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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.

Manufacturers may retain additional condom samples and re-test them at regular intervals (e.g. every six months) during the trial. If the retained samples fail to meet the airburst and freedom from holes' requirements of ISO 25841, then consideration should be given to terminating the trial.

6.5.5 Sampling of control condoms for bench testing

Sampling plans based on ISO 25841:2014, Annex B, should be used to confirm compliance with appropriate statistical principles.

6.6 Randomization

Typically, the most efficient design for a condom functionality study, in terms of subjects and condom numbers, is a randomized, crossover study. With the crossover study design, study subjects are first given a set of one condom type, use them, 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.

6.7 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.

6.8 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 (CRF) 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.

6.9 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:

a) purpose of study and duration of participation;

b) clear definitions (with illustrations) of the key outcome measures (acute failure events) that study participants are expected to report, e.g. breakage, slippage, invagination, misdirection, and any adverse events (there should be a thorough explanation and demonstration of each type of acute failure event, preferably using a pelvic model);

c) correct condom use;

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

e) careful review of the "individual condom use" 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.

6.10 Interviews and data collection

6.10.1 Schedule for interviews and condom distribution

The protocol should have a schedule for:

a) enrolment interview:

— questionnaire, enrolment including training on device use and different types of failure events;

— provide condoms and condom use CRFs

b) mid-study interview, if crossover design:

— collect condom use forms from first set, any unused condoms;

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

NOTE If three different types of condoms are being tested (i.e. for a three-arm study), collect CRFs for the second set and any unused condoms. Provide a third set of condoms and individual condom use CRFs.

c) exit interview:

— collect condom use forms from the second (or third) set, any unused condoms.

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

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

e) others, 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 turned in to the investigator at a later visit.

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

6.10.3 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 sufficient number of individual condom use CRFs for self-reports of acute failure events and other information.

Clinical function studies of condoms are heavily reliant on user reports and memory recall. To minimize the impact of recall bias, it is recommended that a limited number of condoms (e.g. five) of each type be used in less than a two-week to three-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. To reduce memory recall bias, every effort should be made to minimize the time between the sex act and completion of the CRF, i.e. no more than a few hours.

The individual condom use CRF should provide for entries to collect the following event information for each condom:

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 out of the vagina during intercourse;

h) external retention feature of the condom pushed inside the vagina partially or fully;

i) penis inserted between the female condom and the vaginal wall;

j) any other clinical failure events identified in the risk analysis or pilot study;

k) semen leakage from condom, noticed by user;

l) use of additional lubricant;

m) 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 condom has been removed from the vagina. Breaks which are known to have occurred after removal of the female condom from the vagina should be considered non-clinical breakage events.

Annex F includes a sample individual condom use CRF that one can model.

6.10.4 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;

d) others.

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

6.10.5 Compiling data from CRFs

The protocol should also explain how data will be accumulated from the individual 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) for each type of clinical failure event (e.g. clinical breakage), the number of condoms with that type of failure;

d) for each type of non-clinical failure event (e.g. tearing condom while opening package), the number of condoms with that type of failure;

e) the total number of condoms with at least one clinical failure event;

f) the total number of condoms with at least one failure event (clinical or non-clinical);

g) number of condoms used for oral sex or anal sex.

6.11 Data integrity

6.11.1 General

The clinical function study for a female condom is highly dependent upon user self-reports of clinical failure event type(s) from each coital act. Considering the limits of human memory, the timeframe for recording these data by the user should be as immediate to each coital act as possible. Therefore, to help ensure accuracy, reliability, and traceability of all data, the study protocol should address selection of study couples, instructions for study participants, timeframes for reporting events, design of coital diaries and other CRFs, study schedules, as well as distribution of study condoms (test and control) and overall collection of study data.

Compared to male condoms, female condoms have more types of failure events, and this can require considerable probing to ensure the failure events are correctly described. There is potential for underestimating and overestimating these events unless questions are clear and the coital diaries are checked carefully. This often requires direct contact with interviewers. It is therefore advisable to design clinical function studies of female condom to include face-to face interviews at each step of data collection.

6.11.2 Interactive voice response systems (IVRS)

If using the telephone to collect daily coital information, sponsors are advised to implement interactive voice response systems (IVRS) that pose pre-recorded questions and enabling participants to respond using the keypad of their telephone. The advantage of this approach is that resources are “time stamped” and can potentially uncover participant fraud.

6.11.3 Mail-in and web-based data reporting

Because a condom breakage and slippage study relies on patient reported outcomes, it is possible to conduct such a study and allow study couples to submit their reports by mail or Internet.

This does not substitute for face-to-face interviews at study entry and completion. In this situation, procedures should be in place to minimize the potential for participant fraud.

The following are examples of procedures that should allow a third-party audit to validate the study and its underlying data.

a) Clinical investigators should keep the envelopes when couples return information by mail. If no CRFs will be returned via mail, couples should be asked to send a personal identifier by mail (for example, name of pet, oldest sibling, name of high school, etc.) which can be used to verify the participants' identity in future contacts. The investigator should keep the envelope and information in the letter for verification of enrolment.

b) To verify the couple's participation, the informed consent document could request that, in addition to the collection of electronic data or data collected via the postal service, the clinical investigator might contact the study couple via telephone when either the sponsor monitors or the government agency conducts inspections of the clinical investigator's facility. Or, if the couple cannot be reached by telephone that day, a letter will be sent with a post card (pre-addressed to the investigator) that will verify that the couple is a participant in the study. The telephone contact might ask for personal information that could verify the individual's participation. The post card should have the postal stamp and date of the couple's post office which could be compared with the couple's known address and the post card could require additional information that would help verify the couple's participation.

Study sponsors also need to be mindful of computerized systems used to create, modify, maintain, archive or transmit clinical data (e.g. e-Patient Reported Outcomes). The primary focus should be on computerized systems used at clinical sites to collect data in order to ensure the quality and integrity of electronic data, but same principles might be applied to computerized systems belonging to contract research organizations, data management centres and sponsors. Regulatory bodies that review such studies and other persons using the data from computerized systems should have confidence that the data are no less reliable than data in paper form.

6.11.4 Web-based data collection systems, additional suggestions

Given the self-report nature of these condom studies, use of web-based data collection systems can be possible in certain regions with selected user populations. Conducting studies by web, email and postal communication can assist recruitment and facilitate the execution of the study. Loss to follow up might be reduced because there are fewer visits to the study centre.

When conducting such studies, the manufacturer and/or organizations responsible for the study should take steps to ensure the following:

a) that full details of the proposed study are provided to potential subjects to enable them to make an informed assessment of the risks prior to entering the study;

b) that contact details are provided to allow potential subjects to ask questions prior to entering the study;

c) that written informed consent is obtained from both partners prior to enrolment and the provision of any samples;

d) that adequate questions are asked to identify any participants that do not meet the inclusion criteria, that should be excluded on the basis of one or more of the exclusion criteria or for whom the trial can pose a special risk;

e) that adequate advice is provided to the subjects about what actions to take if they experience any of the listed failure events or if there is any adverse reaction to the condom. The subjects should be provided with relevant contact details including telephone numbers and addresses to facilitate seeking advice from the study centre or other nominated sources of help and information;

f) that adequate records are kept about the provision and return of samples and documentation including any questionnaires, record sheets, report forms, etc.

The manufacturer or organizations concerned should take steps to verify that participants are genuine, meet the inclusion criteria and do not conflict with any of the exclusion criteria. Verification

of addresses, using appropriate databases and follow-up interviews, in person or by phone, with a randomly selected proportion of the study population, are ways of achieving this.

6.12 Control of distribution chain

The principles of ISO 13485 should be followed in the production of both test and control condoms. In general, all condoms used in a clinical trial, both test and control condoms, should have been produced, tested, and foiled to production specifications for manufacturing, testing, lubrication and packaging. Documentation to this effect should be as complete as possible. At a minimum, each condom foil/individual container should be labelled with the batch number and the expiry date. The individual foil/container, the consumer package or both should protect the condoms from environmental damage as is appropriate for the product for at least the duration of the clinical trial period.

The manufacturer should take steps to ensure that the batch records are fully completed and approved by QC/QA prior to dispatch, along with the necessary shipping documents to the clinical study centre. The manufacturer should also ensure that an adequate number of samples are retained for any follow-up investigations that can become necessary.

The clinical study centre should take steps to complete their receiving and inventory records and make checks on the sample packs to ensure they are free from any damage during transit.

The clinical study centre should store the samples according to the manufacturer's directions until they are ready to be given out to the study participants. The clinical study centre should follow the procedures for coding and any further labelling required as defined in the study protocol. The centre should also ensure that, for traceability purposes, the individual foil/container with the manufacturer's batch number and expiry date remain visible to the user.

6.13 Analysis of returned condoms

It can be useful to analyse condoms that broke or slipped during the clinical trial. This kind of evaluation is a significant element in a general quality systems approach to device manufacture. It might also help explain some of the study findings when the trial is complete. Annex H contains a sample protocol for treating returned condoms. Annex H also includes diagrams illustrating a number of examples of condom break types.

WARNING — The study described in Annex H requires direct contact with contaminated devices. It is strongly recommended that operators should wear gloves during the operation to reduce risks of any infectious accidents.

6.14 Other methodological details

The study protocol can address the following concerns:

a) language of instructions and CRFs and availability for review;

b) regional differences in condom usage that could affect applicability of results to worldwide;

c) social, cultural, and economic setting of the study population, particularly literacy, access to medical care, community and family values, etc.

d) naive condom users can experience higher rates of failure events until they become familiar with the products[10]; a brief pre-planned condom use run-in period can be appropriate before enrolling study couples into the trial;

e) if the study calls for run-in periods (learning period before use of test condom "counts" towards clinical failure rates) or wash-out periods (time period between use of test and control condoms), the protocol should provide the methodological details for these, including how such data will be managed;

f) monitoring clinical studies: functionality trials are a requirement for certain regulatory approvals; in this case, the protocol or standard operating procedures should include a comprehensive monitoring plan as follows:

   1) to ensure the data are in compliance with Good Clinical Practice (GCP), Institutional Review Board (IRB) policies, as well as local regulatory regulations;

   2) to standardize the clinical data monitoring;

   3) to ensure the validity, accuracy and integrity of the data. A suitably qualified external trial monitor should be appointed to monitor the trial throughout its course from initiation to study close-out.

6.15 Statistical analysis plan

6.15.1 General

The statistical analysis plan (SAP) should be developed and written with details on how the clinical study data will be analysed and interpreted. The SAP should be written and finalized prior to study implementation.

The following subclauses give examples of the components that should be considered when writing the SAP.

The design, analysis and interpretation of female condom functionality studies should not be done without the help of an experienced statistician, familiar with non-inferiority testing and methods for making valid statistical inferences.

6.15.2 Primary study hypothesis

The primary end point in a clinical validation study of female condom functionality is total clinical failure, as defined in 3.10. The primary research objective is to determine whether the expected total clinical failure rate of a new female condom is comparable to the expected total clinical failure rate of a legally marketed female condom when used during vaginal intercourse. The clinical research question should be re-phrased in statistical terms as a non-inferiority hypothesis. For example, the expected difference in total clinical failure rates, between the test and control condoms, is less than the non-inferiority margin (δ) specified in ISO 25841.

Therefore, the statistical plan should present a precise statement of the prospective study hypothesis in statistical terms, i.e. null (H_0) and alternative (H_A) hypotheses. For a study based on a non-inferiority model, this would typically look something like:

— H_0: Expected test condom total clinical failure rate – expected control condom total clinical failure rate $\geq \delta$

— H_A: Expected test condom total clinical failure rate – expected control condom total clinical failure rate $< \delta$

If the null hypothesis of inferiority is rejected using an appropriate test statistic, then the alternate hypothesis of non-inferiority is accepted.

The failure rates observed in the clinical study based on a small number of condom uses per couple are only estimates of the expected rates that would be observed if an infinite number of condoms had been used. It is not sufficient for the observed difference in failure rates to be $<\delta$ to conclude non-inferiority. Rather, it is necessary that the study results provide a high degree of confidence that the difference in expected rates is $<\delta$.

6.15.3 Secondary study hypotheses

Based on the results from pilot studies and other factors (e.g. design or market feedback), it can be reasonable to test whether the new female condom performs better than the control female condom. As part of the SAP, study sponsors might prospectively specify a secondary hypothesis for superiority. If the study results support the primary conclusion of non-inferiority, then the secondary hypothesis might be tested.

Study sponsors should also develop secondary hypotheses to address each type of condom failure as individual variables, again comparing the test condom to the control condom. These should be done as non-inferiority analyses using a δ for each individual variable that is a little smaller than that specified in the normative standard for total failure rate. For example, ISO 25841 specifies a δ of 3,0 % for testing the total failure rates. Based on currently available female condom data, as well as results from the pilot study(ies), an appropriate δ (smaller than 3 %) should be chosen to test each type of failure.

6.15.4 Study design

Typically, the most efficient study design for a condom functionality study is a two-period crossover trial.

The study should enrol a sufficient number of subjects (or couples) so that a minimum of two hundred (200) complete the study. Because of attrition, it is prudent to enrol extra participants to ensure sufficient numbers at end of study. For example, if one expects a 15 % loss to follow up, then the study should enrol at least 235 subjects (or couples).

The study should ensure a minimum 1 000 uses of each condom type during vaginal intercourse.

The study population and investigational sites should be heterogeneous and represent the target population. Therefore, the study should include multiple investigational sites, and the number of study couples enrolled should be evenly distributed across sites.

Couples should be asked to use a specified number of condoms of each type during consecutive acts of vaginal intercourse in the first condom use period, followed by the same number of uses of the alternate condom type in a second and subsequent use period. Instances of condom use for anal intercourse should be excluded from the primary analysis. The number of each type of condom used (e.g. five if there are 200 participating couples) should be chosen to ensure that at least 1 000 uses of each condom type are available for the primary analysis.

Because some couples might not use their allocated number of condoms, it can be useful to provide all participating couples with extra condoms to help ensure the target number of 1 000 condom uses. Alternatively, the study design could specify a larger number of participating couples.

6.15.5 Statistical analysis

It is recommended that the statistical analysis plan be specified prior to implementation of the study. This includes plans for primary analyses, as well as all key subgroup and secondary analyses.

Primary analyses should be performed using all available condom use data. Data from all study sites should be pooled unless statistically significant and clinically meaningful interactions between centre and condom type are detected. If such interactions are observed, comparisons should be made separately for each centre. Any missing data (e.g. due to non-use or data errors) should be ignored in the primary analyses unless patterns are identified which suggest condom type comparisons can be biased. If such patterns are observed, efforts should be made to identify their causes and effects on analyses.

Analyses should be based on a confidence interval approach to non-inferiority testing[1] based on the null and alternative hypotheses specified in 6.15.2.

The outcomes of each condom use by a particular couple are expected to be more alike than the outcomes of condom use by another couple. This will result in correlated data that should be accounted for in the statistical analysis. One approach would be to use Generalized Estimating Equations (GEE)

with an identity link function and an independent working correlation structure[6]. This method is described in further detail for condom studies by Reference [10].

The proportion of test and control female condoms experiencing clinical failure will be calculated. The difference in proportions, and an upper one-sided 95 % confidence limit for the difference, will be reported. An upper limit that is less than δ will be interpreted as statistical evidence that the test condom is non-inferior to the control female condom with respect to total clinical failure.

An upper one-sided 97,5 % confidence limit for the difference of less than 0 % could be further interpreted as statistical evidence that the test female condom is superior to control condom.

Study power is the probability of concluding non-inferiority. In addition to the number of enrolled couples and condom uses, the power of the study will depend on the degree of correlation and the true rates for total clinical failure. Although these quantities are unknown, sample size calculations can typically be made assuming a correlation of no more than 0,2. Also, to be conservative, one should assume failure rates corresponding to the upper range of expected rates in the target population (e.g. 5 %). Rough estimates of expected failure rates can be determined from pilot study results, as well as a review of the published literature.

NOTE Annex A provides an example formula for the power calculation.

6.15.6 Additional statistical comments and concerns

Low total clinical failure proportions (<0,5 %) in the control arm can make implementing a condom clinical function study challenging; careful choice of the study population to minimize this possibility is essential.

Strongly consider a pilot study if there is no objective data on the anticipated clinical failure rates of the test condom in the study population.

6.16 Clinical study results: Review and interpretation

6.16.1 General

When the clinical validation study and statistical analysis is completed, it is important to critically evaluate the results to determine whether the test female condom performs acceptably well in comparison to the control condom. Principles for such an evaluation include careful consideration of the control condom characteristics, characteristics of the couples participating in the study, reliability of user self-reporting, and the rates for all the failure events.

6.16.2 Total clinical failure rates for control condom

Based on past studies of female condoms, the total clinical failure rates during actual use should be in the range from 0,5 % to 5,0 % for female condoms. If the total clinical failure rates for the test condom fall outside of this range, then a rationale should be provided to justify the validity of the trial. One should carefully investigate the design and conduct of the study to determine if there are any unusual factors that could have contributed to the unusually high or low rates (e.g. study population factors, breaches in data integrity, participant fraud, etc.).

NOTE The published literature cites total clinical failure rates for female condoms that range from 2 % to 20 %. However, the 20 % failure rate and some of the other higher reported failure rates are believed to be inaccurate, the result of misclassifying non-clinical failure events. In more recent studies, there have been better instructions for the study subjects (including definitions of types of clinical failures) and better-designed coital diaries. This has led to more reliable reporting of total clinical failure rates in the range of 0,5 % to 5,0 %.

6.16.3 Non-inferiority

The primary hypothesis for the clinical validation study is that the performance of the test condom is not inferior to that of a selected control condom with respect to total clinical failure events.

The study should be sufficiently documented to allow an evaluator to independently reproduce the statistical results.

If the upper one-sided 95 % confidence limit for the difference in the total clinical failure rates (test minus control) is less than δ, the conclusion is that the test condom is non-inferior to the standard control condom. One can then reasonably conclude that the test condom is comparable in performance to the control condom used in the study.

If the upper bound on the confidence interval around the difference in rates exceeds δ, then the evaluator should systematically explore the underlying reasons. One obvious reason might be that the test condom is inferior to the control condom. However, other factors, including the user population and methodological problems, can also explain such study findings.

6.16.4 Superiority

If the upper one-sided 97,5 % confidence limit of the difference in total clinical failure rates is less than 0 %, this can be interpreted as statistical evidence that the test condom is superior to the control condom with respect to total clinical failure.

6.16.5 Safety (adverse events)

Any reports of adverse events or complaints should be thoroughly investigated to determine whether the new female condom poses an unacceptable safety risk in comparison to the control condom. Individual complaints of irritation, burning, itching, bleeding, etc. should be followed up with clinical evaluation. The study report should fully address these events. For each event, provide information on severity, duration, and relatedness and how each event was clinically resolved.

6.16.6 What happens if one is unable to conclude non-inferiority?

If the study data do not allow one to conclude that the total clinical failure rate of the test condom is less than δ higher than the corresponding control condom rate, then one cannot make a statistical conclusion of non-inferiority.

Upon request, an evaluator could critically review the study design and data to determine whether the test condom can still be considered suitable for marketing. Under this circumstance (no statistically-based conclusion of non-inferiority), a regulatory body might consider other factors, such as:

a) the individual failure event differences between condom types;

   NOTE Under these circumstances, there can be a role for a follow-up study and/or a meta-analysis of this and previous studies.

b) beneficial qualities of the test condom that can increase condom use;

c) labelling mitigation (e.g. to be used only by persons who are latex sensitive, place test results in labelling, etc.).

Annex A
(informative)

Formula for power calculation

Denote the true (unknown) test and control condom failure probabilities as *FT* and *FC*, respectively, and let $\Delta = FT - FC$. Also, define the correlation between condom uses by ρ, and assume that each couple uses Z condoms of each type. Then the number of couples required to have $P \times 100$ % power (e.g. $P = 0,9$ corresponds to 90 % power) to conclude non-inferiority is given in Formula (A.1):

$$N = \left\{G\left(P\right) + 1,645\right\} 2 \times \mathrm{Var}\left(\Delta\right) \Big/ \left\{\left(\delta - \Delta\right) 2\right\} \tag{A.1}$$

where

$$\mathrm{Var}\left(\Delta\right) = F_{\mathrm{T}}\left(1 - F_{\mathrm{T}}\right) \times \left\{1 + \left(Z - 1\right)\rho\right\} \Big/ Z + F_{\mathrm{C}}\left(1 - F_{\mathrm{C}}\right) \times \left\{1 + \left(Z - 1\right)\rho\right\} \Big/ Z - 2\rho \times \left\{F_{\mathrm{T}}\left(1 - F_{\mathrm{T}}\right) \times F_{\mathrm{C}}\left(1 - F_{\mathrm{C}}\right)\right\} 1 / 2$$

is a measure of the variance of the difference in failure rates and where $G(\cdot)$ is the inverse cumulative normal probability function.

For example, if $F_{\mathrm{T}} = F_{\mathrm{C}} = 0,05$, $\rho = 0,2$, and each couple uses $Z = 5$ condoms per type, then $\mathrm{Var}(\Delta) = 0,015\ 2$. In order to have 90 % power, $G(0,9) = 1,282$, and $N = 145$ couples should be enrolled for $\delta = 0,03$.

If one does not perform a crossover trial, then Formula (A.1) provides the number of couples that should use each type (i.e. there should be $2N$ total enrolled couples) where $\mathrm{Var}(\Delta) = F_{\mathrm{T}}(1 - F_{\mathrm{T}}) \times \{1+(Z - 1)\rho\}/Z + F_{\mathrm{C}}(1 - F_{\mathrm{C}}) \times \{1 + (Z - 1)\rho\}/Z$.

For the above example (alternate to the crossover design), $N = 326$ couples would have to use five condoms of one type plus 326 different couples would have to use five condoms of the other type to achieve 90 % power, i.e. 652 total couples, 326 in each arm.

Annex B
(informative)

Pilot clinical investigation (sample outline)

B.1 General

The following is an outline for conducting a clinical feasibility study of a new condom to obtain a preliminary estimate of clinical failure rates during use. As with the pivotal study, such feasibility studies should also comply with ISO 14155.

B.2 Study design

— Randomized, two-period, crossover design.

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

— n = 50 couples who complete study, typically need to recruit approximately 60 couples to account for loss-to-follow-up.

— Each couple should use at least five of each of the test and control condoms.

— Each couple should be given two consecutive weeks to complete each set of condoms.

— Each couple should complete a diary of each coital event in which a condom is used.

NOTE Refer to Annex F for a sample diary.

— At the end of the two-week use period for each condom, the couple should be interviewed either by phone, Internet or by clinic visit, the latter being preferred.

— Clinical end points should be failure events identified per the risk assessment and genito-urinary adverse events.

— Socio-economic data should be collected and recorded (e.g. age, race, education level, etc.).

— Financial payment to panellists should be made at the end of the study.

B.3 Inclusion criteria

— Couples not at risk of pregnancy (using alternate contraception).

— No known sexually transmitted infections, including HIV/AIDS.

— If possible, couples should be experienced condom users, minimum 10 female condoms used in the last 12 months.

— Study subjects should be between 18 to 45 years of age.

— Monogamous heterosexual couples who agree to practice vaginal sex only during the study.

B.4 Exclusion criteria

— Couples who work for the clinical testing laboratory or who are relatives of staff of the clinical test laboratory.

— Participants with known allergy to the materials used in test and control female condom.

— Participants with known sensitivity to the residual chemicals used in the manufacture the materials used in test and control female condom.

— Female partner is pregnant, has a suspected pregnancy, or desire to become pregnant during the course of the study.

— Couples where one knowingly has a urinary tract infection, sexually transmitted infection, or other vaginal infection.

B.5 Informed consent

Participating study subjects should be given appropriate informed consent. See 6.4.

B.6 Adverse event report form

A draft template is attached (see Annex G).

B.7 Statistical analysis

— To be determined, 95 % confidence interval.

— Confounding factors to be noted are couples who cluster break on either the test or control product, and if more than 20 % of the recruited fail to complete the study.

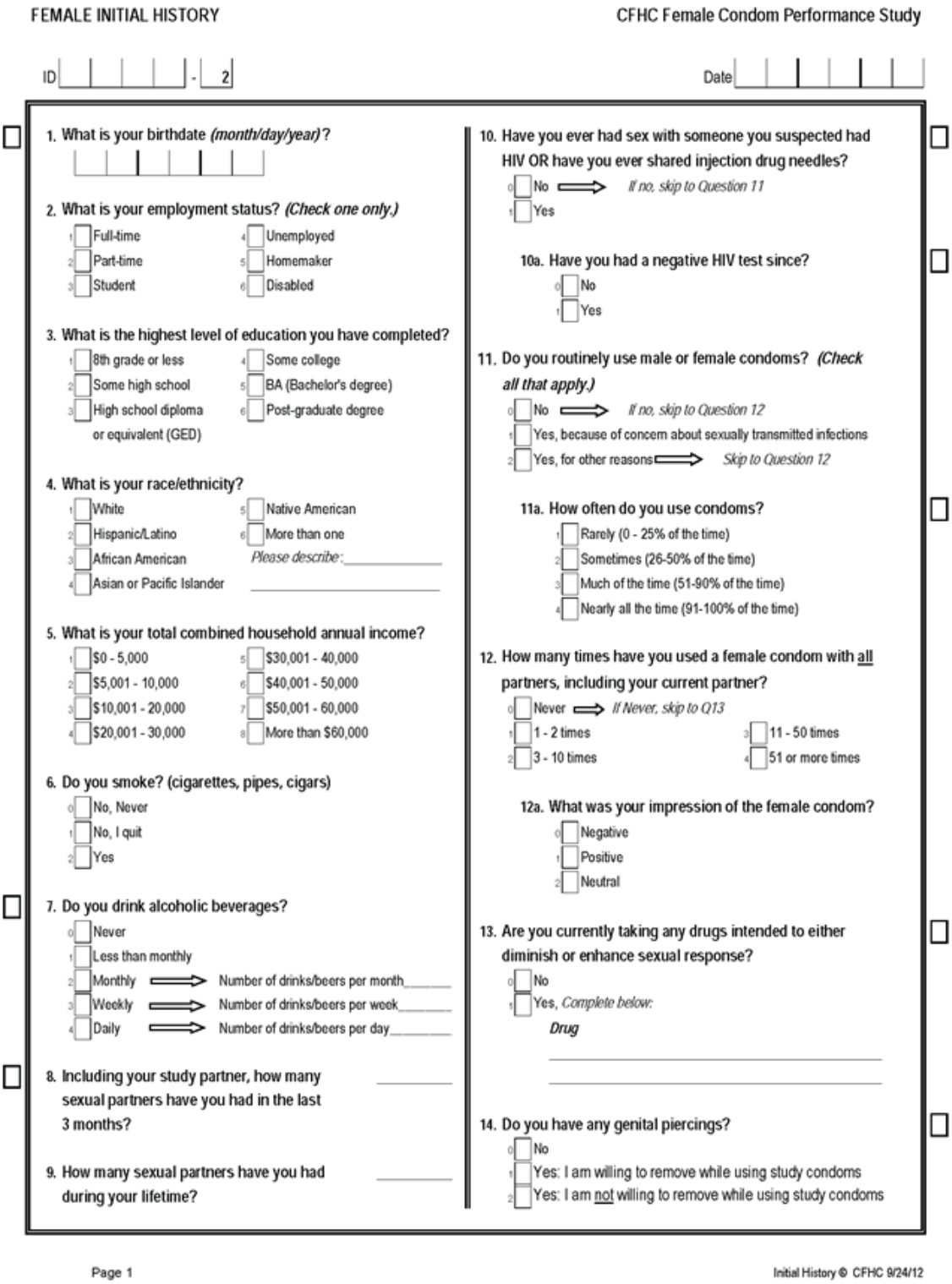
Annex C
(informative)

Time and events schedule for individual study subject (sample)

Study procedures	Screening/ Admission	Follow-up period		
		Visit 1 (Study entry)	Visit 2 (Mid-study)	Visit 3 (Study completion)
		Week 0	Week 2 to 3	Week 4 to 6
Selection criteria	✓			
Informed consent		✓		
Randomization and group assignment		✓		
Receive coital diary		✓	✓	
Receive condoms		✓	✓	
Collect unopened condoms			✓	✓
Collect coital diary			✓	✓
Coital diaries reviewed			✓	✓
Assessment of problems including adverse events			✓	✓

Annex D
(informative)

CRF — Study entry (sample)



FEMALE INITIAL HISTORY

CFHC Female Condom Performance Study

ID ____ - 2

Date ____

1. What is your birthdate *(month/day/year)*?

2. What is your employment status? *(Check one only.)*
   - 1 Full-time
   - 2 Part-time
   - 3 Student
   - 4 Unemployed
   - 5 Homemaker
   - 6 Disabled

3. What is the highest level of education you have completed?
   - 1 8th grade or less
   - 2 Some high school
   - 3 High school diploma or equivalent (GED)
   - 4 Some college
   - 5 BA (Bachelor's degree)
   - 6 Post-graduate degree

4. What is your race/ethnicity?
   - 1 White
   - 2 Hispanic/Latino
   - 3 African American
   - 4 Asian or Pacific Islander
   - 5 Native American
   - 6 More than one

   Please describe: _____

5. What is your total combined household annual income?
   - 1 $0 - 5,000
   - 2 $5,001 - 10,000
   - 3 $10,001 - 20,000
   - 4 $20,001 - 30,000
   - 5 $30,001 - 40,000
   - 6 $40,001 - 50,000
   - 7 $50,001 - 60,000
   - 8 More than $60,000

6. Do you smoke? (cigarettes, pipes, cigars)
   - 0 No, Never
   - 1 No, I quit
   - 2 Yes

7. Do you drink alcoholic beverages?
   - 0 Never
   - 1 Less than monthly
   - 2 Monthly ⇒ Number of drinks/beers per month_____
   - 3 Weekly ⇒ Number of drinks/beers per week_____
   - 4 Daily ⇒ Number of drinks/beers per day_____

8. Including your study partner, how many sexual partners have you had in the last 3 months? _____

9. How many sexual partners have you had during your lifetime? _____

10. Have you ever had sex with someone you suspected had HIV OR have you ever shared injection drug needles?
    - 0 No ⇒ *If no, skip to Question 11*
    - 1 Yes

    10a. Have you had a negative HIV test since?
    - 0 No
    - 1 Yes

11. Do you routinely use male or female condoms? *(Check all that apply.)*
    - 0 No ⇒ *If no, skip to Question 12*
    - 1 Yes, because of concern about sexually transmitted infections
    - 2 Yes, for other reasons ⇒ *Skip to Question 12*

    11a. How often do you use condoms?
    - 1 Rarely (0 - 25% of the time)
    - 2 Sometimes (26-50% of the time)
    - 3 Much of the time (51-90% of the time)
    - 4 Nearly all the time (91-100% of the time)

12. How many times have you used a female condom with <u>all</u> partners, including your current partner?
    - 0 Never ⇒ *If Never, skip to Q13*
    - 1 1 - 2 times
    - 2 3 - 10 times
    - 3 11 - 50 times
    - 4 51 or more times

    12a. What was your impression of the female condom?
    - 0 Negative
    - 1 Positive
    - 2 Neutral

13. Are you currently taking any drugs intended to either diminish or enhance sexual response?
    - 0 No
    - 1 Yes, *Complete below:*

    Drug

    _____

    _____

14. Do you have any genital piercings?
    - 0 No
    - 1 Yes: I am willing to remove while using study condoms
    - 2 Yes: I am <u>not</u> willing to remove while using study condoms

Page 1

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ID [ ][ ][ ][ ] - 2

15. Are you currently participating in any other clinical studies?
    - 0 [ ] No
    - 1 [ ] Yes, Describe:_____

16. Do you want you/your partner to become pregnant?
    - 3 [ ] Yes, in the next 3 months
    - 2 [ ] Yes, in 3 months to a year
    - 1 [ ] Yes, in a year or more
    - 0 [ ] No, never

17. Do you have any current genital or urinary tract infections, OR other genital problems like itching or burning, OR are you currently using any internally applied or oral medications to treat a genital condition?
    - 0 [ ] No
    - 1 [ ] Yes, describe:_____

18. In the past 60 days, have you had any surgery or biopsy of your genitals (vulva/vagina/cervix)?
    - 0 [ ] No
    - 1 [ ] Yes, Describe:_____

19. In the past 6 months, have you had the following:

Chlamydia	0 [ ] No	1 [ ] Yes
Trichomoniasis	0 [ ] No	1 [ ] Yes
Gonorrhea	0 [ ] No	1 [ ] Yes
HIV	0 [ ] No	1 [ ] Yes
Syphilis	0 [ ] No	1 [ ] Yes
Ist Genital Herpes outbreak	0 [ ] No	1 [ ] Yes

20. Are you allergic to nitrile (synthetic latex), polyurethane, silicone or Astroglide?
    - 0 [ ] No
    - 1 [ ] Yes, Describe:_____

21. Do you <u>currently</u> have any other serious health problem that would interfere with your study participation?
    - 0 [ ] No
    - 1 [ ] Yes, Describe:_____

Page 2

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ID ____ ____ ____ ____ - 2

FEMALE ONLY:

28. How would you describe your living arrangement?
    1. ☐ Married to study partner
    2. ☐ Not married to *but* living with study partner
    3. ☐ Not married to *or* living with study partner

☐ 29. How long have you been with your current partner?
    - ☐ Less than one year: _____ months
    - ☐ One year or more: _____ years

☐ 30. What is your current method of birth control?
    1. ☐ Birth control pills
    2. ☐ Depo Provera shot
    3. ☐ Contraceptive patch
    4. ☐ IUD
    5. ☐ Sterilization (tubal ligation/vasectomy)
    6. ☐ Other, Describe:_____

☐ 30a. How long have you used your current method?
    0. ☐ Less than 3 months
    1. ☐ 3-6 months
    2. ☐ 6-12 months
    3. ☐ More than one year

☐ 30b. Have you used your current method consistently since your last menstrual period?
    0. ☐ No
    1. ☐ Yes

☐ 31. Have you ever been pregnant?
    0. ☐ No
    1. ☐ Yes, in the last two months
    2. ☐ Yes, more than two months ago

32. How often do you and your partner use additional lubricants during vaginal intercourse?
    0. ☐ Never
    1. ☐ Rarely
    2. ☐ Sometimes
    3. ☐ Often

    If yes, what lubricants do you use? _____

33. <u>In your lifetime</u>, how many times have you had each of the following?

	Never	1-2x	3+x
Yeast infection	0 ☐	1 ☐	2 ☐
Other vaginal infection	0 ☐	1 ☐	2 ☐

If yes to Other infection, Describe:_____

_____

34. Have you ever been diagnosed with any of the following?

	Never	Yes
Polycystic ovarian syndrome	0 ☐	1 ☐ ☐
Abnormal vaginal anatomy such as vaginal septum or pelvic prolapse	0 ☐	1 ☐ ☐

If yes Describe:_____

35. Do you use a vaginal device to support your bladder, uterus, vagina or rectum? ☐
    0. ☐ No
    1. ☐ Yes

For RA use : F Height _____ (Inches) F Weight _____ (Pounds)

RA/#:_____/_____ Date:____/____/____ Edited by:_____ Date:____/____/____ Batch:_____-_____

Annex E
(informative)

CRF — Mid-study (sample)

ACCEPTABILITY QUESTIONNAIRE — **CFHC Female Condom Performance Study**

Circle one: FEMALE MALE — Set #: _____

ID _____ - _____ Birthdate _____ Date Completed _____

1. What ONE thing did you *like* MOST about the study condom you just used?

_____

2. What ONE thing did you like LEAST about the study condom you just used?

_____

3. On a scale of 1 to 5 please circle the number that best describes your overall experience with this type of condom. Please be careful to circle only one response for each question.

A.	*Female:* Ease of condom insertion *Male:* Ease of insertion of penis into condom		Very difficult 1	2	3	4	Very easy 5
B.	Ease of following instructions		Very difficult 1	2	3	4	Very easy 5
C.	Did this condom get easier to use from the 1st to the 4th condom?		Much harder 1	2	3	4	Much easier 5
D.	Comfort of condom during sex		Uncomfortable 1	2	3	4	Very comfortable 5
E.	Movement of the condom during sex		Very bothersome 1	2	3	4	Not bothersome 5
F.	Satisfaction with feeling of sex		Not satisfying 1	2	3	4	Very satisfying 5
G.	Satisfaction with lubrication during sex		Not satisfying 1	2	3	4	Very satisfying 5
H.	Ease of removing condom	NA, did not remove 0	Very difficult 1	2	3	4	Very easy 5
I.	Sexual satisfaction compared to male condoms	NA, never used a male condom 0	Prefer male condom 1	2	3	4	Prefer this female condom 5
J.	Overall preference compared to male condoms		Prefer male condom 1	2	3	4	Prefer this female condom 5
K.	Sexual satisfaction compared to sex without *any* condoms		Prefer no condom 1	2	3	4	Prefer this female condom 5

4. How highly would you recommend the study condom you just used?

1 ☐ Highly recommend
2 ☐ Recommend
3 ☐ Recommend with reservations
4 ☐ Not recommend, *Why not?* _____

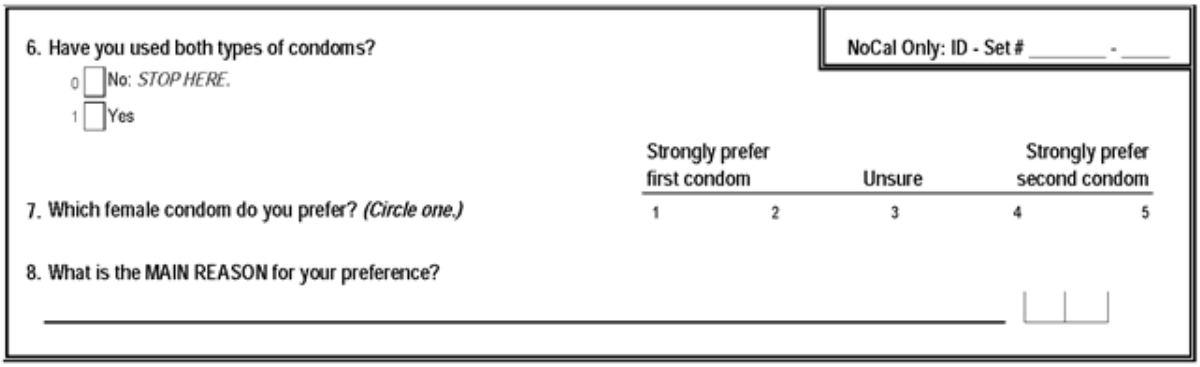
5. How would you improve this condom?

_____

_____

MORE QUESTIONS ON THE BACK →

Acceptability Survey © CFHC 5/21/10


6. Have you used both types of condoms?

0 ☐ No: *STOP HERE.*

1 ☐ Yes

NoCal Only: ID - Set # _____ - _____

	Strongly prefer first condom		Unsure		Strongly prefer second condom
7. Which female condom do you prefer? *(Circle one.)*	1	2	3	4	5

8. What is the **MAIN REASON** for your preference?

_____ ☐☐

RA Init/#:_____/_____ Date:____/____/____ Edited by:_____ Date:____/____/____ Batch:_____-_____

Acceptability Survey © CFHC 9/24/12

NOTE CFHC granted permission for its CRFs to be used in condom function studies.

Annex F
(informative)

CRF — Single use of female condom (sample)

The following is a paper-based example of a case report form (CRF) that could be used to capture the key failure event information after use of an individual female condom, e.g. slippage, breakage, invagination, and misdirection events. It is critical that study participants enter this information into the CRF as soon after each coital act as practicable. They should NOT wait several days or a week and then try to recall events from multiple coital acts over that period.

It is not unusual for study sponsors to attempt to collect additional use information from the study participants. Keep in mind that the CRF for an individual condom use should be clear and easy to follow. Any attempt to collect non-primary outcome data should be weighed against the potential for making the CRF more confusing.

This CRF was provided by CONRAD (Arlington, Virginia, USA). It is a three-page form that includes a diagram for marking where, if applicable, breakage occurs on the condom. CONRAD provided permission for study sponsors to adapt this form for their own condom function studies. Questions in red are of primary interest.

CONDOM USE QUESTIONNAIRE - 1. Condom A 2. Condom B **Condom #**

ID **Female Birthdate** | | **Date Used** | |

OPENING & DONNING THE CONDOM

1. How did you open the condom package? (Check one.)

1 With fingers 3 With sharp object
2 With teeth 4 Other, *Describe*:_____

2. Did the condom break or tear while opening the package?

0 No 1 Yes: *Answer Question 22 only.*

3. Did the condom appear to be in good condition?

1 Yes 0 No, *Explain*:_____

4. Was the condom inserted?

1 Yes 0 No, *Explain and answer Question 22 only:*

_____

5. When was the condom inserted?

1 Before intercourse started: _____ minutes before
2 After intercourse started: _____ minutes after

6. Who inserted the condom?

1 Woman 2 Man 3 Both

7. How was the condom inserted?

1 Inserted in vagina per instructions
2 Put on penis first
3 Other, *Describe*:_____

INTERCOURSE INFO

8. Did you have vaginal intercourse using this condom?

1 Yes 0 No, *Explain and answer Question 22 only:*

_____

9. Did you use the study lubricant during this condom use? *(Check all that apply.)*

0 No, not used
On the penis: 1 Before intercourse and/or 1 During intercourse
In the vagina: 1 Before intercourse and/or 1 During intercourse
On the inside of the condom: 1 Before intercourse and/or 1 During intercourse
On the outside of the condom: 1 Before intercourse and/or 1 During intercourse

10. Did you add any other, non-study lubricant?

0 No
1 Yes, lubricant with spermicide (N-9 or nonoxynol-9)
2 Yes, lubricant without spermicide
3 Yes, unsure if lubricant contained spermicide: *Specify exact name:*

_____

11. While wearing this condom, which of the following sexual positions did you use? *(Check all that apply.)*

1 Front entry, man on top
1 Front entry, woman on top
1 Rear entry, woman on knees
1 Rear vaginal entry, woman on side or stomach
1 Standing
1 Anal intercourse
1 Other, *Explain:*_____

12. How long did you have vaginal intercourse while wearing this condom? _____ minutes

REMOVING & DISPOSING OF THE CONDOM

13. How did you remove the condom?

1 Twisted the outer ring, and pulled the condom out
2 Pulled the condom straight out (without twisting)
3 Other, *Describe*:_____

14. During removal, was there any spillage of semen?

0 No
1 Yes, onto woman's genital area
2 Yes, away from woman's genital area

15. When did you remove the condom?

1 Before intercourse ended: _____ minutes before
2 After intercourse ended: _____ minutes after
U Don't know/Not sure

16. How did you dispose of the condom?

1 Put it in the trash 0 Other, *Explain*:_____

17. If you just used Condom B, in what condition was the insertion capsule after removal of the condom?

N N/A, used Condom A
1 Totally dissolved
2 Partially dissolved, *Explain*:_____
3 Not dissolved at all, *Explain*:_____
4 Did not notice

D09-108 Condom Report © 4/30/10

PROBLEMS USING THE CONDOM

NoCal Only: ID-#:_____

18. Did the penis ever go between the condom and the vagina? *(Check all that apply.)*

- 0 ☐ No: *Skip to Question 19.*
- 1 ☐ At insertion of the penis: 1 ☐ 1 time *or* 2 ☐ More than once
- 1 ☐ During intercourse: 1 ☐ 1 time *or* 2 ☐ More than once
- U ☐ Don't know

18a. **What did you do when you noticed this problem?** *(Check all that apply.)*

- 1 ☐ Stopped intercourse, reinserted the penis into the condom, and continued
- 1 ☐ Continued intercourse without any attempt to adjust condom
- 1 ☐ Removed the condom and continued intercourse without it
- 1 ☐ Removed the condom and stopped intercourse
- 1 ☐ Other, *Explain:*_____

19. Did the outer ring of the condom ever get pushed into the vagina?

- 0 ☐ No: *Skip to Question 20.*
- 1 ☐ Yes: 1 time
- 1 ☐ Yes: More than 1 time
- U ☐ Don't know

19a. **What did you do when you noticed this problem?** *(Check all that apply.)*

- 1 ☐ Stopped intercourse, adjusted the condom, and continued
- 1 ☐ Continued intercourse without any attempt to adjust condom
- 1 ☐ Removed the condom and continued intercourse without it
- 1 ☐ Removed the condom and stopped intercourse
- 1 ☐ Other, *Explain:*_____

20. During intercourse, did the condom ever completely SLIP OUT of the vagina?

- 0 ☐ No: *Skip to Question 21.*
- 1 ☐ Yes, clung to penis: 1 ☐ 1 time *or* 2 ☐ More than once
- 1 ☐ Yes, did not cling to penis: 1 ☐ 1 time *or* 2 ☐ More than once
- U ☐ Don't know

20a. **What did you do when you noticed this problem?** *(Check all that apply.)*

- 1 ☐ Stopped intercourse, reinserted the condom into the vagina, and continued
- 1 ☐ Removed the condom and continued intercourse without it
- 1 ☐ Removed the condom and stopped intercourse
- 1 ☐ Other, *Explain:*_____

21. During withdrawal of the penis after intercourse, did the condom completely SLIP OUT of the vagina?

- 0 ☐ No
- 1 ☐ Yes, clung to penis
- 1 ☐ Yes, did not cling to penis
- U ☐ Don't know

22. Did the condom ever break?

- 0 ☐ No: *Skip to Question 23.*
- 1 ☐ Yes, while opening package
- 2 ☐ Yes, after opening package but before inserting it
- 3 ☐ Yes, while trying to insert it
- 4 ☐ Yes, after inserting it but before intercourse began
- 5 ☐ Yes, during intercourse
- 6 ☐ Yes, during withdrawal of penis from vagina
- 7 ☐ Yes, during removal of condom from vagina
- 8 ☐ Don't know when
- 9 ☐ Other, *Describe*:_____

22a. **Where did the condom break?** *Check the answer that best applies. Refer to diagram.*

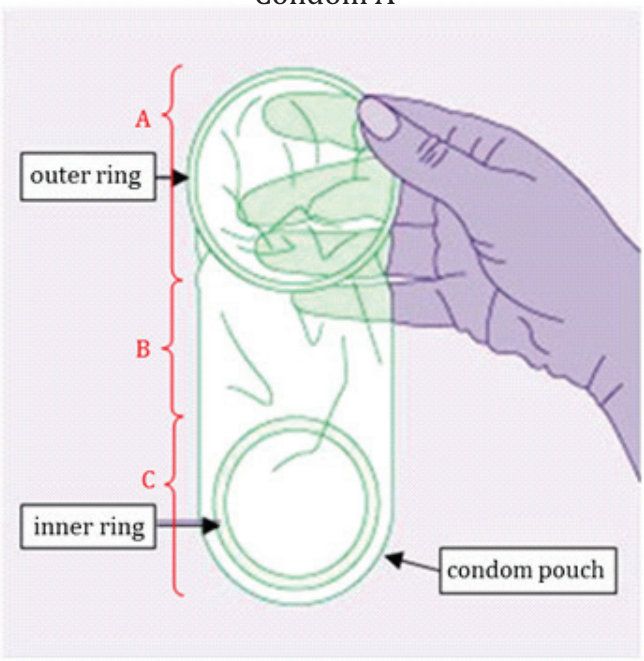
- 1 ☐ Near outer ring- see Section A on diagram
- 2 ☐ In the middle- see Section B on diagram
- 3 ☐ At the tip- see Section C on diagram
- 4 ☐ In more than one place

22b. **If you just used Condom B, did the condom break along the seam?**

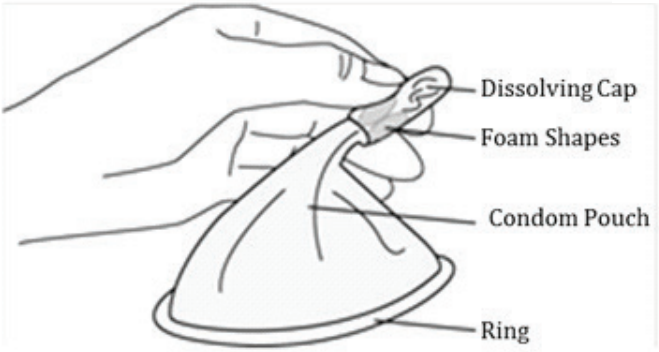
- N ☐ N/A, used Condom A
- 0 ☐ No, not along seam
- 1 ☐ Yes, along seam
- U ☐ Don't know

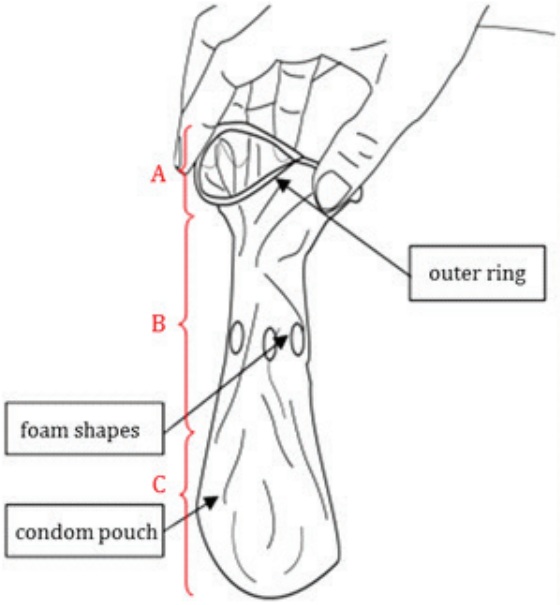
Diagram S

Condom A



Condom B





Annex G
(informative)

CRF — Adverse event (sample)

Time Began _____ Time Ended _____ Interview Length _____

Interviewer's Initials: _____ Date: _____

- **If a subject reaches you directly:** "What is your name? _____ (Subject Name). I would like to ask you some questions about your experience with the test products. It will take around 5 minutes. Is this a good time for you to discuss it now?" (If not, reschedule day _____ time _____ - is there a number where I may reach you? _____)

- **If a subject left you a message:** "May I speak to _____ (Subject Name)? This is _____ from _____. You are participating in a study with the _____. You had called and left a message about a reaction to one of our test products. I would like to ask you some questions about your experience with the test products. It will take around 5 minutes. Is this a good time for you to discuss it now?" (if not, reschedule day _____ time _____ - is there a number where I may reach you? _____)

1. "What is the product that you were using when you experienced your reaction?"

   _____

2. "Would you describe what happened?" (circle symptoms from no. 3 as they are mentioned)

   _____

3. "Would you say that your _____ (symptom) was mild, moderate or severe?"	Subject's Assessment		
	Mild	Moderate	Severe
Itching			
Burning/stinging			
Redness			
Bumps			
Other: _____			
Other: _____			

4. "How soon after you put the product on did you first experience this reaction?"
5. "How long did your reaction last?" _____
6. "Have you seen a doctor?" _____ yes _____ no (skip to 10)
7. "May we contact your doctor?" _____ yes _____ no
8. "What is your doctor's name?" _____
9. "What is your doctor's telephone number?" (_____) _____ - _____

10. “Have you experienced similar reactions with similar products?”_____ yes _____ no

“Which products?” _____

“I recommend that you stop using the product if you have not already done so and do not use any additional test products we gave you. If you wish to see a physician and have not already done so, and your physician determines that your reaction is product-related, please provide us with a copy of your doctor’s note with his name and office number so that we may review it for reimbursement. Call me back if you have any problems. Thank you for your time and patience.”

Annex H
(informative)

Protocol for evaluation of returned used condoms

H.1 General

The following is a suggested protocol for evaluating condoms that are returned after a tear or break during use. It was designed for male condoms and so should be adapted for female condoms. Figure H.2 and Figure H.3 give detailed step-by-step procedures.

H.2 Disinfection of returned used condoms

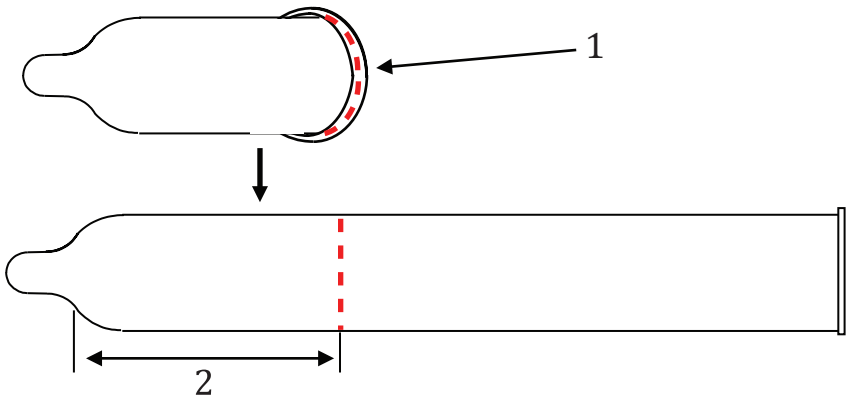
WARNING — This study requires direct contact with condoms that might be contaminated with infectious microbes. To reduce the risk of an infectious accident, it is strongly recommended that the operator wear surgical or exam gloves, safety glasses, and a lab coat whenever handling the used condom.

H.2.1 Remove the returned used condom ("the sample") from its plastic shipping bag.

H.2.2 Examine the sample and record observations, if any.

H.2.3 If the sample is not fully unrolled, mark its unrolled part within oil-based marker. If the sample is wet and not possible to mark, photograph it. Then, unroll the sample to the rim (see Note).

NOTE In Figure H.1, the mark illustrates the length of the sample unrolled onto the user's penis. If the length is extremely short, the user might not have unrolled the condom to the base of the penis before use, in that case, the risk of slippage might increase.



Key

1 marking

2 length of the sample unrolled onto the penis

Figure H.1 — Marking the returned condom

H.2.4 Prepare a disinfection solution (see Figure H.2).

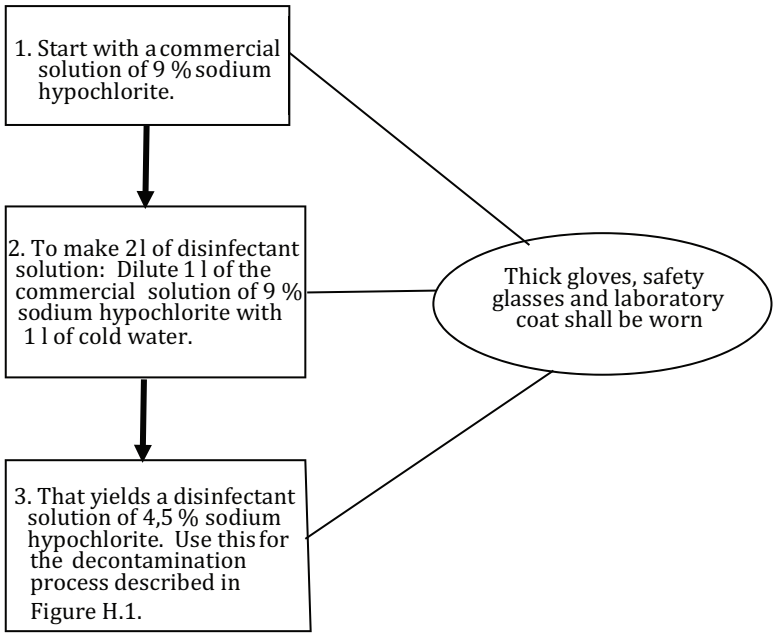


Figure H.2 — Preparation of the disinfectant solution (4,5 % sodium hypochlorite)

Instructions:

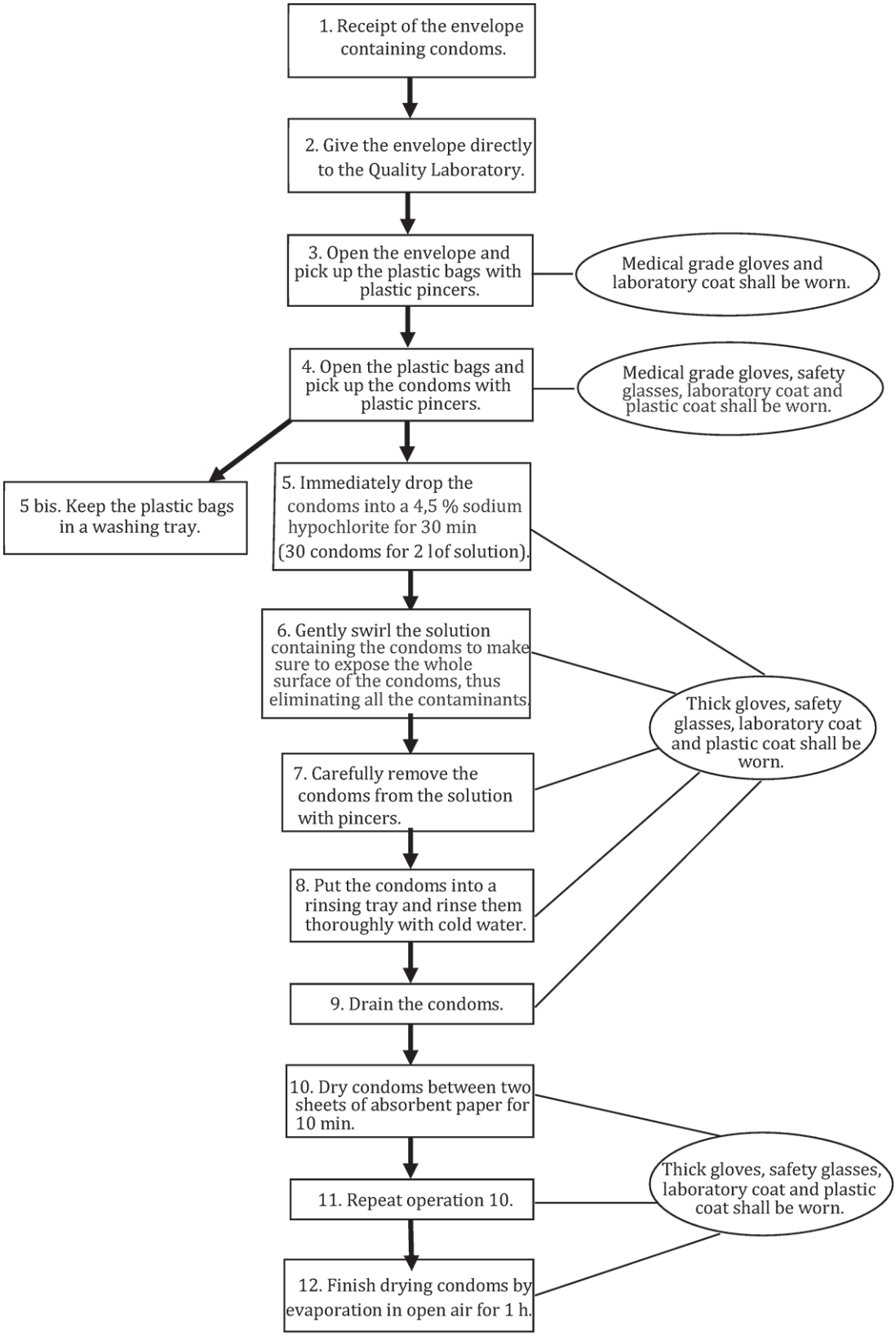
a) The commercial solution can be stored for 6 months, keeping away from the heat and direct light.

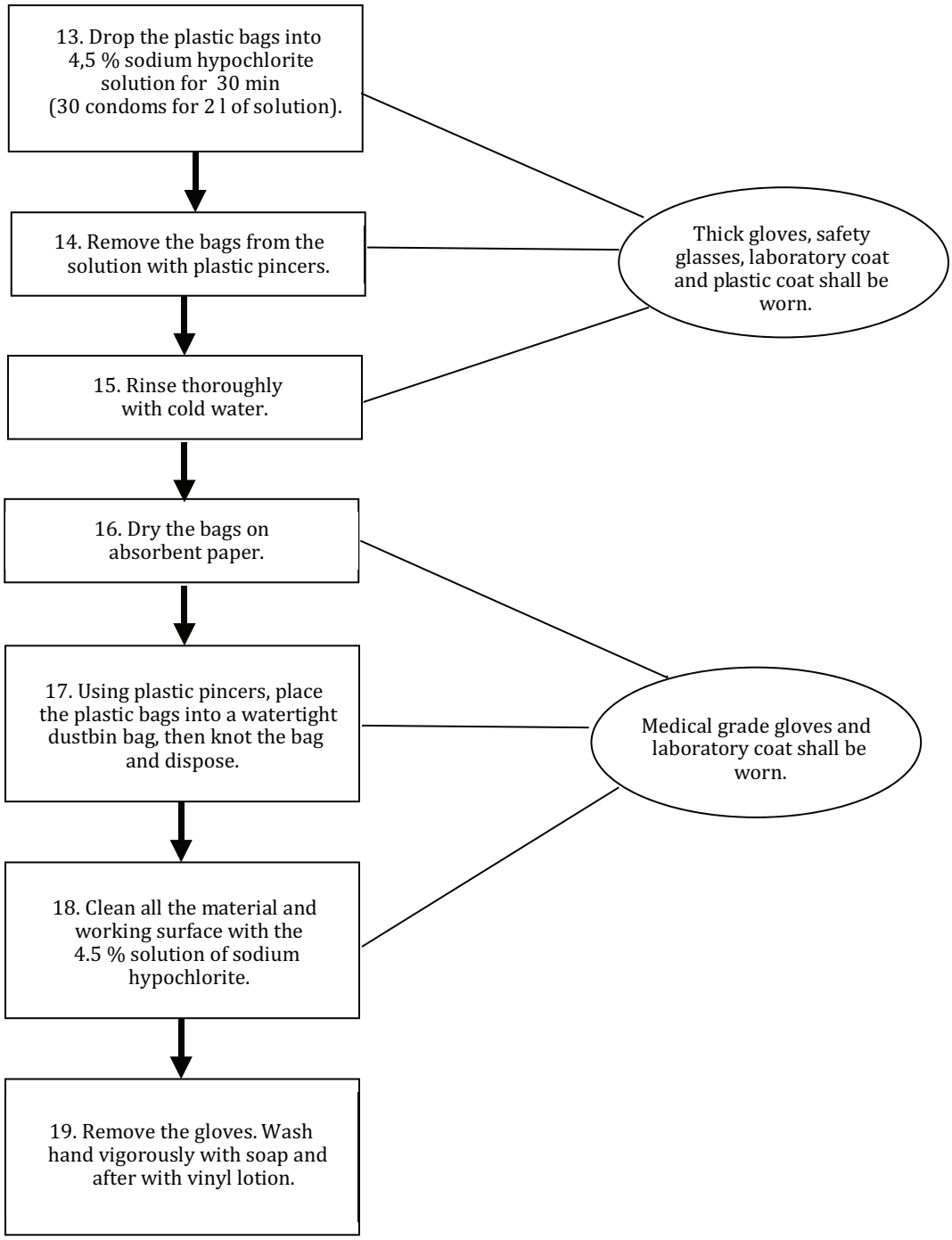
b) The diluted 4,5 % solution, if free from protein, can be stored for 1 week at room temperature.

c) Properly disposed of diluted solution after its use to disinfect a condom sample. Make freshly prepared diluted solution for the next set of used condoms.

H.2.5 Following the step-wise procedures given in Figure H.3, prepare the condom for evaluation.

NOTE There are alternate methods for disinfecting the condom samples. To disinfect by boiling, about 15 min might be required. For chemical disinfection, be sure to use a chemical agent that does not adversely affect the physical properties of the condoms. In any case, continue to use exam or surgical gloves.





NOTE Steps 1 and 2: Administrative Department. Step 3 to 19: Quality Laboratory.

Figure H.3 — Returned condoms, procedure for condom decontamination

H.2.6 Rinse the disinfected sample with water and apply a suitable powder (e.g. silica) to absorb moisture.

H.3 Observation

H.3.1 Place the sample on a mandrel of similar diameter.

NOTE If a condom manufacturer does the observations, then it is best done using one of the condom mandrels from the dipping process.

H.3.2 Make sketches or take photos of the sample, esp. the torn parts.

H.3.3 Record observations (see Note).

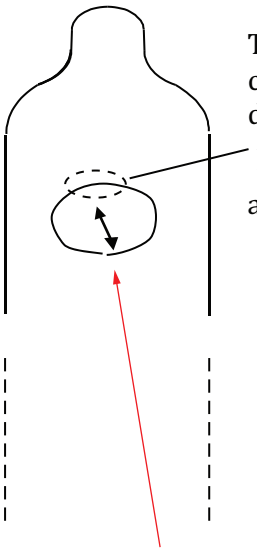
NOTE It is helpful to observe the torn parts and find the starting point of the tear.

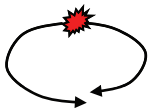
H.3.3.1 Examples of observations, how to find the starting point.

In the image below,  and  indicate the starting point of the tear. The red arrow indicates a gap.

"Circular tear"

The starting point of the circular tear is often determined at the diagonal line  , in the highlighted area.

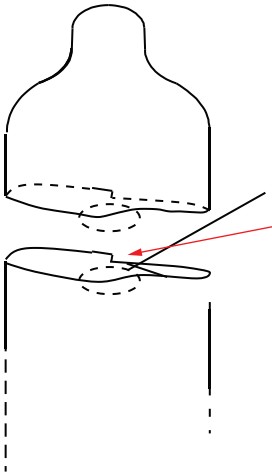


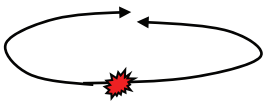


If a gap is observed on the circular tear portion, the starting point of the tear is often determined at the opposite side of the gap.

"Split tear"

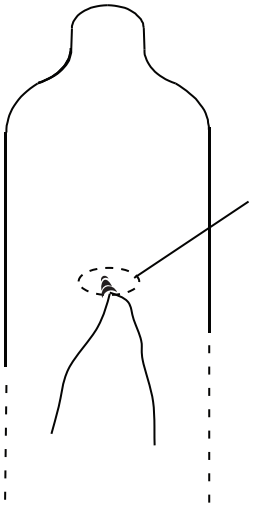
The starting point of the tear is often determined at the opposite side (to that of a circular tear) in the highlighted area.

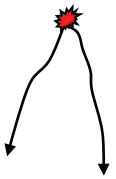




"V shape tear"

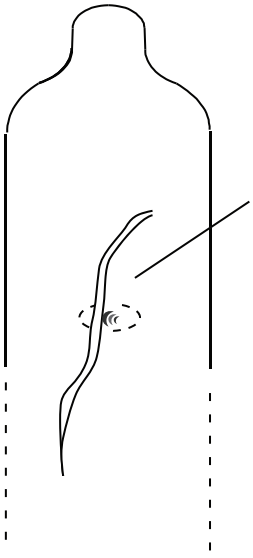
The starting point is often found at the closed end of V.



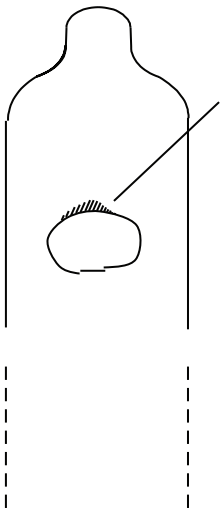


"Crack tear"

The starting point is often found at the part where conditions of the film are not normal.



H.3.3.2 Examples of the starting point or tear.



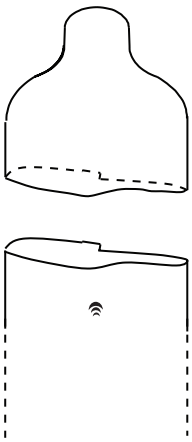
The film elongated and tore due to the load exceeding the strength limit. Possible reactions are:

a) Strength of the film itself was poor.

b) The condom did not fit the penis well and adhered too tightly to the side of the penis.

c) Air was present between the condom and the penis, and the condom burst during the sexual intercourse.

d) When taking out, the condom film was damaged by the pouch.



The hard item scratches the film. During the sexual intercourse, the condom was torn at the scratched part. Possible reasons are:

a) The condom is already scratched during the production process.

b) The user scratches the condom with his/her nails or rings.

H.4 Tensile measurements

After making the visual observations described above, the Quality Laboratory should conduct tensile testing of the sample to determine whether it has acceptable strength. Using a test specimen taken from the sample, either ring or dumbbell, the Quality Laboratory should follow appropriate standards or published procedures for tensile testing. For example, for dumbbell specimens, you could use the method described in Reference [23]. However, if the country where the sample was used already has a standard for tensile testing of condoms, then typically one would apply that national standard.

WARNING — Some methods for disinfection might adversely affect the physical properties of a condom and lead to unexpectedly poor results from tensile testing. Consider this when developing your in-house protocol.

H.5 Records

Record the following items:

a) sketches and/or photos of the sample;

b) any observations reported by the study couple;

c) results of tensile testing, if possible; and

d) any conclusions on presumed causes of the tear, based on evidence from a) to c).

NOTE See Reference [24] for the description of "blunt puncture".

H.6 Conclusion

It is often difficult to determine the underlying cause of a condom tear based only on a single sample of a torn condom. Therefore, the Quality Laboratory should re-evaluate all torn samples after the study is complete and determine if there are any trends.

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General principles

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[15] Schroder KEE, Carey MP, Vanable PA Methodological challenges in research on sexual risk behavior: II. accuracy of self-reports. 26(2):104-123 (2003)

Female condoms, functionality studies of acute failure events

The following is a partial list of published articles in peer-reviewed journals, describing good quality studies designed to measure event rates for in-use slippage, breakage, mis-direction, and invagination.

[16] Beksinska M. Performance of the Reality® polyurethane female condom and a synthetic latex prototype: a randomized crossover trial among South African women. Contraception. 2006, **73** pp. 386–393

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Evaluation of broken condoms

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Relevant ISO standards for guidance

The following documents are referred to in the text of this guidance. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies

[25] ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

[26] ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

[27] ISO 14971, *Medical devices — Application of risk management to medical devices*

[28] ISO 16037, *Rubber condoms for clinical trials — Measurement of physical properties*

[29] ISO 25841:2014, *Female condoms — Requirements and test methods*

ICS 11.200
Price based on 40 pages