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Mechanical contraceptives — Guidance for clinical evaluation of intra-uterine contraceptive devices (IUDs)

Contraceptifs mécaniques — Directives pour l'évaluation clinique des dispositifs contraceptifs intra-utérins

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 11249 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 requirements of ISO 7439:2011.

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 for a Clinical Investigation Plan (CIP) as described in ISO 14155. It is intended 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.

Mechanical contraceptives — Guidance for clinical evaluation of intra-uterine contraceptive devices (IUDs)

1 Scope

This International Standard 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 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 guidance 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

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 7439, *Copper-bearing contraceptive intrauterine devices — Requirements and tests*

ISO 10993-1:2003, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

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

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

ISO 15225, *Medical devices — Quality management — Medical device nomenclature data structure*

ISO/TR 16142, *Medical devices — Guidance on the selection of standards in support of recognized essential principles of safety and performance of medical devices*

ISO/TS 19218, *Medical devices — Coding structure for adverse event type and cause*

ICH E3, Structure and content of clinical study reports

ICH E6, Good clinical practice: Consolidated guideline

ICH E8, General considerations for clinical trials

ICH E9, Statistical principles for clinical trials

Evaluation of clinical data: A Guide for Manufacturers and Notified Bodies, MEDDEV. 2.7.1, April 2003

3 Terms and definitions

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

3.1
adverse device effect
ADE
adverse event related to the use of a medical device

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 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, users or other persons whether or not related to the investigational device

Note 1 to entry: This includes events related to the investigational device or the comparator.

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 related activities and documents performed by an independent entity not involved in the conduct of the clinical investigation to determine whether the clinical investigation related activities were conducted, and the data were recorded, analysed and accurately reported according to the clinical investigation plan, standard operating procedures, this International Standard and applicable regulatory requirements

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

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

3.5
case report form
CRFs
set of printed, optical or electronic documents for each subject on which information to be reported to the sponsor is recorded as required by the CIP. 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, undertaken to assess the safety and/or performance of a medical device

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, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation

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 International Standard.

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

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

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

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

3.12
ectopic pregnancies
pregnancy located outside the uterine cavity

3.13
end point <primary>
principal indicator to assess the primary hypothesis of a clinical investigation. There may be more than one primary end point

3.14
end point <secondary>
indicator to assess the secondary hypotheses of a clinical investigation. There may be more than one secondary end point

3.15
ethics committee
EC
independent body whose responsibility it is to review clinical investigations in order to protect the rights safety and well-being of human subjects participating in a clinical investigation

Note 1 to entry: For the purposes of this International Standard, "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 may differ by country or region.

3.16
expulsion
complete: expulsions into or from the vagina
partial: IUD partially in the uterine canal requiring removal from the cervix

3.17
hypothesis
testable statement, resulting from the objective, regarding the investigational device safety and/or performance that is used to design the clinical investigation and that can be accepted or rejected based on results of the clinical investigation and statistical calculations

Note 1 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
A party not involved in the conduct of a clinical investigation, 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 having been provided 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 uterine cavity

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

3.22
intra-uterine contraceptive device (IUD)
device placed in the uterine cavity for the purpose of preventing pregnancy. The abbreviation IUCD may be used in some publications

3.23
investigator
any individual member of the investigation site 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 is carried out

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

3.25
investigational device
medical device being assessed for safety and performance in a clinical investigation

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:

a) intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

    i. diagnosis, prevention, monitoring, treatment or alleviation of disease,

ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury,

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

iv. supporting or sustaining life,

v. control of conception,

vi. disinfection of medical devices, and

b) 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

3.29
point of enrolment
time at which, following recruitment, a subject signs and dates the informed consent form

3.30
recruitment
active efforts to identify subjects who may be suitable for enrolment into the clinical investigation

3.31
serious adverse device effect
SADE
adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

3.32
serious adverse event
SAE
adverse event that

c) led to a death,

d) led to a serious deterioration in the health of the subject that:

i. resulted in a life-threatening illness or injury, or

ii. resulted in a permanent impairment of a body structure or a body function, or

iii. required in-patient hospitalization or prolongation of existing hospitalization, or

iv. resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

e) 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.

3.33
sponsor
individual or organization taking responsibility and liability for the initiation and/or implementation of a clinical investigation

Note 1 to entry: When an investigator 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.

3.34
subject
individual who participates in a clinical investigation

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

3.35
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.

3.36
unanticipated serious adverse device effect
USADE
serious adverse device effect 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, ensure the scientific conduct of the clinical investigation and the credibility of the results, define 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

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

5.1 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.

5.2 Informed consent

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.

5.2.1 Process of obtaining informed consent

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

5.2.2 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.

a) Informed consent signature

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

6 Clinical Investigation Plan

Clinical Investigational Plan (CIP) is a document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation. The term "protocol" is synonymous to "Clinical Investigation Plan". However, protocol has many different meanings, some not related to clinical investigations, and these can differ from country to country. Therefore, the term Clinical Investigation Plan is used in this Guidance.

The CIP should be prepared using the guidance given in Annex A of ISO 14155.

7 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 shall 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.

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

8.1 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 should justify the design of the proposed clinical investigations described in Clause 10 below. The review should be relevant to the intended purpose of the IUD and the proposed method of use. It shall also help in the identification of relevant end-points and confounding factors that shall be considered, and the choice and justification of comparator(s).

8.2 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.

8.3 Previous clinical experience

The CIP should contain:

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.

8.4 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.

9 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:

i. the upper limit of the 95 % two-sided confidence interval for the one-year pregnancy rate computed using life table methods shall be ≤ 2 %;

ii. one-year expulsion rates computed using life table methods shall be ≤ 10 %;

iii. one-year discontinuation rates computed using life table methods shall be ≤ 35 %.

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

See 10.1 c) below.

NOTE 1 When analysing the outcome of the study it is useful to report results for specific subsets of the population such as nulliparous subjects.

NOTE 2 When calculating discontinuation rates, the discontinuations should be device related only

10 Design of the clinical investigation

10.1 General

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

The CIP should contain:

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

ISO 7439 requires that contraceptive efficacy rates should be determined in a randomized controlled trial using TCu380A, if possible, as the control device. If not, another IUD with a well-established pregnancy rate that complies with the requirements in Clause 4.2 of ISO 7439 should be used as the comparator (historical control).

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

i. a true randomization schedule should be used

ii. full allocation concealment should be ensured

iii. the type of device should be masked to the participants, those providing the care at follow-up, and those doing the analysis.

c) The primary and secondary end points, with rationale for their selection and measurement

The primary end point for an IUD study should be unintended intrauterine pregnancy. Primary statistical analysis should address the following:

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

ii. the one-year expulsion rate computed using life table methods; and

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

Secondary end points include:

i. ectopic pregnancies;

ii. all pregnancies;

iii. expulsions;

iv. uterine or cervical perforations;

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 choice;

xvi. total discontinuation rate;

xvii. continuation rate;

xviii. loss to follow up.

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.

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.

The following table provides standard definitions 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.

Table 1 — Definitions, diagnosis and date of termination

Outcome	Definition	Diagnosis	Date of study termination
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 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 termination.
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 termination.
Removals due to bleeding related problems	Unacceptable excessive or irregular vaginal bleeding, scanty or absent bleeding.	Self reported	The date the IUD is removed
Removals due to pain	Unacceptable pelvic pain, attributed to the correctly sited IUD by the wearer or the investigator (dysmenorrhea, cramps, arid backache).	Self reported	The date the IUD is removed
Removals due to bleeding and pain	Unacceptable pelvic pain and vaginal bleeding, as above	Self reported	The date the IUD is removed
Total 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
Perforations	IUD embedded in or passed through the uterine wall or cervix	Ultrasound/ X-Ray/Surgical	Date of diagnosis

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, structural integrity (assessed by visual or SEM inspection).

10.2 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 control IUD. If TCu380 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 the clinical investigation.

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

10.3 Subjects

The CIP should describe:

a) The 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: Enrolment of women under age 18 and over age 35 if possible is encouraged to provide safety, efficacy, and tolerability data in these ages.

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

Some studies may wish to include additional inclusion criteria. For examples, see Annex A.

b) The exclusion criteria for subject selection

The WHO Medical Eligibility Criteria for Contraceptive Use lists conditions for which an IUD is inappropriate. See Annex A.

c) Criteria and procedures for subject withdrawal or discontinuation

See Table 1.

d) The point of enrolment

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

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

See 10.5.

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

10.4 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.

   A full description of the insertion technique of the test and control 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.

   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, have to be dated accurately and participants should be seen as soon as possible after the event. See 10.1.

   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 needs to be determine by ultrasound scan to confirmation 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 may compromise outcomes or the interpretation of results.

   These may include, for example, subject baseline characteristics, concomitant medication, the use of other medical devices, or subject-related factors such as age, gender or lifestyle. 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 diseases. 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.

10.5 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:

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

ii. the one-year expulsion rate computed using life table methods

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

A randomized control arm should be included in the trial using the TCu380A, if possible, as the control device. If not, use another IUD with a well-established pregnancy rate as the historical control. The results from the control 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 shall be ≤ 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.

Any trial should include at least 1 600 women-years of exposure for the device under test.

The control arm using TCu380A 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. The standard refers to absolute pregnancy rate in the study device, i.e. is independent of the performance of the control 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. It will not, however, provide reliable evidence on how the new device compares to other IUDs and numerous biases could affect any comparison with historical or concurrent controls. The evidence would be of little value in clinical practice, as it would not assist in selecting the best device for a woman.

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 an IUD trial is typically set at 95 % (Type 1 error of 5 %) with a study power of 80 % (Type 2 error of 20 %).

d) expected drop-out rates,

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

f) provision for an interim analysis, where applicable,

g) criteria for the termination of the clinical investigation on statistical grounds,

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

i) specification of subgroups for analysis,

j) procedures for accounting for all data,

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

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

m) in multicentre clinical investigations, the minimum and maximum number of subjects to be included for each centre.

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

11 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 in 10.1 d).

b) Definitions of serious adverse events and serious adverse device effects and where appropriate unanticipated serious adverse device effects

   See Table 1 in 10.1 d).

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

The WHO *Selected Practice Recommendations for Contraceptive Use* (2004) provides recommended management for women experiencing menstrual abnormalities when using a copper-bearing IUD, and for the management of pelvic inflammatory disease.

12 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.

13 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 may not be accepted for publication.

The CIP should:

a) specify whether the results of the clinical investigation will be submitted for publication;

b) specify the conditions under which the results of the clinical investigation will be offered for publication.

In accordance with the national regulations the intent to carry out a clinical investigation, as well as the results thereof, may need to be entered in a public database.

Annex A
(informative)

Exclusion and inclusion criteria for IUD trials

This annex provides an example of possible exclusion criteria that should be applied to subjects being enrolled in IUD clinical trials and possible inclusion criteria for specific population groups.

The WHO *Medical Eligibility Criteria for Contraceptive Use* lists conditions for which an IUD is inappropriate. Fourth edition, 2010 (ISBN: 978 92 4 1563888) lists the following:

— pregnancy;

— postpartum 48 h to < 4 weeks;

— puerperal sepsis;

— Following second trimester abortion and post septic abortion;

— systemic lupus erythematosus (SLE) with severe thrombocytopenia;

— unexplained heavy vaginal bleeding (suspicious for serious condition) before evaluation;

— gestational trophoblastic disease with or without detectable elevated ß-hCG levels, or malignant disease;

— cervical cancer while awaiting treatment;

— endometrial cancer;

— ovarian cancer;

— uterine fibroids – with distortion of the uterine cavity;

— anatomical abnormalities – with distorted uterine cavity in a manner that is incompatible with IUD insertion or correct placement;

— current pelvic inflammatory disease;

— current sexually transmitted infections – current purulent cervicitis or chlamydial infection or gonorrhea or high risk of sexually transmitted infections;

— tuberculosis – pelvic;

— Has AIDs and is not on anti-retroviral therapy and is clinically unwell.

— Exclusive breast feeding amenorrhoea (LAM)

Inclusion criteria that may be considered

The WHO Medical Eligibility Criteria for Contraceptive Use lists conditions for which an IUD is appropriate. Fourth edition, 2010 (ISBN: 978 92 4 1563888) and can be considered

— Have or have not had children

— Are not married

— Are of any age including adolescents and women over 40

— Have just had an abortion or miscarriage (if no evidence of infection)

— Have had an ectopic pregnancy

— Have had pelvic inflammatory disease

— Have anaemia

— Are infected with HIV on antiretroviral therapy and doing well as long as risk of infection is monitored

— Women with known cardio vascular disease – as long as they are monitored

— Women with known diabetes – as long as they are monitored

Annex B
(informative)

Timing of insertion of IUD: When can an IUD be inserted?

The WHO *Selected Practice Recommendations for Contraceptive Use* 2004 provides advice on the when an IUD can be inserted.

Having menstrual cycles: A woman can have a copper-bearing IUD inserted any time within the first 12 days after the start of menstrual bleeding, at her convenience, not just during menstruation. No additional contraceptive protection is needed.

The copper-bearing IUD can also be inserted at any other time during the menstrual cycle, at her convenience, if it is reasonably certain that she is not pregnant. No additional contraceptive protection is needed.

Switching from another method: She can have the copper-bearing IUD inserted immediately, if it is reasonably certain that she is not pregnant. There is no need to wait for her next menstrual period. No additional contraceptive protection is needed.

Bibliography

[1] ISO 10993 (all parts), *Biological evaluation of medical devices*

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

[3] ISO 15223, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied*

[4] EN 1041, *Information supplied by the manufacturer of medical devices*

[5] Medical eligibility criteria for contraceptive use. 4th Ed World Health Organisation, Geneva 2009 available at: http://whqlibdoc.who.int/publications/2010/9789241563888_eng.pdf

[6] Selected practice recommendations for contraceptive use. 2nd Ed World Health Organisation, Geneva 2004 available at: http://whqlibdoc.who.int/publications/2004/9241562846.pdf

[7] Global Harmonization Task Force, Information Document Concerning the Definition of the Term Medical Device [SG1/N29R16:2005], available at: http://www.ghtf.org/documents/sg1/sg1n29r162005.pdf

[8] Global Harmonization Task Force. Clinical Evaluation [SG5/N2R8:2007] available at: http://www.ghtf.org/documents/sg5/sg5_n2r8_2007final.pdf

[9] Global Harmonization Task Force, Essential Principle of Safety and Performance of Medical Devices [SG1-N41R9:2005] available at: http://www.ghtf.org/documents/sg1/sg1n41r92005.pdf

[10] Declaration of Helsinki available at: http://www.wma.net/e/ethicsunit/helsinki.htm

[11] MEDDEV 2.7.1, Evaluation of clinical Data: A Guide for Manufacture and Notified Bodies, (2003) available at: http://ec.europa.eu/enterprise/medical_devices/meddev/2_7.pdf

[12] MEDDEV 2.12-1, Guidelines on a medical devices vigilance system, available at: http://ec.europa.eu/enterprise/medical_devices/meddev/2_12_1-rev_5-2007-fin2.pdf

[13] MEDDEV 2.12-2, Guidelines on post market clinical follow-up available at: http://ec.europa.eu/enterprise/medical_devices/meddev/2_12-2_05-2004.pdf

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