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Copper-bearing intrauterine contraceptive devices — Guidance on the design, execution, analysis and interpretation of clinical studies

Dispositif intra-utérin au cuivre à but contraceptif — Recommandations relatives à la méthodologie, la réalisation, l'analyse et l'interprétation des résultats des études cliniques

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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*.

Introduction

This clinical study guidance is intended to help in the design, execution, analysis, and interpretation of clinical studies conducted in accordance with the requirements of ISO 7439.

Intrauterine devices (IUD) are highly effective at preventing pregnancy. A new device aims at maintaining or improving the efficacy of intrauterine contraception and/or reducing the side effects associated with IUDs, such as excessive menstrual bleeding. Trials evaluating new or modified IUDs should be conducted to the highest standards and this guidance will help those preparing for an IUD trial.

This guidance is based on the structure and content of a clinical investigation plan (CIP) as described in ISO 14155 to assist in the writing of a CIP and includes sections of the CIP that are of special relevance to IUD trials.

This guidance also draws on the experience gained in preparing the Cochrane systematic review of trials of copper-containing IUDs, which has been used to inform the updating of the WHO/UNFPA Specification for TCu380A IUD.

It is important that persons designing, running, and analysing clinical studies of new IUDs are familiar with all relevant standards for research designed to protect the rights, safety and well-being of human subjects.

This guidance should be read in conjunction with ISO 14155.

Clinical studies are also subject to local regulations and, in most countries, require prior approval from the local regulatory body.

Copper-bearing intrauterine contraceptive devices — Guidance on the design, execution, analysis and interpretation of clinical studies

1 Scope

This document provides guidance on the design and conduct of clinical studies to determine the performance characteristics of new intrauterine devices. It also provides advice on the analysis of data when the study is completed, as well as interpretation of these results by manufacturers, researchers and regulatory bodies.

It is intended to ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results, and to assist sponsors, monitors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

Certain clinical trial concerns are not addressed in this document, including subject compensation, confidentiality of subjects and their records, use of local ethics committees, etc. These and many other clinical trial design issues are covered in great 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:

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

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

3.1
adverse device effect
ADE
adverse event (3.2) related to the use of a *medical device* (3.27)

Note 1 to entry: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any *malfunction* (3.26) of the medical device.

Note 2 to entry: This includes any event that is a result of a use error or intentional misuse.

3.2
adverse event
AE
any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in *subjects* (3.35), users or other persons whether or not related to the *investigational device* (3.25)

Note 1 to entry: This includes events related to the investigational device or the *comparator* (3.10).

Note 2 to entry: This includes events related to the procedures involved.

Note 3 to entry: For users or other persons, this is restricted to events related to the investigational device.

3.3
audit
systematic examination of *clinical investigation* (3.6) related activities and documents performed by an independent entity not involved in the conduct of the clinical investigation

Note 1 to entry: The examination will determine whether the clinical investigation related activities were conducted, and the data were recorded, analysed and accurately reported, according to the *clinical investigation plan* (3.7), standard operating procedures, this document and applicable regulatory requirements.

3.4
blinding/masking
procedure in which one or more parties to the *clinical investigation* (3.6) are kept unaware of the treatment assignment(s)

Note 1 to entry: Single-blinding usually refers to the *subject(s)* (3.35) being unaware of the treatment assignment(s). Double-blinding usually refers to the subject(s), clinical investigator(s), monitor, and, in some cases, centralized assessors being unaware of the treatment assignment(s).

3.5
case report form
CRF
set of printed, optical or electronic documents for each *subject* (3.35) on which information to be reported to the *sponsor* (3.34) is recorded as required by the CIP

Note 1 to entry: There may be more than one case report form per subject.

3.6
clinical investigation
systematic investigation in or on one or more human *subjects* (3.35), undertaken to assess the safety and/or efficacy of a *medical device* (3.27)

Note 1 to entry: "Clinical trial" or "clinical study" are synonymous with "clinical investigation".

3.7
clinical investigation plan
CIP
document that states the rationale, *objectives* (3.28), design and proposed analysis, methodology, monitoring, conduct and record-keeping of the *clinical investigation* (3.6)

Note 1 to entry: The term "protocol" is synonymous to "CIP". However, protocol has many different meanings, some not related to clinical investigations, and these can differ from country to country. Therefore, the term CIP is used in this document.

3.8
clinical investigation report
written document summarizing the design, execution, statistical analysis and results of a *clinical investigation* (3.6)

3.9
clinical performance
behaviour of a *medical device* (3.27) and/or the response of the *subject* (3.35) to that medical device in relation to its intended use when correctly applied to appropriate subjects

3.10
comparator
medical device (3.27), therapy (e.g. active control), placebo or no treatment, used in the reference group in a *clinical investigation* (3.6)

3.11
deviation
instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP

3.12
ectopic pregnancy
pregnancy located outside the uterine cavity

3.13
primary end point
indicator to assess the primary *hypothesis* (3.17) of a *clinical investigation* (3.6)

Note 1 to entry: There might be more than one primary end point.

3.14
secondary end point
indicator to assess the secondary *hypotheses* (3.17) of a *clinical investigation* (3.6)

Note 1 to entry: There might be more than one secondary end point.

3.15
ethics committee
EC
independent body whose responsibility is to review *clinical investigations* (3.6), protocols and procedures in order to protect the rights, safety and well-being of human *subjects* (3.35) participating in a clinical investigation

Note 1 to entry: For the purposes of this document, "ethics committee" is synonymous with "research ethics committee", "independent ethics committee", or "institutional review board". The regulatory requirements pertaining to ethics committees or similar institutions can differ by country or region.

3.16
expulsion
inadvertent movement of the IUD into or from the vagina, including partial expulsion, requiring removal of the IUD from the cervix

3.17
hypothesis
testable biostatistical statement, derived from the study *objective* (3.28), for evaluating the *investigational device* (3.25) safety and/or performance

Note 1 to entry: The hypothesis is used to design the *clinical investigation* (3.6) and stipulates the statistic(s) used to accept or reject the results of the clinical investigation.

Note 2 to entry: The primary hypothesis is the determinant of the investigational device safety and/or performance parameters and is usually used to calculate the sample size. Secondary hypotheses concerning other points of interest can also be evaluated.

3.18
independent party
party not involved in the conduct of a *clinical investigation* (3.6), except for their specifically assigned responsibilities in order to avoid bias or a conflict of interest

3.19
informed consent process
process by which an individual is asked to voluntarily participate in a *clinical investigation* (3.6) having been provided with information about the clinical investigation

Note 1 to entry: Informed consent is documented by means of a written, signed and dated informed consent form.

3.20
intrauterine pregnancy
normally sited pregnancy within the uterine cavity

3.21
insertion instrument
instrument designed to place an IUD in the uterine cavity

3.22
intrauterine contraceptive device
IUD
device placed in the uterine cavity for the purpose of preventing pregnancy

Note 1 to entry: The abbreviation IUCD may be used in some publications.

3.23
investigator
any individual member of the *investigation site* (3.24) team designated and supervised by the principal investigator at an investigation site to perform critical clinical investigation-related procedures and/or to make important clinical investigation-related decisions

Note 1 to entry: An individual member of the investigation site team can also be called "sub-investigator" or "co-investigator".

3.24
investigation site
institution or site where the *clinical investigation* (3.6) is carried out

Note 1 to entry: For the purpose of this document, "investigation site" is synonymous with "investigation centre".

3.25
investigational device
medical device (3.27) being assessed for safety and performance in a *clinical investigation* (3.6)

Note 1 to entry: This includes marketed medical devices that are being evaluated for new intended uses, new populations, new materials or design changes.

3.26
malfunction
failure of a device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP

3.27
medical device
any instrument, apparatus, implement, machine, appliance, implant, software, material, or other similar or related article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury,

— investigation, replacement, modification, or support of the anatomy or of a physiological process,

— supporting or sustaining life,

— control of conception,

— disinfection of medical devices, and

— providing information for medical purposes by means of in vitro examination of specimens derived from the human body

and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

3.28
objective
major purpose(s) for conducting the *clinical investigation* (3.6)

3.29
perforation
puncture of the uterus, as may be caused by a uterine sound or insertion tube or by an *intrauterine contraceptive device* (3.22)

3.30
point of enrolment
date at which, following *recruitment* (3.31) and signing and dating the informed consent form, a *subject* (3.35) is enrolled in a study

3.31
recruitment
active efforts to identify *subjects* (3.35) who might be suitable for enrolment into the *clinical investigation* (3.6)

3.32
serious adverse device effect
SADE
adverse device effect (3.1) that has resulted in any of the consequences characteristic of a *serious adverse event* (3.33)

3.33
serious adverse event
SAE
adverse event (3.2) that

a) led to a death,

b) led to a serious deterioration in the health of the *subject* (3.35) that

- resulted in a life-threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function,
- required in-patient hospitalization or prolongation of existing hospitalization,
- resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or

c) led to foetal distress, foetal death or a congenital abnormality or birth defect

Note 1 to entry: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be a serious adverse event.

3.34
sponsor
individual or organization taking responsibility and liability for the initiation and/or implementation of a *clinical investigation* (3.6)

Note 1 to entry: When an *investigator* (3.23) initiates, implements and takes full responsibility for the clinical investigation, the investigator also assumes the role of the sponsor and is identified as the sponsor-investigator.

3.35
subject
individual who participates in a *clinical investigation* (3.6)

Note 1 to entry: A subject can be either a healthy volunteer or a patient.

3.36
thread
attachment to an IUD for the purpose of verifying the presence of and enabling the removal of the IUD

Note 1 to entry: The thread is intended to lie in the cervical canal and the vagina when the body of the device is placed correctly in the uterine cavity.

3.37
unanticipated serious adverse device effect
USADE
serious adverse device effect (3.32) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

Note 1 to entry: There should be a distinction in the report between anticipated and unanticipated serious adverse device effects.

4 Planning an IUD trial — Good clinical practice

ISO 14155 addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes.

The principles set forth in ISO 14155 should apply to all trials conducted on IUDs. ISO 14155 specifies general requirements intended to protect the rights, safety and well-being of human subjects and ensure the scientific conduct of the clinical investigation and the credibility of the results. It defines the responsibilities of the sponsor and principal investigator, and assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

5 Ethics

5.1 General

Clinical investigations should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki[24]. This protects the rights, safety and well-being of clinical investigation subjects, which are the most important considerations and are required by the Declaration to prevail over interests of science and society. This should be understood, observed, and applied at every step in the clinical investigation.

5.2 Ethics of IUD trials

Trials of a new IUD are justified if they are likely to demonstrate improved performance, whether by improving efficacy, reducing side-effects or improved bleeding pattern, or potentially reducing costs when compared to standard IUDs such as TCu380A.

5.3 Informed consent

5.3.1 General

Informed consent should be obtained in writing and documented before any procedure specific to the clinical investigation is applied to a subject. The informed consent form consists of an information form and an informed consent signature form.

5.3.2 Process of obtaining informed consent

The procedures specified in ISO 14155 should be followed when obtaining informed consent.

5.3.3 Information to be provided to the subject

The procedures relating to information to be provided to the subject specified in ISO 14155 should be followed. The risks relating to pregnancy should be clearly pointed out.

The procedures specified in ISO 14155 should be followed when obtaining informed consent signature. The subject's signature should be obtained before enrolling into the study and an IUD is inserted.

6 Identification and description of the investigational device

The CIP should contain:

a) a summary description of the intrauterine device and its intended purpose;

b) the manufacturer of the device;

c) the model or type name and/or number and accessories, if any, to permit full identification;

d) a description as to how traceability will be achieved during and after the clinical investigation, for example, assignment of lot numbers, batch numbers, or serial numbers;

e) the intended purpose of the intrauterine device in the proposed clinical investigation. If purposes other than contraception are intended, these should be described;

f) the populations and indications for which the intrauterine device is intended when in general use;

g) a description of the intrauterine device including any materials that will be in contact with tissues or body fluids;

h) instructions for insertion and use of the IUD including any necessary storage and handling requirements, preparation for use and any precautions to be taken after use, e.g. disposal;

i) a summary of necessary training and experience needed for the use of the IUD;

j) a description of the necessary medical or surgical procedures involved in the use of the investigational device.

7 Preliminary investigations and justification for the design of the clinical investigation

7.1 Literature review

Although the clinical requirements for copper bearing IUDs are specified in ISO 7439, it is nevertheless recommended that a literature review is undertaken during the planning stage for any clinical trials on IUDs.

The CIP should contain:

a) the conclusions of a critical review of the relevant scientific literature and/or unpublished data and reports;

b) a list of the literature reviewed.

The conclusions from this literature review may impact on the design of the proposed clinical investigations. The review should be relevant to the intended purpose of the IUD and the proposed

method of use. It should also help in the identification of relevant end-points and confounding factors that should be considered, and the choice and justification of comparator(s).

7.2 Preclinical testing

The CIP should contain a summary of the relevant preclinical testing that has been performed on the IUD to justify its use in human subjects, together with an evaluation of the results of such testing.

7.3 Previous clinical experience

The CIP should contain:

a) a summary of the results from previous clinical investigations and clinical usage, if any, that are relevant to the proposed clinical investigation;

b) relevant experience, if any, with the IUD, or medical devices with similar features, including that relating to other indications for use of the IUD;

c) an analysis of adverse device effects and any history of modification or recall.

7.4 Investigational device and clinical investigation risks and benefits

The CIP should contain:

a) anticipated clinical benefits;

b) residual risks associated with the IUD, as identified in the risk analysis report;

c) risks associated with participation in the clinical investigation;

d) anticipated adverse device effects;

e) possible interactions with concomitant medical treatments;

f) steps that will be taken to control or mitigate the risks;

g) risk/benefit rationale.

NOTE The risk management process, which includes risk analysis, risk/benefit assessment and risk control, is described in ISO 14971.

8 Objectives and hypotheses of the clinical investigation

The CIP should contain:

a) Claims and intended performance of the IUD that are to be verified

ISO 7439 describes three requirements that the IUD will be judged against:

1) the upper limit of the 95 % two-sided confidence interval for the one-year pregnancy rate computed using life table methods (ISO 7439 specifies ≤ 2 %);

2) one-year expulsion rates computed using life table methods (ISO 7439 specifies ≤ 10 %);

3) one-year discontinuation rates for clinical reasons computed using life table methods (ISO 7439 specifies ≤ 35 %).

NOTE 1 Regulatory bodies from some countries can require analysis of the clinical data in more than one way in order to evaluate outcomes of interest in different ways. For instance, besides the requirement for life table analysis, referenced above, a regulatory body can require a primary analysis applying the Kaplan Meier statistic. The regulatory body can additionally ask that the cumulative Pearl Index be calculated. See Bibliography for additional information on the use of these various statistics[16][17][18].

NOTE 2 Typically, the life table analysis is used to evaluate each individual year of use, as well as evaluating the full duration of use covered by the entire study.

NOTE 3 There can be subsets from the data analysis where the limits cited above can be exceeded.

b) Risks and anticipated adverse device effects that are to be assessed

See 9.1 c) below.

NOTE 4 When analysing the outcome of the study, it is useful to report results for specific subsets of the population such as nulliparous subjects.

When calculating discontinuation rates, the discontinuations should be device related only.

9 Design of the clinical investigation

9.1 General

The scientific integrity of, and the validity of, the data from the clinical investigation depend substantially on its design.

The CIP should contain the following.

a) A description of the type of clinical investigation to be performed (e.g. comparative, blinded, parallel design, without a comparator group) with rationale for the choice.

ISO 7439 requires that contraceptive efficacy rates should be determined in a randomized trial using TCu380A, if possible, as a comparator device. If not, another IUD with a well-established pregnancy rate that complies with the requirements in ISO 7439:2015, 4.2, shall be used as the comparator.

NOTE 1 The comparator arm using TCu380A is included in the trial to confirm that no bias is introduced due to the study methodology and/or the population using the index device. This can be demonstrated if an average of 360 women in the comparator arm are followed during the first year of use.

b) A description of the measures to be taken to minimize or avoid bias, including randomization and blinding/masking. Specifically,

1) a true randomization schedule should be used, and

2) as far as is practical, it is recommended that the type of device should be masked to the participants, those providing the care at follow-up, and those doing the analysis.

NOTE 2 Depending on the study design, masking is not necessary.

c) The primary and secondary end points

1) The primary end points for IUD studies are:

i) the upper 95 % confidence level, two-sided confidence interval for the one-year pregnancy;

ii) rate computed using life table methods;

iii) the one-year expulsion rate computed using life table methods;

iv) the one-year discontinuation rate computed using life table methods.

2) Recommended secondary end points are as follows. A rationale should be included for any additions or deletions to the list:

i) ectopic pregnancies;

ii) all pregnancies;

iii) expulsions;

iv) uterine or cervical perforations (if perforation occurs at the time of insertion, then the subject should be excluded from the efficacy evaluation. Depending upon the cause of the perforation, it may be recorded as an adverse event);

v) removals due to bleeding;

vi) removals due to pain;

vii) removals due to both bleeding and pain;

viii) total removals for bleeding and/or pain;

ix) removals due to pelvic inflammatory disease;

x) removals for other medical reasons;

xi) total medical removals;

xii) removals for planned pregnancy;

xiii) removals for other personal reasons;

xiv) total removals for personal reasons;

xv) removals at clinical investigator's discretion;

xvi) total discontinuation rate;

xvii) continuation rate;

xviii) loss to follow up.

3) Data on the following parameters should be collected:

i) effects on bleeding pattern;

ii) in case a pregnancy occurs with an IUD *in situ*, the outcome of this pregnancy;

iii) other side effects;

iv) complications during removal, e.g. severe pain, broken IUD, broken thread hospitalization.

4) Additional data that may be collected include:

i) fertility rates 1 year following the removal of the IUD, in women who desire pregnancy;

ii) menstrual pattern after IUD removal;

iii) cumulative pregnancy rates for each year of use;

iv) IUD continuation rates for each year;

v) endometrial changes due to the IUD.

d) The methods and timing for assessing, recording, and analysing variables

Assessment should occur at the scheduled follow-up visits after first menses, 3, 6 and 12 months after insertion and yearly thereafter, at other attendances for subjects experiencing problems with the device and at discontinuation from the study.

Table 1 provides standard descriptions of the primary and secondary outcomes, methods of diagnosis and advice on calculating the date of termination from the study required for the life table analysis. The date of termination for IUD removals is the date of removal, but certain conventions

are required for pregnancies, expulsions and perforations. Depending on the reason for the study termination, the time of study termination may be censored. For example, the data collected may indicate that pregnancy occurred between the month 6 and month 9 visits but not the precise date of conception. Consequently, statistical techniques for dealing with censored data may be required for a proper analysis.

e) Procedures for replacement of subjects, if any

Participants withdrawn from the study for whatever reason are not replaced.

f) Physical properties of IUDs after removal

Following the removal of an IUD, the following data should be collected if at all possible: amount of copper released (determined by removal and weighing of the copper components), tensile force (according to ISO 7439) and structural integrity (assessed by visual or SEM inspection).

Table 1 — Definitions, diagnosis and date of termination

Outcome	Definition	Diagnosis	Date of pregnancy determination
Intrauterine pregnancy	Normally sited pregnancy within uterine cavity	Positive pregnancy test with confirmed intrauterine pregnancy using ultrasound, histological tissue, or birth. Excludes "chemical" pregnancies in which a positive pregnancy test is not confirmed clinically	The date of conception, estimated from the best available information, is the date of pregnancy determination/study termination.
Ectopic pregnancies	Pregnancy located outside the uterine cavity	Confirmed pregnancy outside the uterine cavity, surgically or rarely by ultrasound and medical management	The date of conception, estimated from the best available information, is the date of pregnancy determination.
All pregnancies	Combined intrauterine and ectopic pregnancies		
Expulsions	Complete: expulsions into or from the vagina Partial: IUD partially in the uterine canal requiring removal from the cervix Both noticed and unnoticed by the wearer. Excludes those expulsions not noticed by the wearer that are associated with conception (classified as pregnancy) and expulsions during pregnancy	Clinical or ultrasound diagnosis	In complete expulsions, noticed by the wearer, the date on which the expulsion occurred is the date of termination. In cases of noticed and unnoticed partial expulsions, the date of the removal of the IUD is the date of pregnancy determination.
Removals due to bleeding related problems	Unacceptable excessive or irregular vaginal bleeding, scanty or absent bleeding	Self-reported	The date the IUD is removed is the date of study termination.

Table 1 *(continued)*

Outcome	Definition	Diagnosis	Date of pregnancy determination
Removals due to pain	Unacceptable pelvic pain, attributed to the correctly sited IUD by the wearer or the investigator (dysmenorrhea, cramps, and backache)	Self-reported	The date the IUD is removed is the date of study termination.
Removals due to bleeding and pain	Unacceptable pelvic pain and vaginal bleeding, as above	Self-reported	The date the IUD is removed is the date of study termination.
Total removals for bleeding and/or pain	Includes all removals for bleeding and/or pain reported together or separately, and attributed to the IUD by the wearer or the investigator	Self-reported	
Removals due to pelvic inflammatory disease	Pelvic inflammatory disease	Clinical or laparoscopic diagnosis	The date the IUD is removed is the date of study termination.
Perforations	IUD embedded in or passed through the uterine wall or cervix	Ultrasound/X-ray/ surgical	Date of diagnosis is the date of study termination.
Removals for other medical reasons	Includes removals because of physical complaints by user or partner attributed to the IUD, whether considered relevant by the investigator or not, and removals for treatment of concurrent conditions, even if apparently unrelated to the device Excludes removals after partial expulsion (classified as expulsion) and removals during pregnancy or after delivery (classified as pregnancy)		The date the IUD is removed is the date of study termination.
Total medical removals	Combined removals for all medical reasons		
Removals for planned pregnancy	Includes all removals requested by the wearer for the purpose of becoming pregnant	Self-reported	The date the IUD is removed is the date of study termination.
Removals for other personal reasons	Includes removals for nonmedical reasons, other than those classified as done at the investigator's choice, removals at the wearer's request without explanation, and removals because contraception is no longer needed. Excludes removals for planning pregnancy	Self-reported	The date the IUD is removed is the date of study termination.
Total removals for personal reasons	Combined removals for all personal reasons		
Total discontinuation rate	Combined removals for all reasons		
Continuation rate	Complement of the total discontinuation rate		

Table 1 *(continued)*

Outcome	Definition	Diagnosis	Date of pregnancy determination
Loss to follow up	Includes women three or more months overdue for a scheduled visit from whom no information was obtained by telephone, mail, electronically or home visit		The date of the last clinic visit or other contact is the date of study termination.
Effects on bleeding pattern	Bleeding: evidence of blood loss that requires the use of sanitary protection with a tampon, pad or pantyliner. Spotting: evidence of minimal blood loss that does not require new use of any type of sanitary protection, including pantyliners Episode of bleeding/spotting: bleeding/spotting days bounded on either end by 2 days of no bleeding or spotting	Self-declared Recorded on paper diary or electronically	
The outcome of pregnancy	All pregnancies conceived during use of the IUD or within 7 days after removal or recognized full expulsion of the IUD should be included in the calculation of pregnancy rates. Pregnancies in women in whom partial expulsion was identified (usually at the time of pregnancy diagnosis) should also be included. The exposure time used in calculating the pregnancy rate should include all exposures through removal or total expulsion of the IUD.		
Other side effects			
Complications during removal	e.g. severe pain, broken IUD, broken thread		

9.2 Investigational device(s) and comparator(s)

a) A description of the investigational device(s) and/or comparator(s), if used.

b) A justification of the choice of comparator(s).

ISO 7439 recommends that TCu380A be the comparator IUD. If TCu380A is not used as the comparator, another IUD with a well-established pregnancy rate should be used.

c) A list of any other medical device and/or medication to be used during insertion of the device and the ongoing clinical investigation that could impact on the outcome of the study (such device and/or medication would not form a third arm of the study).

During the investigation, side effects such as pain and bleeding thought to be caused by the test or comparator device can be treated medically.

9.3 Subjects

The CIP should include inclusion and exclusion criteria as listed below.

NOTE 1 Some inclusion and exclusion criteria might impact on study outcomes such as pregnancy and expulsion rates.

a) Inclusion criteria for subject selection

— Subjects: The study should include subjects similar to those for whom the device is intended. Recruited subjects should come from heterogeneous practice settings so as to include a diverse population of study participants.

— Age: Sufficient women under the age of 35 should be recruited to ensure the sample size criteria specified in 9.5 b) can be met.

NOTE 2 Enrolment of women under age 18 and over age 35, if possible, is encouraged to provide safety, efficacy, and tolerability data for these age groups. It is recommended that a cohort of premenopausal women over the age of 35 are included in the study and as many women as possible under the age of 18 are recruited.

NOTE 3 Women over the age of 35 are excluded from the primary analysis of pregnancy, expulsion and discontinuation rates when assessing conformance to ISO 7439. A secondary analysis of women over the age of 35 is conducted to look at pregnancy, expulsion and discontinuation rates in this older age group.

— Weight: Enrolment of some obese women should be encouraged for efficacy and safety data (Non-hormonal contraception is preferable for obese women, but it may be more difficult to insert an IUD in heavier women, especially very heavy women.).

— Parity: A sufficient number of nulliparous subjects should be enrolled to support efficacy and safety conclusions in this population.

— Sexual activity: Women in the study should be sexually active, and it might be necessary to specify a minimum frequency of sexual activity to prevent biasing the outcome of the study.

Some studies may include additional inclusion criteria. For examples, see Annex A. If the age, weight, and parity recommendations given above result in a subject group which does not reflect the demographics of the target population, then statistical techniques (such as weighted averages) should be used to compensate for the disparities.

b) Exclusion criteria for subject selection

The selected exclusion criteria should be listed. The WHO Medical Eligibility Criteria for Contraceptive Use lists conditions for which an IUD is inappropriate. See Annex A. This document may be used as a guide to determine the exclusion criteria.

NOTE 4 The WHO eligibility criteria are primarily based on clinical and safety considerations. Some can affect the study outcomes; for example, including post-partum women of less than 4 weeks might increase expulsion rates.

Some studies may include additional exclusion criteria, for example, if a specific design of IUD is only intended for a subset of the population.

c) Criteria and procedures for subject withdrawal or discontinuation

It is recommended that women who are more than 3 months overdue for an appointment should be dropped from the study and that their data should be censored at the last appointment they kept. For women who inform the investigator that they are withdrawing from the study, an effort should be made to hold a final appointment and to learn the reason for the withdrawal. Their data will then be censored based on the results of those efforts.

For further information, see Table 1.

d) The point of enrolment (as defined in 3.30)

e) Total expected duration of the clinical investigation

While the standard is set for performance in the first year of use, the duration of the clinical trial should be similar to the expected use of the IUD and should be for a minimum of 5 years.

f) Expected duration of each subject's participation (subjects are expected to remain in the study for 5 years of use or until the product is removed or lost due to one of the explanations given in Table 1)

g) The number of subjects required to be included in the clinical investigation

See 9.5.

h) The estimated time needed to include this number (i.e. enrolment period)

9.4 Procedures

The CIP should contain:

a) A description of all clinical investigation-related procedure(s) the subjects undergo during the clinical investigation

Timing of insertion: See Annex B on WHO advice on timing of insertion.

NOTE Advice is given, if appropriate, on any pain medication or prophylactic antibiotics that can be used at the time of insertion.

A full description of the insertion technique of the test and comparator devices should be provided.

Follow-up visits should be scheduled for after the first menses, at 3 months, 6 months, 12 months and then annually. Pelvic examination should be performed to confirm the presence of the IUD, for example. If practical, an ultrasound scan should be conducted at 3 months to accurately locate the position of the IUD. If the strings cannot be visualized at a clinic visit, ultrasound or X-rays should be used to confirm that the IUD is present.

Participants should be instructed to return to the clinic at any other time that they experience any other problem with the device, and should be free to return at any time and request removal.

All withdrawals from the trial, whether for pregnancy, side effects or other reasons, should be dated accurately and participants should be seen as soon as possible after the event.

In the event of a pregnancy, the date of conception and the outcome of the pregnancy should be determined.

In the event of a pregnancy detected within 3 months of withdrawal from the trial, the date of conception should be determined, by an ultrasound scan if possible, to confirm whether the pregnancy occurred with the device in situ.

b) A description of those activities performed by sponsor representatives (excluding monitoring)

c) Any known or foreseeable factors that might compromise outcomes or the interpretation of results

These can include, for example, subject baseline characteristics, concomitant medication, the use of other medical devices, or subject-related factors such as age, parity, weight/BMI, uterine fibroids, socioeconomic status, and educational level. The methods for addressing these factors in the clinical investigation, for example, by subject selection, clinical investigation design (such as stratified randomization) or by statistical analysis should be described.

The follow-up period during the clinical investigation should permit the demonstration of performance over a period of time sufficient to represent a realistic test of the performance of the investigational device and allow identification and assessment of any risks associated with adverse device effects over that period.

Describe whether concomitant barrier contraception is permitted routinely to prevent sexually transmitted infections. Barriers are encouraged for concomitant use with IUDs for the purpose of sexually transmitted infection prevention, but not for contraception. It is recognized that this could impact on the absolute rate. The participants should keep a record of condom use. Barrier use is not expected for routine use.

The CIP should address how pregnancy rates will be computed taking into account barrier contraceptive use. Both occasional and regular barrier contraceptive use need to be considered.

The CIP should specifically address what, if any, medical care for the subjects will be provided after the clinical investigation is completed.

9.5 Statistical considerations

a) Statistical design, method and the analytical procedures

Contraceptive efficacy rates should be determined in a monadic two-arm study design.

The test arm should be designed to determine the following primary end points:

1) the upper 95 % confidence level, two-sided confidence interval for the one-year pregnancy rate computed using life table methods;

2) the one-year expulsion rate computed using life table methods;

3) the one-year discontinuation rate computed using life table methods.

A randomized comparator arm should be included in the trial to confirm that no bias is introduced due to the study methodology and/or the population using the index device. ISO 7439 refers to an absolute pregnancy rate in the study device, i.e. independent of the performance of the comparator device. A single arm study that incorporates design, conduct and analysis proposed in the guidance (apart from randomization) will provide a broad picture of the IUD performance.

The TCu380A, if possible, should be used as the comparator device. If not, use another IUD conforming to ISO 7439 with a well-established pregnancy rate as the historical comparator. The results from the comparator arm should be compared to literature results for the same device to confirm that no bias has been introduced into the study by the choice of study population or study design.

The cut-off date for the analysis should be at least 3 months before the analysis is begun to make sure that no pregnancies are overlooked.

b) Sample size

Appropriate statistical methods should be used to calculate the sample size to ensure that the upper limit of the 95 % two-sided confidence interval for the one-year pregnancy rate computed using life table methods is ≤ 2 %, taking into account the expected outcome from the study, the nature of the population and the objectives of the study. All the assumptions used to arrive at the estimate should be recorded. Allowances should be made for loss to follow up and early removal of the device.

Power calculations, based on a level of significance of 95%, should be used to determining the sample size. A preliminary estimate of the rates for the primary end points is necessary for the calculation and the calculation will need to be run for each end point independently. The end point requiring the largest sample size will determine the final sample size for the investigation.

The power calculation for the comparator arm should be conducted independently of the power calculation for the treatment arm and can be based on the historical performance of the comparator device. The investigators should consider the implications of the importance of being close to the historical limits for the comparator device on the outcome of the study.

ISO 7439 specifies that any trial should include at least 20 000 woman months for the device under test.

NOTE 1 Assuming a true pregnancy rate of 1 % for TCu380A, the approximate 95 % level, two-sided confidence interval for the first year pregnancy rate would be 0,2 % to 2,7 %. Depending on the attrition rate in the study cohort, this could be achieved by enrolling between 450 and 500 women. Hence, the upper limit of the 95 %, two-sided confidence interval for the Tcu380A ought not to be greater than 2,7 %.

NOTE 2 A randomized controlled study designed as an equivalence trial with an average number of 720 and 360 women in each arm would declare as equivalent two devices with true pregnancy rates of 1 % if the difference in observed pregnancy rates was ≤ 2,1 %. Therefore, a study of this size will have very limited significance.

Randomized controlled trials are preferred because they can provide data of sufficient quality that can later be used in clinical practice and can be combined with other trials in meta-analysis, thereby reducing the size required for later studies.

c) Level of significance and the power of the clinical investigation

The level of significance for the trial is typically set at 5 % and the power 80 %.

d) Expected drop-out rates

When planning the trial, allowance should be made for the number of expected drop-outs. Drop-out rates in contraceptive efficacy trials can be high. Failure to recruit sufficient subjects can compromise the statistical power of a study.

e) Pass/fail criteria to be applied to the results of the clinical investigation

The statistical plan should include the pass/fail criteria that have been set for the trial. The appropriate statistical hypothesis should be detailed.

f) Provision for an interim analysis, where applicable

If applicable, any provisions made for an interim analysis should be included in the CIP. The need for an interim analysis should be justified along with any conditions that need to be met or which will trigger an interim analysis.

g) Criteria for the termination of the clinical investigation on statistical grounds

The statistical basis for any criteria to terminate the investigation should be detailed in the CIP.

h) Procedures for reporting any deviation(s) from the original statistical plan

The reporting procedures for reporting any deviations from the original statistical plan should be detailed in the CIP.

i) Specification of subgroups for analysis

Any subgroups selected to be subject to statistical analysis should be clearly identified in the CIP together with the justification for selecting these subgroups.

j) Procedures for accounting for all data

Verification procedures designed to ensure that all data are included in the analyses should be included in the CIP.

k) Treatment of missing, unused or spurious data, including drop-outs and withdrawals

Procedures for addressing missing, unused or spurious data, including drop-outs and withdrawals, should be included in the CIP.

l) A justification for excluding particular information from the testing of the hypothesis, if relevant

m) Procedures and reasons for excluding any information from inclusion in the statistics used for hypothesis testing should be included in the CIP along with any appropriate justification.

n) For multicentre clinical investigations, the maximum and minimum number of subjects per centre should be included in the CIP along with a justification for the numbers.

Special reasoning and sample size(s) might apply for the early clinical investigation(s), e.g. feasibility clinical investigation(s).

10 Adverse events, adverse device effects and non-medical complaints

The CIP should provide:

a) definitions of adverse events and adverse device effects;

See Table 1.

b) definitions of serious adverse events and serious adverse device effects and, where appropriate, unanticipated serious adverse device effects;

See Table 1.

c) list of foreseeable adverse events and anticipated adverse device effects, their likely incidence, mitigation and/or treatment.

NOTE The WHO Selected Practice Recommendations for Contraceptive Use[20] provides information on management for women experiencing menstrual abnormalities when using a copper-bearing IUD, and for the management of pelvic inflammatory disease.

11 Early termination or suspension of the clinical investigation

The CIP should describe:

a) criteria and arrangements for early termination or suspension of the clinical investigation for the whole clinical investigation or for one or more investigation sites;

b) criteria for access to and breaking the blinding/masking code for early termination or suspension of the clinical investigation, if the clinical investigation involves blinding/masking technique;

c) requirements for subject follow up.

12 Publication policy

It is highly desirable that all results of the clinical investigation should be offered for publication in scientific journals. It is accepted that submitted papers might not be accepted for publication and that submission of the results for publication is not required for compliance with this document.

The CIP should specify whether and under what conditions the results of the clinical investigation will be submitted for publication. It may be necessary to include the reasons for carrying out a clinical investigation and the subsequent results in a public database.

