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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

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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).

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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.

