.

NOTE Local regulations can require additional labelling.

5.5.3 Control condom made from natural rubber latex

The control condom selected for the breakage and slippage study should meet the following conditions.

a) Normal production condoms should be used, subject to any special packaging required to mask the product for the trial.

b) The condom should be selected from a standard commercial design that is representative of condoms typically found in the market. Unusual designs should not be selected unless specifically justified by the trial design, in which case the scope of any claims supported by the trial can be subject to limitations.

c) A standard type and quantity of lubricant should be used, preferably a 100 cSt to 350 cSt polydimethylsiloxane fluid. The quantity of lubricant should be 400 mg to 600 mg, as measured in ISO 4074:2015, Annex C. Equivalent lubricants based on aqueous and glycol formulations are acceptable provided they have no deleterious effect on the properties of the condoms. The selection of an unusual lubricant can result in any claims supported by the trial being subject to limitations.

d) Selection of appropriate control condom should be justified with respect to study population of market and condom design and quality.

5.5.4 Expiration date of control condom

Condoms should be selected from expiration date as specified in ISO 4074 or ISO 23409, from a single manufacturing lot (if possible) that is at least 2 years before expiration date at the commencement of the trial. Where possible, full manufacturing records should be available for the lot and the lot should be identified for full traceability. The lot should be thoroughly mixed and homogenized before the trial or any testing commences.

5.5.5 Storage conditions

Condoms should be distributed and stored under such conditions that they are protected from prolonged exposure to temperatures in excess of 32 °C and any other environmental factors that could affect their quality. Storage conditions should be recorded and fully traceable.

5.5.6 Trial duration exceeds 1 year

If the duration of the trial exceeds 1 year, the study sponsor should retain samples of both the test and control condoms (per initial sampling plan) and store them under the same conditions as the trial condoms. The retained samples should be retested at the end of the trial to confirm ongoing compliance with the airburst and freedom from holes requirements of ISO 4074 or ISO 23409, as appropriate, and characterize the properties of the condom. The results of any retests should be included in the trial report.

Manufacturers can retest the condoms at regular intervals (e.g. every 6 months) during the trial. If, at any stage, the retained samples fail to meet the airburst and freedom from holes requirements of ISO 4074 or ISO 23409, then consideration should be given to terminating the trial.

5.5.7 Sampling of control condoms for bench testing

Sampling plans based on ISO 4074:2015, Annex B should be used to confirm compliance with the requirements of ISO 4074. Sampling plans based on ISO 23409:2011, Annex B should be used to confirm compliance with the requirements of ISO 23409.

5.6 Randomization

Typically, the most efficient design for a condom functionality study, in terms of couple and condom numbers, is a randomized, crossover study. With the crossover study design, study subjects are first

given a set of one condom type to use and then return for a set of the other condom type. The protocol should contain a provision for the randomization scheme designating the sequence, e.g. test condoms first and control condoms second or the other way around.

5.7 Allocation concealment and study masking

To the degree possible, product assignment should be masked from study couples, investigators and data analysts after randomization. The study protocol should describe such masking procedures.

5.8 Use of additional lubricant

Lubricant is normally applied to the test and control condom before packaging. However, some test condoms can require users to apply lubricant. In addition, some users can desire additional lubricant.

The study protocol should address whether additional lubricants can be used with the condoms. The protocol should also specify the type and amount of lubricant available for the user. In addition, the case report forms should capture the use of any lubricants, including the type, amount (to the degrees possible) and location applied.

If the lubricant supplied to the study subjects is different from the lubricant applied prior to packaging, then material screening and testing should be conducted to ensure that any additional lubrication does not have any deleterious effects on either the test or control condoms.

NOTE It might be possible to adapt the testing principles of ASTM D7661 for testing the effects of lubricant on condom properties. ASTM D7661 is a test method to assess the compatibility of unlubricated natural rubber latex male condoms with lubricants.

5.9 Instructions and interactions with study couples

Detailed verbal and written instructions, as well as training, on correct condom use should be documented in the protocol and provided to all study participants.

The training and instructions should carefully address the following:

a) purpose of study and duration of participation;

b) clear definitions (with illustrations) of key outcome measures (clinical slippage, clinical breakage and safety);

c) correct condom use;

d) time frames for using test and control condoms and recording data;

e) careful review of the “Individual Condom Use” case report form (CRF) and any other CRFs with instructions on how to properly complete them;

f) telephone and/or other contact information for study coordinator.

In addition, couples should be instructed to contact research staff immediately if they encounter any problems related to the study. Serious adverse reactions should be reported immediately to the study sponsor and the ethics committee.

5.10 Interviews and data collection

5.10.1 Schedule for interviews and condom distribution

The protocol should have a schedule for CRF distribution.

a) enrolment interview:

   — questionnaire, enrolment, provide condoms and condom use CRFs.

   For crossover studies, only the first set of condoms should be distributed at the enrolment interview.

b) mid-study interview, if crossover design:

   — collect individual condom use CRFs from first set and any unused condoms;

   — provide second set of condoms and individual condom use CRFs.

c) exit interview:

   — collect individual condom use CRFs from the second set and any unused condoms.

For the purpose of this document, CRFs can be paper-based or electronic. Examples of CRFs are provided in the annexes.

5.10.2 Enrolment interview

The protocol should have provisions for an initial interview for obtaining informed consent from both partners, ensuring that inclusion/exclusion criteria are met and to provide study participants with instructions and initial set of condoms.

There should be an Enrolment CRF to collect the following data on the study participant:

a) age, condom experience, reproductive history and other demographic information;

b) risk of STI and pregnancy;

c) method of contraception used during study;

d) ability to comply with the study protocol (e.g. length of relationship, frequency of intercourse, problems with erection/ejaculation, use of genital jewellery, etc.);

e) other, e.g. data on circumcision, genital mutilation (modification), as appropriate.

If desired, the protocol might contain provisions for a penis measurement kit. The kit should allow for a consistent means of measuring erect penis length and circumference. This information should be provided to the investigator at a later visit.

Annex D is a sample form for initial entry into the study (study entry CRF).

5.10.3 Individual condom use CRF

Per the randomization scheme, the protocol should contain a provision for providing the designated number of condoms (test or control) to the participating couples together with appropriate CRFs. The Condom Use CRF should provide for entries to collect the following event information for each condom.

Condom breakage and slippage studies are heavily reliant on user reports and memory recall. To minimize the impact of recall bias, a limited number of condoms (e.g. five) of each type should be used over no more than a 2-week to 3-week time period. Study instructions should direct participating

couples to complete the CRF for individual condom use as soon as possible after each sex act. The time frame should be no more than a few hours, not days, to reduce memory recall errors.

a) package opened (yes/no);

b) type of intercourse: vaginal, oral, anal;

c) condom broken prior to intercourse while opening package or putting condom on;

d) condom broken during intercourse;

e) condom broken during withdrawal;

f) location of break, if any;

g) condom slipped completely off penis during intercourse;

h) condom slipped completely off penis during withdrawal;

i) semen leakage from condom, noticed by user;

j) use of additional lubricant;

k) safety-related events: burning, itching, irritation, etc.

The study sponsor can collect information on user acceptability.

Study couples should be instructed to examine the condom carefully after the penis is withdrawn but before the condom is removed from the penis. Breaks which are known to have occurred during removal of condom from penis should not be included in the calculation of clinical failure.

Annex F includes several CRFs from earlier studies that were used for recording the events of a single condom use. Study sponsors are encouraged to adopt one of these sample Condom Use CRFs for their own use.

5.10.4 Mid-study CRF, crossover trial

If a crossover trial is conducted, then the protocol should have a provision for a mid-study interview at which the initial set of individual condom use CRFs is collected from the participating couples and a second set of condoms and CRFs is given to the couple. A mid-study interview CRF could collect additional data on

a) problems with condom use,

b) acceptability,

c) safety, and

d) other.

Annex E is a sample mid-study CRF that might be adopted.

5.10.5 Compiling data from CRFs

The protocol should also explain how data will be collected from the Condom Use CRFs from each study arm and compiled on the following:

a) number of packages opened;

b) number of condoms used for vaginal intercourse;

c) number of condoms broken prior to intercourse while opening package or putting condom on;