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Condoms — Guidance on clinical studies —

Part 2: Female condoms, clinical function studies based on self-reports

Préservatifs — Lignes directrices relatives aux études cliniques —

Partie 2: Préservatifs féminins, analyse fonctionnelle des défaillances graves sur la base d'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

There is limited information on the safety and effectiveness of female condoms. Therefore, clinical validation of any new female condom is necessary to ensure that its performance during actual use is not inferior to the performance of female condoms of existing designs.

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 ISO 25841 for female condoms. In addition to information regarding the clinical validation study, this document provides recommendations on risk assessment, pilot studies, and statistical analysis plans. Annexes include previously used case report forms (CRF) and protocols that can be modified or adapted.

To date, there has been considerable variation in female condom designs and materials. Many female condoms are held in place with external rings and are often anchored within the vagina using rings, sponges or other unique designs. From the published literature, the most common acute failure events associated with female condom use are breakage, slippage, invagination and misdirection. However, the definitions for these acute failure events have been inconsistent from one published study to another. A sponsor planning to conduct a female condom study should review the definitions in this document to determine their applicability for the product.

For further information regarding definitions of female condom failures, refer to Reference [12] and Reference [16]. Also, note that the definitions used in this document are based on existing designs and might need to be expanded or adapted according to the female condom under investigation. Other types of acute failure events (unique to a particular design) can be identified as part of the risk assessment per ISO 14971 or during the pilot study.

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.

It should also be noted that 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, conducting, and analysing clinical studies of new female condoms should be familiar with all relevant requirements for research involving human subjects, including ethical considerations. For additional information, refer to ISO 14155.

Condoms — Guidance on clinical studies —

Part 2: Female 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 25841 for female condoms.

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

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 female condoms broken or torn during intercourse or withdrawal divided by the number of female condoms used during intercourse

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

3.3
clinical slippage
condom slipping completely out of the vagina during intercourse

Note 1 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 female condoms that slipped completely out of the vagina divided by the number of female condoms used during intercourse

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

3.5
clinical misdirection
insertion of the penis between the female condom and the vaginal wall

3.6
clinical misdirection rate
number of female condoms that misdirect divided by the number of female condoms used during intercourse

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

3.7
clinical invagination
external retention feature of the female condom that is partially or fully pushed into the vagina during intercourse

3.8
clinical invagination rate
number of female condoms that invaginate divided by the number of female condoms used during intercourse

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

3.9
clinical failure event
clinical breakage (3.1), *clinical slippage* (3.3), *clinical misdirection* (3.5) or *clinical invagination* (3.7)

3.10
total clinical failure
number of female condoms with at least one acute failure event that results in potential vaginal exposure to semen and other penile discharge

Note 1 to entry: Any condom that experiences multiple *clinical failure events* (3.9) only counts as a single clinical failure.

Note 2 to entry: Includes condoms with the following failures: *clinical breakage* (3.1), *slippage* (3.3), *misdirection* (3.5), *invagination* (3.7), or any failure event(s) in the risk assessment as described in Clause 4.

3.11
total clinical failure rate
number of female condoms with clinical failure divided by the number of female condoms used during intercourse

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

3.12
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, slippage, invagination, or misdirection) is recorded 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.

3.13
non-inferiority margin
δ
statistical term used to identify a clinically meaningful difference 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.

4 Risk assessment

A risk assessment for the product shall be conducted in accordance with ISO 14971. This assessment should identify all safety and effectiveness concerns, including potential mechanisms of condom failure and the results of the pilot study. All possible acute failure events should be considered in the design of the female condom, and clinical investigations should be designed to capture information on each possible type of failure.

The risk assessment should address whether each acute failure event leads to potential vaginal exposure to semen and other penile discharge during condom use, and therefore whether each failure event is designated clinical or non-clinical.

Manufacturers should make this risk assessment available to regulatory bodies.

5 Pilot clinical studies

A pilot study helps to identify and evaluate the different types of acute failure events of the new female condom prior to initiation of a larger clinical investigation (see ISO 25841:2014, Clause 8). The acute failure rates obtained in the pilot study will influence the statistical calculations of power and sample size for the pivotal study. The risk assessment (see Clause 4) should be conducted prior to the pilot study and then repeated after the pilot study, with any new types of failure events reported in the pilot study to be classified as either clinical or non-clinical failures.

In addition, the pilot study can help identify potential safety concerns, including condom features that could cause abrasions or irritation during use. It is recommended that study subjects in the pilot study undergo a post-coital physical examination as soon after condom use as practicable. Such exams should be conducted by an experienced clinician.

Investigators should provide detailed verbal and written instructions on appropriate condom insertion and use to all study participants and demonstrate correct condom placement using a pelvic model.

Collection of user acceptability information will be useful to evaluate product acceptability and to guide further product improvements prior to the larger clinical investigation.

For additional information, see 6.15 and 6.16.

Annex B contains a sample outline for a pilot clinical study.

6 Clinical validation investigation

6.1 Objectives of clinical validation investigation

The protocol should state the purpose of the study, e.g. to evaluate the performance of a new female condom (test condom) during vaginal intercourse compared to a control female condom. The protocol should clearly state the hypothesis being tested (i.e. whether the non-inferiority margin between the total clinical failure rates for test and control condoms complies with the requirements specified in of ISO 25841:2014, 8.3).

NOTE Please refer to the WHO guidelines on clinical studies for additional information.

The primary objective of this study is to compare the total clinical failure rates of the test and control condoms.

Secondary objectives are to evaluate each different type of failure event identified in the risk analysis (e.g. slippage, breakage, invagination, misdirection, etc.) by comparing the new female condom to the control female condom for each type of failure event. In addition, there should be an evaluation of total condom failure (i.e. sum of total clinical and total non-clinical failures).

The secondary objectives of the research should also include safety and acceptability. Safety will be determined by the proportion of women reporting adverse events reported during condom uses and by condom type. Acceptability will be measured by the calculated frequency of key acceptability end points including ease of insertion and removal, like or dislike of product attributes, adequacy and feel of lubrication, etc.

These studies might also collect incidental data on female condom use during anal sex; however, that is not the primary objective.

6.2 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 measure is total clinical failure, representing the total number of test or control condoms for which one or more acute failure events (as defined in Clause 3) are reported by the users.

b) Secondary outcome measures should include all types of acute failure events, reported individually.

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):

   1) any non-clinical failure rates;

   2) total failure rate (clinical and non-clinical);

   3) user acceptability.

6.3 Study subjects

6.3.1 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, and

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.

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.

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.

6.3.2 Enrolment of study subjects

6.3.2.1 General

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

6.3.2.2 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, subdermal implant, 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 female condoms during time of participation;

f) agree not to use male condom when using female condom in a single sex act;

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

h) able to understand instructions for correct use of female condoms;

i) no known sexually transmitted infections, including HIV/AIDS;

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

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

l) 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;

m) 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.

6.3.2.3 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) either partner knowingly has a sexually transmitted infection,

d) an itinerant person who might not be able to complete the study, e.g. migrant workers,

e) male partner has known erectile or ejaculatory dysfunction,

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

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

it is possible to conduct a condom clinical function study in a population at risk of pregnancy, i.e. not using a back-up contraceptive. In fact, this might 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 might be subject to additional requirements from the local regulatory body.

Commercial sex workers (CSWs) represent an important target population of female condom users. However, including them in this kind of study poses some unique challenges. While this document does not specifically recommend excluding CSWs, great care should be taken when considering this during the study design phase, including provisions to ensure proper steps taken for data collection, as well as applicability to other target populations.

6.4 Informed consent

The purpose and requirements of the study should be explained before prospective subjects are presented with the informed consent form. 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. Subjects should provide written informed consent before they are enrolled in the study. All participants should receive a copy of their signed informed consent form. If the subject recruitment (see 6.3) focuses on monogamous couples, then both partners should be given separate informed consent forms to sign; if the recruitment focuses on female subjects only, then the male partner(s) do not need to sign 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].

6.5 Test and control condoms

6.5.1 General

Both control and test condoms should be tested to establish baseline properties as specified in ISO 25841. This is important because these results are used to establish or verify the specifications of the new condom and to verify that the control condom represents typical production. Sufficient sample sizes should be used.

6.5.2 Test condom

The test condom should continue to 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 eventual product to be commercially marketed. Recognizing that the scale of manufacture can be different than normal production runs, the use of pilot manufacturing equipment is acceptable, so long as it is similar to the equipment to be used during normal production.

b) Test condoms should be selected from a single lot. The compliance of the lot with the specification should be assessed using the sample plans specified in ISO 25841:2014, Annex B.

   If test condoms for the clinical study are selected from more than one lot, then this should be documented and 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 three months. It is not acceptable to mix samples drawn from lots produced using significantly different processes or equipment.

c) As specified in ISO 25841:2014, Clause 9, the airburst properties of test condoms from all lots (preferably only a single lot) used in the study should be determined using a sample size of at least 2 000 condoms. Other properties of the condom should be determined and recorded by adapting the principles described in ISO 16037.

d) For the purposes of the trial, the test condoms may be packed in non-standard packaging, i.e. sequence number 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 labelling information specified in ISO 25841:2014, 13.3 is made available to the study participants.

NOTE Local regulations can require additional labelling.

6.5.3 Control condom

The control condom should continue to meet performance specifications throughout the study.

a) The control condom selected for this study should comply with the requirements in ISO 25841:2014, Clause 8. Normal production condoms should be used, subject to any special packaging required to mask the product for the trial.

b) If possible, control condoms should be selected from a single manufacturing lot that is at least 2 years before the expiration date at the commencement of the trial. Quality of the control condoms should be fully characterized by testing and, if possible, by information from the manufacturer, i.e. expiry date.

c) Control 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.

6.5.4 Trial duration exceeds one year

If the duration of the trial exceeds one year (dating from when the condoms were first tested), 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 re-tested at the end of the trial to confirm ongoing compliance with the specifications for airburst properties, freedom from holes, and any other key condom properties, as established with baseline testing. The results of any re-tests should be included in the trial report.