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Condoms — Guidance on clinical studies —

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

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

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Foreword

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

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

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

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

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

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

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

Introduction

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

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

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

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

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

Condoms — Guidance on clinical studies —

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

1 Scope

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

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

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

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

2 Normative references

There are no normative references in this document.

3 Terms and definitions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 Pilot clinical studies

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

5 Clinical validation investigation

5.1 Objectives of clinical validation investigation

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

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

5.2 Outcome measures

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

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

b) Secondary outcome measures are

   1) clinical slippage rates, and

   2) clinical breakage rates.

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

d) Other outcome measures (optional) are

   1) non-clinical breakage,

   2) non-clinical slippage, and

   3) user acceptability.

5.3 Study subjects

5.3.1 General

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

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

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

5.3.2 Enrolment of study subjects

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

5.3.2.1 Inclusion criteria

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

a) mutually monogamous, current relationship ≥ 3 months;

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

c) 18 years to 45 years of age;

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

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

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

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

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

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

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

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

l) available for follow-up.

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

5.3.2.2 Exclusion criteria

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

If either partner is (or becomes) aware that

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

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

c) subject knowingly has a sexually transmitted infection,

d) commercial sex workers,

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

f) male partner has known erectile or ejaculatory dysfunction,

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

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

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

5.4 Informed consent

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

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

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

5.5 Test and control condoms

5.5.1 General

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

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

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

5.5.2 Test condom

The test condom should meet performance specifications throughout the study.

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

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

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

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

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

NOTE Local regulations can require additional labelling.

5.5.3 Control condom made from natural rubber latex

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

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

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

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

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

5.5.4 Expiration date of control condom

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

5.5.5 Storage conditions

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

5.5.6 Trial duration exceeds 1 year

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

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

5.5.7 Sampling of control condoms for bench testing

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

5.6 Randomization

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

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

5.7 Allocation concealment and study masking

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

5.8 Use of additional lubricant

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

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

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

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

5.9 Instructions and interactions with study couples

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

The training and instructions should carefully address the following:

a) purpose of study and duration of participation;

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

c) correct condom use;

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

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

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

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

5.10 Interviews and data collection

5.10.1 Schedule for interviews and condom distribution

The protocol should have a schedule for CRF distribution.

a) enrolment interview:

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

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

b) mid-study interview, if crossover design:

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

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

c) exit interview:

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

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

5.10.2 Enrolment interview

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

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

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

b) risk of STI and pregnancy;

c) method of contraception used during study;

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

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

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

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

5.10.3 Individual condom use CRF

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

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

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

a) package opened (yes/no);

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

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

d) condom broken during intercourse;

e) condom broken during withdrawal;

f) location of break, if any;

g) condom slipped completely off penis during intercourse;

h) condom slipped completely off penis during withdrawal;

i) semen leakage from condom, noticed by user;

j) use of additional lubricant;

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

The study sponsor can collect information on user acceptability.

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

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

5.10.4 Mid-study CRF, crossover trial

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

a) problems with condom use,

b) acceptability,

c) safety, and

d) other.

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

5.10.5 Compiling data from CRFs

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

a) number of packages opened;

b) number of condoms used for vaginal intercourse;

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

d) number of condoms broken during intercourse or withdrawal (clinical breakage);

e) number of condoms that slipped completely off penis during intercourse or withdrawal (clinical slippage);

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

5.11 Data integrity

5.11.1 General

A condom breakage and slippage study is dependent upon user self-reports of clinical failures 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 ensure accuracy, reliability and traceability of all data, the study protocol should thoroughly address selection of study couples, instructions for study participants, timeframes for reporting events, design of coital diaries and other case report forms (CRFs), study schedules, as well as distribution of study condoms (test and control) and overall collection of study data.

5.11.2 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.

5.11.3 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 (e.g. 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 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.

5.11.4 Web-based data collection systems and 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 can be reduced since couples do not have to visit the study centre.

When conducting such studies, manufacturers 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 couples 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 couples 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 couples about what actions to take if the condom should tear, break or slip off or if there is any adverse reaction to the condom. The couples 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 manufacture 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 telephone, with a randomly selected proportion of the study population are ways of achieving this.

5.12 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.

5.13 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 can 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.

5.14 Other methodological details

The study protocol can be needed to address the following concerns:

a) language of instructions and case report forms 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) it is possible that naive condom users experience higher clinical failure rates until they become familiar with the products[8]; a brief, pre-planned condom use run-in period can be appropriate prior to enrolling study couples;

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: Some regulatory bodies require clinical function studies for the approval of certain condoms. When this is the case, the study protocol or standard operating procedures should include a comprehensive monitoring plan

   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, and

   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.

5.15 Statistical analysis plan

5.15.1 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 condom breakage and slippage studies should not be done without the help of an experienced statistician, familiar with non-inferiority testing and methods for making valid statistical inferences.

5.15.2 Primary study hypothesis

The primary end point in a clinical validation study of a new condom is total clinical failure. The primary research objective is to determine whether the expected total clinical failure rate of a new test condom is comparable with the expected total clinical failure rate of a legally marketed NRL male condom when used during vaginal intercourse. The clinical research question should be rephrased in statistical terms as a non-inferiority hypothesis. (For example, for synthetic condoms, the expected difference in total clinical failure rates, between the test and control condoms, is less than the amount, δ, specified in ISO 23409.)

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 condom non-inferiority study, this would typically look something like:

— H_0: Expected test condom total clinical failure rate – expected control condom total clinical failure rate ≥ δ;

— H_A: Expected test condom total clinical failure rate – expected control condom total clinical failure rate < δ.

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 <δ to conclude non-inferiority. Rather, the study results should provide a high degree of confidence that the difference in expected rates is <δ.

5.15.3 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 condom performs better than the control condom. As part of the SAP, study sponsors might prospectively specify a secondary hypothesis for superiority. If the study results support a conclusion of non-inferiority, then the secondary hypothesis might be tested.

Study sponsors should also develop secondary hypotheses to address the study end points of clinical slippage and breakage as individual variables, again comparing the test condom with 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 23409 specifies a δ of 2,5 % for testing the total failure rates. Based on currently available data, it would be appropriate to use a δ of 2,0 % to test breakage rates and slippage rates individually.

5.15.4 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 couples so a minimum of 200 couples 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 couples.

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

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 might 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.

5.15.5 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[3] based on the null and alternative hypotheses specified in 5.15.2.

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[5]. This method is described in further detail for condom studies in Reference [8].

The proportion of test and control 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 condom with respect to clinical failure.

An upper one-sided 97,5 % confidence limit for the difference that is less than 0 % could be further interpreted as statistical evidence that the test condom is superior to the 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 clinical breakage and slippage rates. 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. 3 %). This need for an estimate of expected failure rates underscores the importance of pilot studies.

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

5.15.6 Additional statistical comments and concerns

Low total clinical failure proportions (<0,5 %) in the control arm can make implementing a functionality 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.

5.16 Clinical study results: Review and interpretation

5.16.1 General

When the clinical validation study and statistical analysis are completed, it is important to critically evaluate the results to determine whether the test condom performs acceptably well in comparison with 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 self-reporting and the rates for slippage and breakage.

5.16.2 Total clinical failure rates for control condom

The total clinical failure rates during actual use should be in the range of 0,5 % to 4,0 % for condoms made from natural rubber latex. If the total clinical failure rates for the control 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, study bias, breaches in data integrity, participant fraud, etc.).

5.16.3 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.

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, then this can be interpreted as statistical evidence that the test condom is non-inferior to the standard control condom. One can then conclude that the test condom is comparable in performance with 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 reason can be that the test condom is inferior to the control condom. However, other factors, including the user population and methodological problems, might explain such study findings.

5.16.4 Superiority

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

5.16.5 Safety (adverse events)

Any reports of adverse events or complaints should be thoroughly investigated to determine whether the test condom poses an unacceptable safety risk in comparison with 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.

5.16.6 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 might still be considered suitable for marketing. Under this circumstance (no statistically-based conclusion of non-inferiority), a regulatory body can consider other factors, such as:

a) the individual clinical slippage and breakage rate 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 F_T and F_C, respectively, and let $\Delta = F_T - F_C$. 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 by Formula (A.1):

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

where

$$\mathrm{Var}(\Delta) = F_T(1 - F_T) \times \{1 + (Z - 1)\rho\}/Z + F_C(1 - F_C) \times \{1 + (Z - 1)\rho\}/Z - 2\rho \times \{F_T(1 - F_T) \times F_C(1 - F_C)\}1/2$$

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

For example, if $F_T = F_C = 0{,}03$, $\rho = 0{,}2$ and each couple uses $Z = 5$ condoms per type, then $\mathrm{Var}(\Delta) = 0{,}009\ 3$. In order to have 90 % power, G (0,9) = 1,282 and $N = 128$ couples should be enrolled for $\delta = 0{,}025$.

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 $\mathrm{Var}(\Delta) = F_T(1 - F_T) \times \{1 + (Z - 1)\rho\}/Z + F_C(1 - F_C) \times \{1 + (Z - 1)\rho\}/Z$.

For the above example (alternate to the crossover design), $N = 287$ couples using five condoms of one type plus 287 different couples using five condoms of the other type to achieve 90 % power, i.e. 574 total couples, 287 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 slippage and breakage during use. As with the pivotal breakage and slippage study, such feasibility studies should also comply with ISO 14155.

B.2 Study design

— *n* = 35 couples, typically need to recruit 40 to 45 couples to finish with 35.

— Each couple to use three condoms of the test product and natural rubber latex control.

— Double-masked randomized crossover design.

— Each couple should be given two consecutive weeks to complete each evaluation (one type of condom).

— Each couple should complete a diary of each coital event when one of the samples is used, including the sexual position used.

— At the end of the use of each product, the couple should be interviewed either by telephone, Internet or by clinic visit, the latter being preferred.

— Clinical end points should be condom slippage and breakage during use, as well as any genito-urinary adverse events.

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

— 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.

— Couples should be experienced condom users, minimum 10 male condoms used in the last 12 months.

— Subjects 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 or a sponsor of the study.

— Participants with known allergy to natural rubber latex or material(s) of test condom.

— Participants with known sensitivity to the residual chemicals used in the manufacture of natural rubber latex condoms or the test condom materials.

— Couples where one knowingly has a sexually transmitted infection.

B.5 Informed consent

Participating study subjects should be given appropriate informed consent. See 5.4.

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)

CALIFORNIA FAMILY HEALTH COUNCIL - INITIAL HISTORY

ID ☐☐☐☐☐-☐ Date ☐☐/☐☐/☐☐

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

2. 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

3. 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, *Describe:* _____

4. Including your study partner, how many sexual partners have you had in the last 6 months? _____

5. Are you allergic to latex or polyurethane?
0 ☐ No
1 ☐ Yes

6. In the last year have you used injection drug needles?
0 ☐ No
1 ☐ Yes

MALE ONLY:

9. On average, how often do you and your current partner have vaginal intercourse?
1 ☐ Less than 4 times per month
2 ☐ 4 - 6 times per month
3 ☐ 7 - 10 times per month
4 ☐ More than 10 times per month

10. In the last year have you had sex with a man?
0 ☐ No
1 ☐ Yes

FEMALE ONLY:

11. 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

12. When did you begin a sexual relationship with your current partner? *(Month/Year)* _____ / _____

13. 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 or vasectomy)
6 ☐ Other, Describe: _____

7. In your lifetime, how many times have you had each of the following?

	Never	1-2x	3+x	→	IF > 0: What is the date of most recent infection/outbreak? Month	Year	→	Were you treated for the infection/outbreak? Yes	No
Trichomonas	0 ☐	1 ☐	2 ☐	→	*If yes:* _____	_____	→	_____	_____
Chlamydia	0 ☐	1 ☐	2 ☐	→	*If yes:* _____	_____	→	_____	_____
Gonorrhea	0 ☐	1 ☐	2 ☐	→	*If yes:* _____	_____	→	_____	_____
Syphilis	0 ☐	1 ☐	2 ☐	→	*If yes:* _____	_____	→	_____	_____
Genital herpes	0 ☐	1 ☐	2 ☐	→	*If yes:* _____	_____			

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

	Never	Yes	
HIV	0 ☐	1 ☐	
Hepatitis	0 ☐	1 ☐	→ *If yes,* What type? _____
HPV/Genital warts (condylomata)	0 ☐	1 ☐	

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

INITIAL HISTORY

ID ☐☐☐☐☐ - ☐☐☐ 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. How often 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. How many sexual partners have you had during your lifetime? _____

9. Including your study partner, how many sexual partners have you had in the last 6 months? _____

10. How many times have you been pregnant *(female)* or responsible for a pregnancy *(male)* ? _____

11. How many times have you used male condoms with <u>all</u> partners, including your current partner?

0 ☐ Never ⟹ *If Never, skip to Q15*
1 ☐ 1 - 2 times
2 ☐ 3 - 10 times
3 ☐ 11 - 50 times
4 ☐ 51 or more times

12. When did you last use a male condom with <u>any</u> partner, including your current partner?

1 ☐ Less than 6 months ago
2 ☐ Between 6 months and 1 year ago
3 ☐ Between 1 and 5 years ago
4 ☐ More than 5 years ago

13. How many times have you experienced a male condom break during vaginal intercourse with <u>other</u> partners (<u>not</u> including your current partner)?

N ☐ Not applicable (no other partners/ no condom use w/other partners)
0 ☐ 0 (Never)
1 ☐ 1 - 2 times
2 ☐ 3 - 5 times
3 ☐ 6 - 10 times
4 ☐ More than 10 times

14. Have you <u>ever</u> used a polyurethane (non-latex) condom?

0 ☐ No ⟹ *If No, skip to Q#15*
1 ☐ Yes
2 ☐ Unsure ⟹ *If Unsure, skip to Q#15*

14a. If Yes, what was your impression of the condom?

0 ☐ Negative
1 ☐ Positive
2 ☐ Neutral

15. Are you allergic to latex or polyurethane, or have you had problems when you used latex or polyurethane products?

0 ☐ No
1 ☐ Yes, Describe:_____

16. Do you have any genital piercings?

0 ☐ No 1 ☐ Yes, Describe:_____

17. Are you currently participating in any other clinical studies?

0 ☐ No
1 ☐ Yes, Describe:_____

ID ☐☐☐☐☐ - ☐

MALE ONLY:

23. On average, how often do you and your current partner have vaginal intercourse?

1 ☐ Less than 4 times per month
2 ☐ 4 - 6 times per month
3 ☐ 7 - 10 times per month
4 ☐ More than 10 times per month

24. How many times have you used a male condom with your current partner?

0 ☐ 0 (Never) ⟹ *If Never, skip to Q#25*
1 ☐ 1 - 2 times
2 ☐ 3 - 10 times
3 ☐ 11 - 50 times
4 ☐ More than 50 times

24a. How many times have you experienced a male condom break during vaginal intercourse with your current partner?

0 ☐ 0 (Never)
1 ☐ 1 - 2 times
2 ☐ 3 - 5 times
3 ☐ 6 - 10 times
4 ☐ More than 10 times

25. Are you circumcised *(see diagram)* ? 0 ☐ No 1 ☐ Yes

26. In your lifetime, how many times have you had each of the following?

				If Rarely or Sometimes:
Difficulty getting an erection:	0 ☐ Never	1 ☐ Rarely	2 ☐ Sometimes	# Times in last month:_____
Difficulty maintaining an erection:	0 ☐ Never	1 ☐ Rarely	2 ☐ Sometimes	# Times in last month:_____
Difficulty achieving ejaculation:	0 ☐ Never	1 ☐ Rarely	2 ☐ Sometimes	# Times in last month:_____

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

	Never	Yes
Undescended testes	0 ☐	1 ☐
Urethra opening on underside of penis . . .	0 ☐	1 ☐

28. In the last year have you had sex with a man?

0 ☐ No
1 ☐ Yes

FEMALE ONLY:

29. 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

30. How long have you been with your current partner?

☐ Less than one year: _____ months
☐ More than one year: _____ years

31. 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
N ☐ I'm pregnant
6 ☐ Other, Describe:_____

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. In your lifetime, 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:_____

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

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

Annex E
(informative)

CRF — Mid-study (sample)

ACCEPTABILITY SURVEY MALE FEMALE

ID _____ - _____ Birthdate _____ Date Form Completed _____ Visit Type (*circle*): 2 3

COMPLETE THIS FORM SEPARATELY FROM YOUR PARTNER. PLEASE RECORD YOUR HONEST OPINIONS.

1. Using the 1 to 7 scale, please circle the number that best describes your experience with the study condom you just used:

		Strongly Disagree						Strongly Agree
a.	The study condom was easy to put on.	1	2	3	4	5	6	7
b.	The study condom had a pleasant smell or no smell.	1	2	3	4	5	6	7
c.	The study condom made little or no noise.	1	2	3	4	5	6	7
d.	The study condom felt soft.	1	2	3	4	5	6	7
e.	The study condom was comfortable.	1	2	3	4	5	6	7
f.	The study condom increased sensitivity and stimulation.	1	2	3	4	5	6	7
g.	The study condom transmitted body heat.	1	2	3	4	5	6	7
h.	I liked the amount of lubricant on the outside of the study condom.	1	2	3	4	5	6	7
i.	I liked the amount of lubricant on the inside of the study condom.	1	2	3	4	5	6	7
j.	I liked the way the lubricant felt.	1	2	3	4	5	6	7
k.	The lubricant on the study condom lasted long enough.	1	2	3	4	5	6	7
l.	The study condom was not messy.	1	2	3	4	5	6	7
m	My overall sexual experience was good while using the study condom.	1	2	3	4	5	6	7
n.	I liked the study condom as much as other condoms I have used.	1	2	3	4	5	6	7
o.	**MALES ONLY:** The study condom fit well.	1	2	3	4	5	6	7

2. Would you purchase a condom like the study condom you just used?

0 ☐ No: *skip to Q4* 1 ☐ Maybe 2 ☐ Yes

3. Would you be willing to pay more for this condom than condoms you've used in the past? Based on a box of 6 condoms, how much more would you pay?

0 ☐ No more 1 ☐ Up to 50¢ more 2 ☐ Up to $1.00 more 3 ☐ Up to $2.00 more

4. What was the ONE thing you liked best about the study condom?

_____ ☐☐

5. What was the ONE thing you liked least about the study condom?

_____ ☐☐

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

1 ☐ Highly recommend 2 ☐ Recommend 3 ☐ Recommend with reservations 4 ☐ Not recommend

RA Init-#:_____-_____ **Date:**_____/_____/_____ **Edited by:**_____ **Date:**_____/_____/_____ **Batch-Record #:**_____ - ___

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

Annex F
(informative)

CRF — Individual condom use (sample)

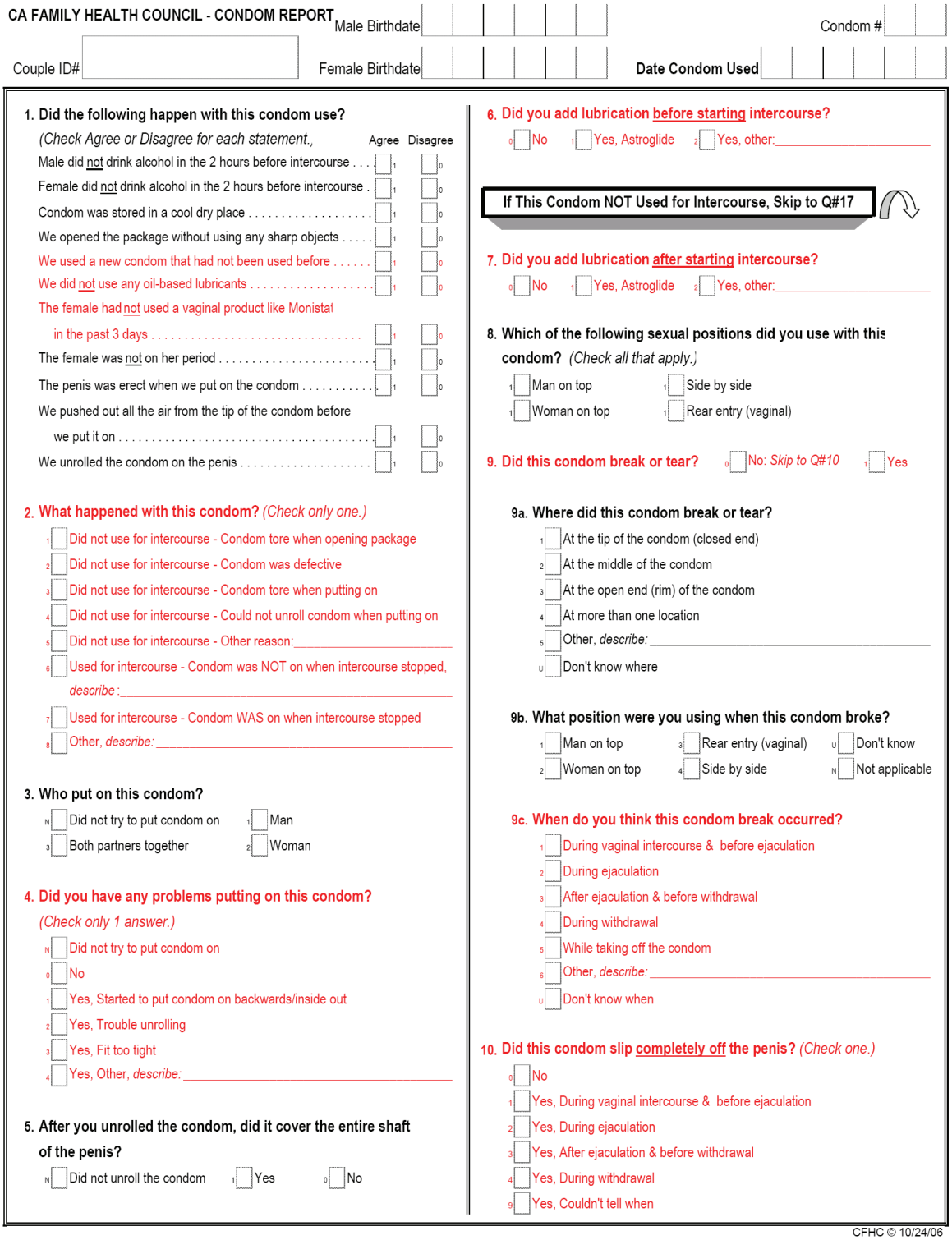
The following are three separate paper-based examples of CRFs used to capture the key event information after condom use, i.e. slippage events and breakage events. It is critical that study participants enter this information into the CRF as soon after each coital act as practicable. They should not 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.

California Family Health Council (CFHC), Family Health International (FHI) and Sagami-France provided the three CRF examples and all three granted permissions for these CRFs to be reproduced or adapted by any interested study sponsor.

EXAMPLE 1 Two-page CRF for individual condom use, submitted by the CFHC.

This CRF is intended to be used as a two-sided form that fits on a single piece of paper. Questions in red are of primary interest.



CA FAMILY HEALTH COUNCIL - CONDOM REPORT

Male Birthdate

Condom #

Couple ID#

Female Birthdate

Date Condom Used

1. Did the following happen with this condom use?

(Check Agree or Disagree for each statement.)

	Agree	Disagree
Male did not drink alcohol in the 2 hours before intercourse	1	0
Female did not drink alcohol in the 2 hours before intercourse	1	0
Condom was stored in a cool dry place	1	0
We opened the package without using any sharp objects	1	0
We used a new condom that had not been used before	1	0
We did not use any oil-based lubricants	1	0
The female had not used a vaginal product like Monistat in the past 3 days	1	0
The female was not on her period	1	0
The penis was erect when we put on the condom	1	0
We pushed out all the air from the tip of the condom before we put it on	1	0
We unrolled the condom on the penis	1	0

2. What happened with this condom? *(Check only one.)*

- 1 Did not use for intercourse - Condom tore when opening package
- 2 Did not use for intercourse - Condom was defective
- 3 Did not use for intercourse - Condom tore when putting on
- 4 Did not use for intercourse - Could not unroll condom when putting on
- 5 Did not use for intercourse - Other reason:_____
- 6 Used for intercourse - Condom was NOT on when intercourse stopped, *describe*:_____
- 7 Used for intercourse - Condom WAS on when intercourse stopped
- 8 Other, *describe:*_____

3. Who put on this condom?

- N Did not try to put condom on
- 1 Man
- 3 Both partners together
- 2 Woman

4. Did you have any problems putting on this condom?

(Check only 1 answer.)

- N Did not try to put condom on
- 0 No
- 1 Yes, Started to put condom on backwards/inside out
- 2 Yes, Trouble unrolling
- 3 Yes, Fit too tight
- 4 Yes, Other, *describe:*_____

5. After you unrolled the condom, did it cover the entire shaft of the penis?

- N Did not unroll the condom
- 1 Yes
- 0 No

6. Did you add lubrication before starting intercourse?

- 0 No
- 1 Yes, Astroglide
- 2 Yes, other:_____

If This Condom NOT Used for Intercourse, Skip to Q#17

7. Did you add lubrication after starting intercourse?

- 0 No
- 1 Yes, Astroglide
- 2 Yes, other:_____

8. Which of the following sexual positions did you use with this condom? *(Check all that apply.)*

- 1 Man on top
- 1 Side by side
- 1 Woman on top
- 1 Rear entry (vaginal)

9. Did this condom break or tear?

- 0 No: *Skip to Q#10*
- 1 Yes

9a. Where did this condom break or tear?

- 1 At the tip of the condom (closed end)
- 2 At the middle of the condom
- 3 At the open end (rim) of the condom
- 4 At more than one location
- 5 Other, *describe:*_____
- U Don't know where

9b. What position were you using when this condom broke?

- 1 Man on top
- 3 Rear entry (vaginal)
- U Don't know
- 2 Woman on top
- 4 Side by side
- N Not applicable

9c. When do you think this condom break occurred?

- 1 During vaginal intercourse & before ejaculation
- 2 During ejaculation
- 3 After ejaculation & before withdrawal
- 4 During withdrawal
- 5 While taking off the condom
- 6 Other, *describe:*_____
- U Don't know when

10. Did this condom slip completely off the penis? *(Check one.)*

- 0 No
- 1 Yes, During vaginal intercourse & before ejaculation
- 2 Yes, During ejaculation
- 3 Yes, After ejaculation & before withdrawal
- 4 Yes, During withdrawal
- 9 Yes, Couldn't tell when

CFHC © 10/24/06

11. Did you experience any of the following while using this condom? *(Check Yes or No for every item.)*

	No	Yes
We started intercourse without the condom	0 ☐	1 ☐
The condom slipped along the shaft of the penis during intercourse *(see Diagram B)*	0 ☐	1 ☐
The condom bunched up during intercourse *(see Diagram C)*	0 ☐	1 ☐
The condom stretched out of shape *(see Diagram D)*	0 ☐	1 ☐
The condom fit was too tight	0 ☐	1 ☐
Not enough lubrication/too dry during intercourse	0 ☐	1 ☐
The condom caught the male's pubic hair	0 ☐	1 ☐
The condom made noise during intercourse	0 ☐	1 ☐
The male lost his erection during intercourse	0 ☐	1 ☐
We used the condom for anal intercourse	0 ☐	1 ☐

12. Did ejaculation occur while wearing this study condom?

1 ☐ Yes
2 ☐ No, Ejaculated without a study condom
3 ☐ No, Ejaculation did not occur with this act of intercourse

13. Did you do the following during withdrawal? *(Check Yes or No for each.)*

	Yes	No
Held on to the ring of condom	1 ☐	0 ☐
Withdrew while penis was still erect	1 ☐	0 ☐

14. Do you think that semen may have leaked from the condom?

0 ☐ No
1 ☐ Yes, When the condom broke
2 ☐ Yes, When the condom slipped off the penis
3 ☐ Yes, When the condom slipped along the penis
4 ☐ Yes, At another time, *describe:* _____
5 ☐ Yes, Don't know when

15. How long did vaginal intercourse last while wearing this condom?

_____ **minutes**

16. Please rate the following. *(Check one box per line.)*	*MALE ANSWERS*				*FEMALE ANSWERS*			
	Excellent	Good	Fair	Poor	Excellent	Good	Fair	Poor
Stimulation during intercourse	1 ☐	2 ☐	3 ☐	4 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Condom lubricant	1 ☐	2 ☐	3 ☐	4 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Overall lubrication during intercourse	1 ☐	2 ☐	3 ☐	4 ☐	1 ☐	2 ☐	3 ☐	4 ☐

	MALE ANSWERS	*FEMALE ANSWERS*
17. Did you experience any discomfort that started while using this condom?	0 ☐ **No:** ***Skip to Q#18*** 1 ☐ **Yes**	0 ☐ **No:** ***Skip to Q#18*** 1 ☐ **Yes**
17a. What ONE discomfort best describes the type? *(Check ONLY most severe)*	1 ☐ Burning 2 ☐ Irritation 3 ☐ Genital itching 4 ☐ Genital rash 5 ☐ Constriction 6 ☐ Diminished sensitivity 7 ☐ Dryness 9 ☐ Other, *describe:* _____	1 ☐ Burning 2 ☐ Irritation 3 ☐ Genital itching 4 ☐ Genital rash 6 ☐ Dimished sensitivity 7 ☐ Dryness 9 ☐ Other, *describe:* _____
17b. How severe was the discomfort?	1 ☐ Mild 2 ☐ Moderate 3 ☐ Severe	1 ☐ Mild 2 ☐ Moderate 3 ☐ Severe
17c. How long did the discomfort last?	1 ☐ Only while wearing the condom 2 ☐ 1 - 10 minutes after the condom was removed 3 ☐ More than 10 minutes but less than 1 hour after 4 ☐ One hour or more after condom was removed	1 ☐ Only while in contact with the condom 2 ☐ 1 - 10 minutes after the condom was removed 3 ☐ More than 10 minutes but less than 1 hour after 4 ☐ One hour or more after condom was removed
17d. Do you know what might have caused the discomfort?	☐ No ☐ Yes, *describe:* _____	☐ No ☐ Yes, *describe:* _____
17e. Did you do anything medically to treat the discomfort?	0 ☐ No 1 ☐ Yes, *describe:* _____	0 ☐ No 1 ☐ Yes, *describe:* _____

18. Who filled out this Condom Report? 1 ☐ Man 2 ☐ Woman 3 ☐ Both partners together

19. Additional comments: _____

EXAMPLE 2 Three-page CRF for individual condom use, submitted by FHI.

BSCUQ1

FAMILY HEALTH INTERNATIONAL

A Comparative Assessment of Synthetic Condom and Natural Rubber Latex Condom:
Failure Modes

CONDOM USE QUESTIONNAIRE

1. Centre number: ☐☐☐ 2. Study number: 9 6 0 9 3. Couple number: ☐☐☐☐

4. Condom type: ☐

1 = Natural Rubber Latex
2 = Synthetic

CONDOM USE DATA

Please complete one of these questionnaires for each condom package opened.
For the following items, please circle the response which best answers the question in some cases, you might be instructed to select more than one answer. Please notice that some questions instruct you to "skip to" other questions based on your response. In these cases, do not answer any of the questions between the original one and the one to which you were instructed to skip.

5. Condom number. Circle one.
Do not use more than 4 condoms for intercourse.

1 2 3 4 5 6

6. Date condom opened ☐☐ Month ☐☐ Day ☐☐☐☐ Year

7. Was the condom stored in a cool, dry place?
Circle one,
0 = No 1 = Yes

8. Did the condom break or tear before putting it on the penis?
Circle one.

0 = No
1 = Yes, ***while*** opening the package
2 = Yes, ***after*** opening, at the condom tip
3 = Yes, ***after*** opening, along the condom shaft
4 = Yes, ***after*** opening, at the condom opening
5 = Yes, ***after*** opening, at other location

If the condom broke before putting it on, do not answer any more questions.

If the condom did not break and you tried to put it on, answer the following questions.

9. Did you use the provided lubricant before putting on the condom?
Circle all that apply.

0 = No
1 = Yes, on the inside of the condom
2 = Yes, on the outside of the condom
3 = Yes, inside the vagina
4 = Yes, inside the anus

10. Did you use another type of lubricant before putting on the condom? *Circle all that apply*.

0 = No
1 = Yes, on the inside of the condom
2 = Yes, on the outside of the condom
3 = Yes, inside the vagina
4 = Yes, inside the anus
*If yes, specify lubricant type*_____

11. Was there any genital contact before putting on the condom?
Circle one.

0 = No
1 = Yes, but no vaginal or anal penetration
2 = Yes, with vaginal or anal penetration

12. Who tried to put on the condom? *Circle one.*

1 = female 2 = male 3 = both

13. Was the penis erect before putting on or trying to put on the condom? *Circle one*.

0 = No 1 = Yes

14. Was the condom unrolled before putting on or trying to put the condom on the penis? *Circle one*.

0 = No 1 = Yes

15. Were you able to put the condom on the penis? *Circle one*.

0 = No
1 = Yes, the condom went on easily
2 = Yes, but the condom did not go easily.

16. Did the condom break while putting it on or trying to put it on, but ***before*** intercourse? *Circle one*.

0 = No
1 = Yes, at the condom tip
2 = Yes, along the condom shaft
3 = Yes, at the condom opening
4 = Yes, other

IF THE CONDOM BROKE WHILE PUTTING IT ON OR TRYING TO PUT IT ON, SKIP TO QUESTION 33.

BSCUQ1

FAMILY HEALTH INTERNATIONAL
A Comparative Assessment of Synthetic Condom and Natural Rubber Latex Condom:
Failure Modes
CONDOM USE QUESTIONNAIRE

STUDY IDENTIFICATION

Centre number: ☐☐☐ Study number: 9 6 0 9 Couple Number: ☐☐☐☐

Condom type: ☐

1 = Natural rubber latex
2 = Synthetic

Answer the following questions if you were able to put the condom on the penis without it breaking.

17. Was the condom pulled/rolled down the shaft of the penis? *Circle one*.

0 = No 1 = Yes

18. After the condom was put on, did it cover the entire penis? *Circle one*.

0 = No 1 = Yes

19. Did you use the provided lubricant after putting on the condom, but before intercourse? *Circle all that apply.*

0 = No
1 = Yes, on the outside of the condom
2 = Yes, inside the vagina
3 = Yes, inside the anus

20. Did you use another type of lubricant after putting on the condom, but before intercourse? *Circle all that apply.*

0 = No
1 = Yes, on the outside of the condom
2 = Yes, inside the vagina
3 = Yes, inside the anus
*If yes, specify lubricant type*_____

21. Did the condom break after putting it on, but before intercourse? *Circle one*.

0 = No
1 = Yes, at the condom tip
2 = Yes, along the condom shaft
3 = Yes, at the condom opening
4 = Yes, other

} *if yes*, skip to Question 33

If you did not have intercourse wearing this condom, skip to Question 33.
otherwise answer the following questions.

22. Did you use the provided lubricant during sex? *Circle all that apply.*

0 = No
1 = Yes, on the penis
2 = Yes, inside the vagina
3 = Yes, inside the anus

23. Did you use another type of lubricant during sex? *Circle all that apply.*

0 = No
1 = Yes, on the penis
2 = Yes, inside the vagina
3 = yes inside the anus
*If yes, specify lubricant type*_____

24. While wearing this condom in which of the following did you engage? *Circle all that apply.*

1 = front entry vaginal sex
2 = rear entry vaginal sex
3 = other vaginal sex
4 = anal sex
5 = oral sex on male partner

25. Did the condom break during sex or while removing the condom from the penis? *Circle one.*

0 = No
1 = Yes, during front entry vaginal sex
2 = Yes, during rear entry vaginal sex
3 = Yes, during other type of vaginal sex
4 = Yes, during withdrawal from the vagina
5 = Yes, during anal sex
6 = Yes, during withdrawal from the anus
7 = Yes, during oral sex on the male partner
8 = Yes, while taking condom off the penis
9 = Yes, other or don't know when

26. Where did the condom break? *Circle one.*

0 = did not break
1 = at the tip of the condom
2 = along the shaft of the condom
3 = at the opening of the condom
4 = other

27. How many minutes was the condom worn during vaginal intercourse ☐☐☐

BSCUQ1

FAMILY HEALTH INTERNATIONAL
A Company Assessment of a Plastic Condom and a Latex Condom:
Failure Modes
CONDOM USE QUESTIONNAIRE

STUDY INDENTIFICATION

Centre number: ☐☐☐ Study number: 9 6 0 9 Couple number: ☐☐☐☐

Condom type: ☐

1 = Latex
2 = Plastic

Answer the following questions ONLY IF the condom was used for vaginal intercourse.
If the condom was NOT used for vaginal intercourse, skip to Question 33.

28. Did the male partner ejaculate while wearing the condom? *Circle one.*

0 = No
1 = Yes, during anal sex
2 = Yes, during vaginal sex
3 = Yes, during other sex

29. Did the condom ring slip from the base of the penis during vaginal intercourse? *Circle one.*

0 = No
1 = Yes, it slipped completely off the penis
2 = Yes, it slipped but not completely off the penis
3 = don't know not sure

30. Was the penis still hard when it was pulled out of the vagina? *Circle one.*

0 = No
1 = Yes

31. Did you hold on to the base of the condom during withdrawal from the vagina? *Circle one.*

0 = No
1 = Yes

32. Did the condom ring slip from the base of the penis during withdrawal from the vagina? *Circle one.*

0 = No
1 = Yes, it slipped completely off the penis
2 = Yes, it slipped but not completely off the penis
3 = don't know not sure

33. Did one or both partners drink alcohol within one hour of using the condom?

0 = No
1 = Yes, only male partner
2 = Yes, only female partner
3 = Yes, both partner

34. Did either of you experience genital burning, irritation, rash, itching, pain or other medical event that began while using this condom? *Circle one.*

0 = No
1 = Yes, only male partner
2 = Yes, only female partner
3 = Yes, both partner

} If 1, 2, or 3, complete *Medical Event form*

Initials of person reviewing form: _____ Date form reviewed: _____

EXAMPLE 3 One-page CRF for individual condom use, submitted by Sagami-France.

Ref number:

SHORT QUESTIONNAIRE

Type condom (**"A"** or **" B"**): ……Day: ……Date:……Time**:** ……

If any additional lubricant use, please indicate the type: ……

Type of intercourse: (*Please rank the cases below, e.g. oral followed by vaginal, please rank 1 for oral and 2 for vaginal, if only one type, please tick below)*

Oral	Vaginal	Anal

Describe your position during intercourse *(e.g. man on top, woman on top, front or rear or side entry)*:

……

1 How long was the foreplay when using this condom? *(tick).*

No foreplay	2-5 min	5-10 min	10-20 min	20-30 min	Longer
No foreplay	2-5 min	5-10 min	10-20 min	20-30 min	Longer

2 How long was the intercourse when using this condom? *(tick)*

2-5 min	5-10 min	10-20 min	20-30 min	Longer
2-5 min	5-10 min	10-20 min	20-30 min	Longer

3 Were you ready when using this condom (if woman is dry this can lead to breakage)? *(Pease tick below).*

YES	NO
YES	NO

4 Did condom break? *(Pease tick below).*

YES	NO

If **YES**, go to question 5, if **NO**, go to 9

5 Where did it break? *(Pease tick below)*

Teat-end	Head	Body

6 When did it break? *(Pease tick below)*

Taking out of packet	During foreplay	During intercourse	Noticed after intercourse

7 Which type of break? *(Pease tick below)*

Small hole	Split	Tear

8 Could you explain why the condom broke?

……

9 Did the condom slip? *(Pease tick below)*

YES	NO

If **YES**, go to question 10, if NO, go to 14

10 When did the condom slip? *(Pease tick below)*

During intercourse	On the withdrawal

11. How far off the penis did the condom slip? *(Pease tick below)*

Right off the penis	¾ down the shaft of the penis	½ down the shaft of the penis	¼ down the shaft of the penis

12 Did you hold the condom when withdrawing? *(Pease tick below)*

YES	NO

13 Did any semen enter the vagina or other orifice? *(Pease tick below)*

YES	NO

14 It is normal to have various sensations on and around the penis and vagina, especially after energetic lovemaking but did you feel something different that you do not feel with your usual condom? *(Pease tick below, multiple answers are accepted)*

Nothing different	Itch	Burning sensation	Prickle
Nothing different	Itch	Burning sensation	Prickle

15 What did you most notice about this condom? *(Pease tick below, multiple answers are accepted)*

Heat transfer	Natural feeling	Thinness	Odourless	Comfort	Sensation
Heat transfer	Natural feeling	Thinness	Odourless	Comfort	Sensation

Please use this area for notes

Annex G
(informative)

CRF — Adverse event (sample)

Time Began: _____ Time Ended: _____ Interview Length: _____

Interviewer's Initials: _____ Date: _____

- **If an individual reaches you directly:** "What is your name? _____ (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 an individual left you a message:** "May I speak to _____ (Name)? This is _____ from _____. You are participating in a study with the Group. 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 (skip to 10)

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?”

_____

Example interviewer response:

“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 in-house evaluation of condoms returned by study subjects after a tear or break during use. Figure H.2 and Figure H.3 give detailed step-by-step procedures.

H.2 Disinfection of returned used condoms

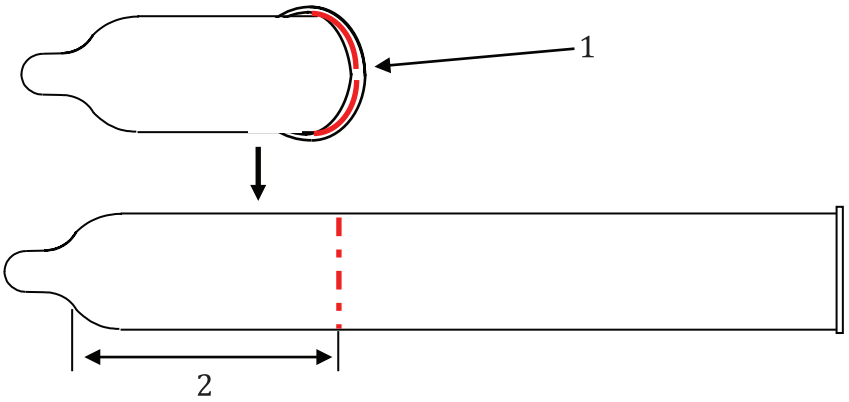
WARNING — This study requires direct contact with condoms that might be contaminated with infectious microbes. To reduce the risk of an infectious accident, it is strongly recommended that the operator wear surgical or exam gloves, safety glasses and a laboratory coat whenever handling the used condom.

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, then 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).

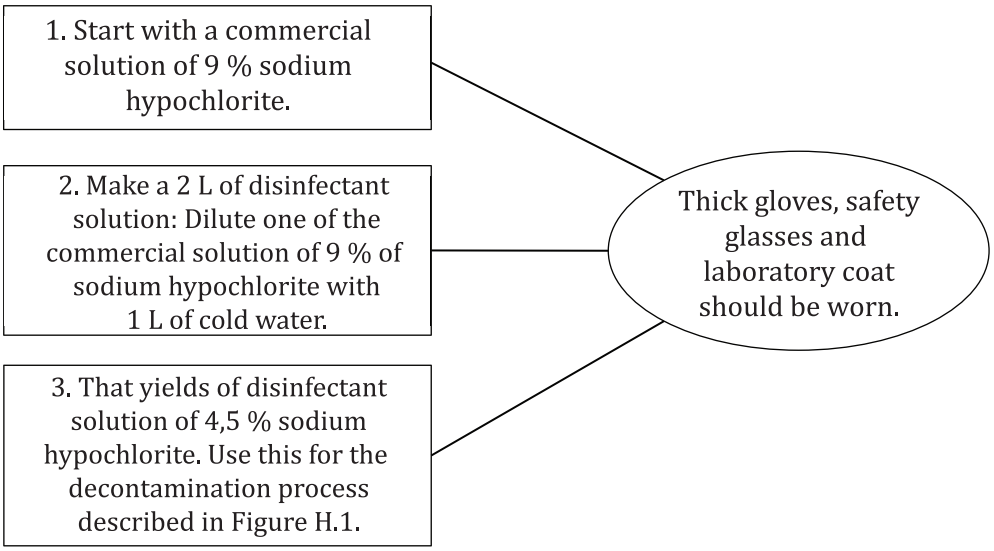


Figure H.2 — Preparation of the disinfectant solution (4,5 % sodium hypochlorite)

Instructions:

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

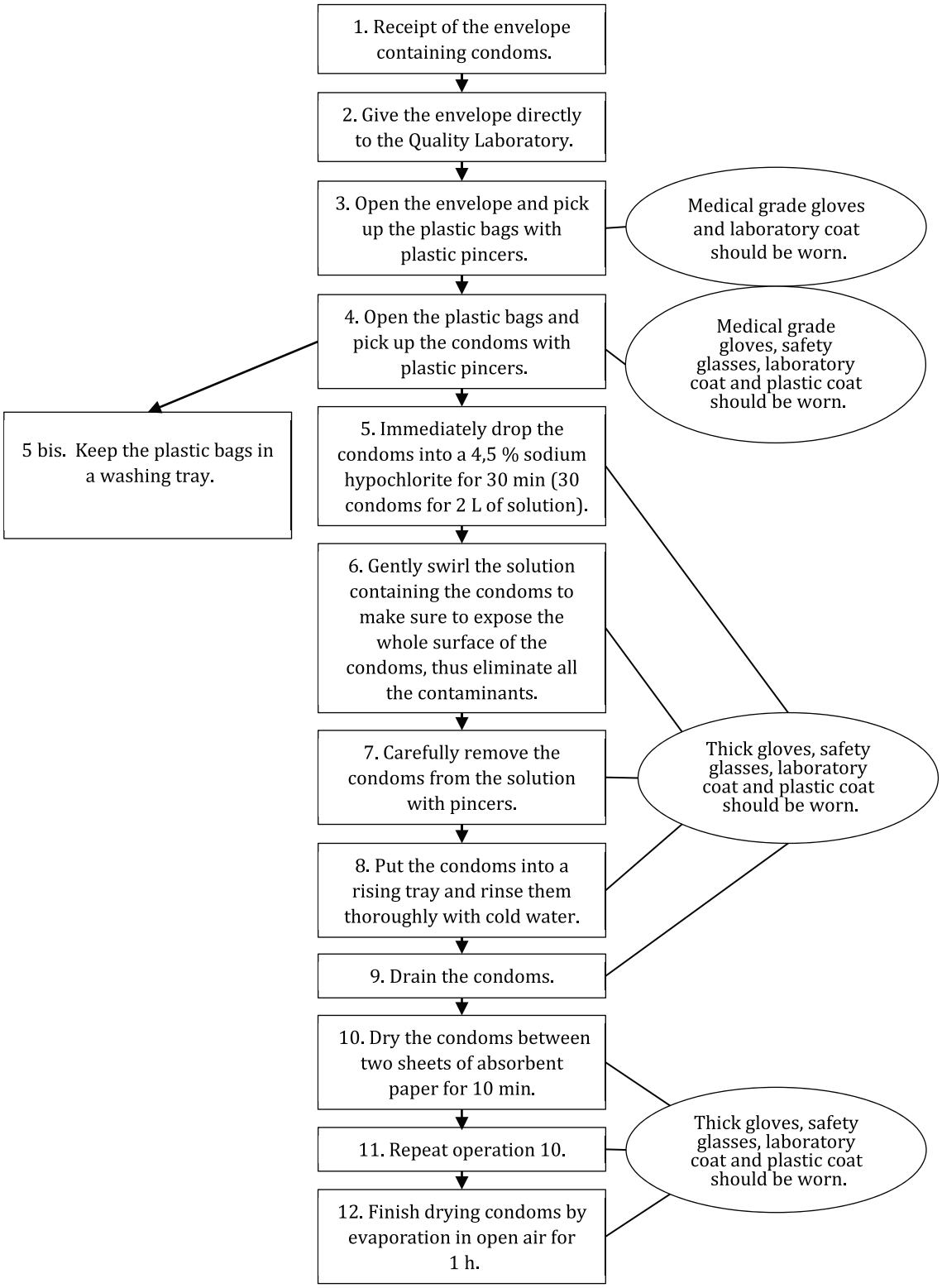
b) The dilutes 4,5 % solution, if free from protein, can be stored for 1 week at room temperature.

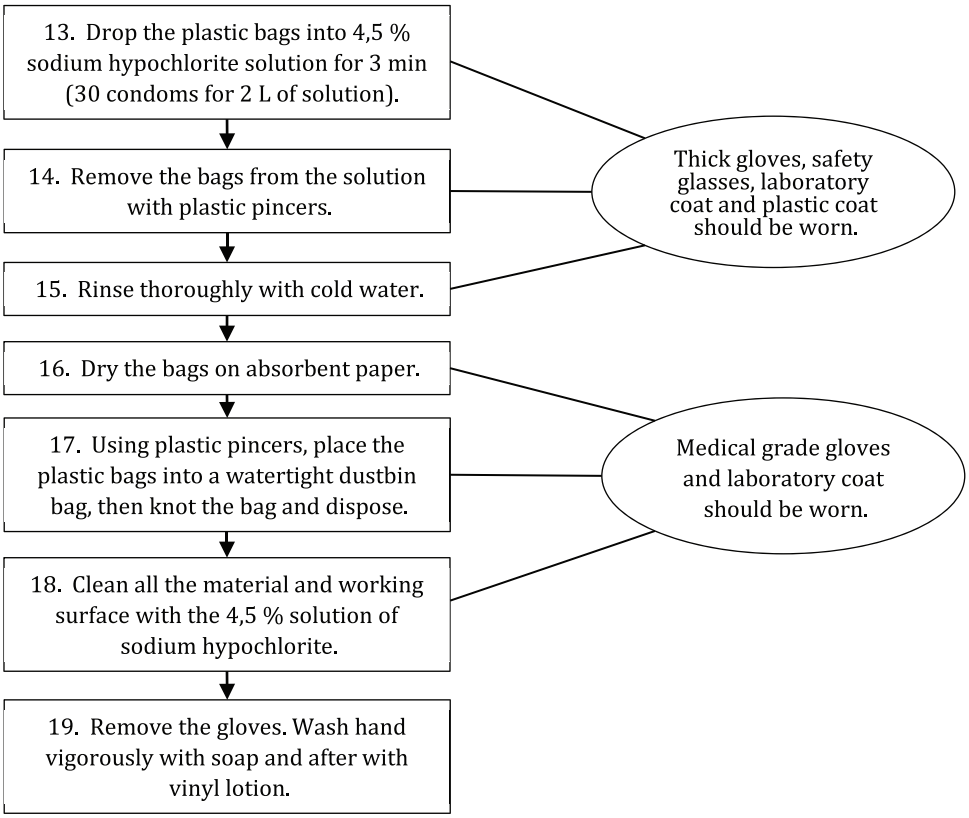
c) Properly disposed of diluted solution after its use to disinfect a condom sample.

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.

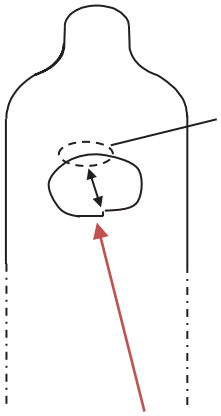
H.3.2 Make sketches or take photos of the sample especially the torn parts.

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.

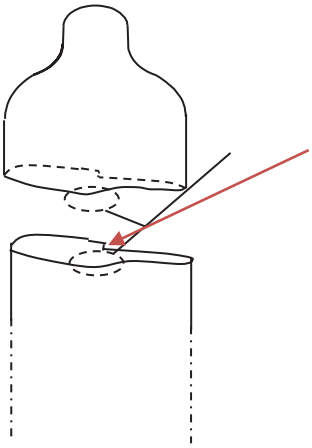
In the image below, ◌ and ✹ indicate the starting point of the tear. The red arrow indicates a gap.



Circular tear

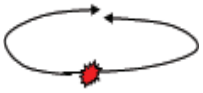
The starting point of the circular tear is often determined at the diagonal line ↕, in the highlighted area.

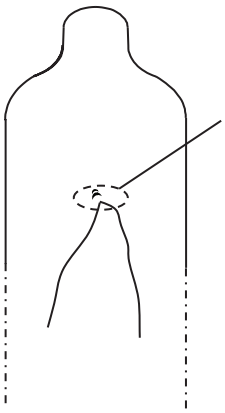
If a gap is observed on the circular tear portion, the starting point of the tear is often determined at the opposite side of the gap.



Split tear

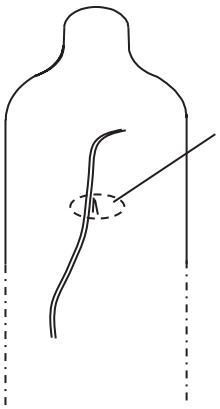
The starting point of the tear is often determined at the opposite side (to that of a circular tear) in the highlighted area.





V shape tear

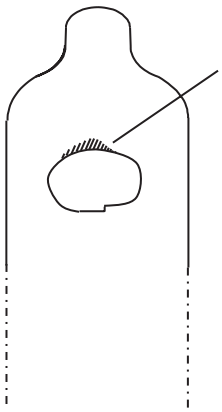
The starting point is often found at the close end of V.



Crack tear

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

H.3.3.2 Examples of the starting point/tear.



Transformation

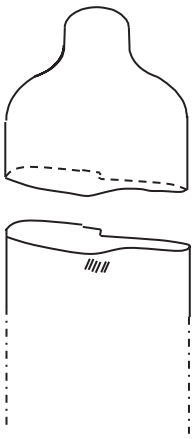
The film elongated and tore due to the load exceeding the strength limit. Possible reasons are as follows.

a) The 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.



Scratch

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

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

b) The user scratches the condom with her/his 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 [22]. 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;

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

NOTE See Reference [23] 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.

Bibliography

General principles

[1] ASTM D7661, *Standard test method for determining compatibility of personal lubricants with natural rubber latex condoms*

[2] Steiner M., Trussell J., Glover L., Joanis C., Spruyt A., Dorflinger L. Standardized protocols for condom breakage and slippage trials: a proposal. *Am. J. Public Health*. 1994, **84** (12) pp. 1897–1900

[3] Blackwelder W.C. Proving the null hypothesis in clinical trials. Control. Clin. Trials. 1982, **3** (4) pp. 345–353

[4] *Computerized systems used in clinical investigations — Guidance for industry* (US Food & Drug, Might 2007). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf

[5] Liang K.-Y., & Zeger S.L. Longitudinal data analysis using generalized linear models. Biometrika. 1986, **73** (1) pp. 13–22

[6] Taylor D.J., & Dominik R.C. Non-inferiority testing in crossover trials with correlated binary outcomes and small event proportions with applications to the analysis of condom failure data. *J. Biopharm. Stat*. 1999, **9** (2) pp. 367–377

[7] Steiner M.J., Lovvorn A.E., Schulz K.F. Bogus participation in clinical trials. *JAMA*. 2001, **285** (3) p. 293

[8] Taylor D.J. Issues in the design, analysis, and interpretation of condom functionality studies. *Contraception*. 2009, **80** (3) pp. 237–244

[9] *Good clinical practice* (ICH-E6) and *Statistical principles for clinical trials* (ICH-E9) available at http://www.ich.org

[10] Schulz K.F., Altman D.G., Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010, **340** p. c332

[11] *Research ethics committees: Basic concepts for capacity-building;* WHO 2009. http://www.who.int/eth/Ethics_basic_concepts_ENG.pdf

[12] *Ethical challenges in study design and informed consent for health research in resource-poor settings*/ Patricia A. Marshall. "TDR/SDR/SEB/ST/07.1"; WHO 2007 http://www.who.int/tdr/publications/tdr-research-publications/ethical-challenges-study-design/en/

Condom studies, selection and recall bias

[13] Graham C.A., Catania J.A., Brand R., Duong T., Canchola J.A. Recalling sexual behavior: a methodological analysis of memory recall bias via interview using the diary as the gold standard. J. Sex Res. 2003, **40** (4) pp. 325–332

[14] Minnis A.M., Steiner M.J., Gallo M.F., Warner L., Hobbs M.M., van der Straten A. Biomarker validation of reports of recent sexual activity: results of a randomized controlled study in Zimbabwe. *Am. J. Epidemiol*. 2009, **170** (7) pp. 918–924

[15] Schroder K.E., Carey M.P., Vanable P.A. Methodological challenges in research on sexual risk behavior: II. Accuracy of self-reports. *Ann. Behav. Med*. 2003, **26** (2) pp. 104–123

Condom studies of breakage and slippage, results

The following is a partial list of published articles in peer-reviewed journals describing good quality studies designed to measure condom slippage and breakage rates.

[16] Callahan M., Mauck C., Taylor D., Frezieres R., Walsh T., Martens M. Comparative evaluation of three Tactylon(TM) condoms and a latex condom during vaginal intercourse: breakage and slippage. *Contraception*. 2000, **61** (3) pp. 205–215

[17] Cook L., Nanda K., Taylor D. Randomized crossover trial comparing the eZ.on plastic condom and a latex condom. *Contraception*. 2001, **63** (1) pp. 25–31

[18] Frezieres R.G., Walsh T.L., Nelson A.L., Clark V.A., Coulson A.H. Breakage and acceptability of a polyurethane condom: a randomized, controlled study. *Fam. Plann. Perspect*. 1998, **30** (2) pp. 73–78

[19] Frezieres R.G., Walsh T.L., Nelson A.L., Clark V.A., Coulson A.H. Evaluation of the efficacy of a polyurethane condom: results from a randomized, controlled clinical trial. *Fam. Plann. Perspect*. 1999, **31** (2) pp. 81–87

[20] Potter W.D., & de Villemeur M. Clinical breakage, slippage and acceptability of a new commercial polyurethane condom: a randomized, controlled study. *Contraception*. 2003, **68** (1) pp. 39–45

[21] Steiner M.J., Dominik R., Rountree R.W., Nanda K., Dorflinger L.J. Contraceptive effectiveness of a polyurethane condom and a latex condom: a randomized controlled trial. *Obstet. Gynecol*. 2003, **101** (3) pp. 539–547

Evaluation of broken condoms

[22] Gerofi J., Shelley G., Donovan B. A study of the relationship between tensile testing of condoms and breakage in use. *Contraception*. 1991, **43** (2) pp. 177–178

[23] White N.D., Hill D.M., Bodemeier S. Male condoms that break in use do so mostly by a "blunt puncture" mechanism. *Contraception*. 2008, **77** (5) pp. 360–365

Relevant ISO standards for guidance

[24] ISO 4074:2015, *Natural rubber latex male condoms — Requirements and test methods*

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

[28] ISO 23409:2011, *Male condoms — Requirements and test methods for condoms made from synthetic materials*

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