ISO 14155:2011 for Investigators

Medical Device Trials

Judith Köhnen, MSc, Labcorp Medical Device and Diagnostic Development

Introduction

The International Organization for Standardization (ISO) is an international standard-setting body composed of representatives from various national standards organizations. ISO is a voluntary organization whose members are recognized authorities on standards, each one representing one country. Most EU member states, the United States and Japan are members of the ISO network. ISO has no legal authority to enforce the standard's requirements unless it has been granted that authority in local laws/regulations. This process has been completed in some countries.

The ISO 14155:2011 is the equivalent of the ICH GCP for Investigational Medicinal Products — we can say it is the modern GCP for Investigational Medical Devices for human subjects.

In this booklet, you will find requirements described in the ISO 14155:2011. We strongly recommend complying with this information. In addition to this standard, you should also comply with your national regulations and legislation. These elements are not covered in this booklet.

The ISO 14155:2011 defines requirements to protect the rights, safety and well-being of human subjects; to ensure that the results of a clinical trial are credible; to confirm the scientific conduct of the clinical study; and to specify the responsibilities of the ethics committees, regulatory authorities and other bodies involved in the clinical trial as well as the responsibilities of the sponsor and the investigators.

Compliance with ISO 14155:2011 is an essential contribution to the overall trial success.

labcorp

Qualifications

As a principal investigator it is your responsibility to perform the daily duties of the clinical research trial and to ensure that the study data as well as the subjects' rights, well-being and safety are protected. This also includes their experiences and compliance with the informed consent process.

- To be qualified to act as an investigator, corresponding experience, education and training in the specific area of the applicable medical device are needed.
- Therefore, an actual and up-to-date curriculum vitae (CV) will be requested by the sponsor. The site staff should also be qualified to support the conduct of the clinical trial at the site.
- The CVs should cover the current position, the education, the medical/dental, and if applicable, surgical experience of the investigator in the specific field of the medical device.
- In addition, the CV, or other appropriate documentation, should confirm that the investigator has experiences with the conduct of clinical trials in accordance with ISO 14155:2011.
- The site should have sufficient capacities, which includes a team on-site that is qualified by proof of training and able to conduct the clinical investigation. Adequate facilities and equipment should be available as needed for the study conduct.

In addition to this, there should be no conflict of interest – including any financial interests – that may interfere with the conduct of the clinical trial and the interpretation of the clinical study results.

Referemce | ISO 14155:2011 | 8.2.4.3 Assessment of the investigation site, 9 Responsibilities of the principal investigator, 9.1 General, 9.2 Qualification of the principal investigator, 9.3 Qualification of investigation site, annex E

Regulatory/EC

All clinical studies should be conducted in accordance with ethical considerations. The Declaration for Helsinki, the ISO and other regulations protect the rights, safety and well-being of subjects. Compliance with those principles is one of the highest priorities when conducting clinical investigations.

- Prior to study start, the following documents are to be submitted to, and approved by, the ethics committee for the study:
- Clinical investigation plan
- Investigator's brochure
- Informed consent form, instructions and any documentation that will be provided to subjects
- Any documentation or advertisements that are used to recruit subjects
- The CV of the principal investigator
- Some ECs also request:
  - Draft CRFs
  - Documents that cover contractual and payment terms
  - Documentation that pertains to any conflict of interest, including financial

During the study there are certain issues that need to be communicated to the EC and/or regulatory authority; these depend on reporting requirements defined by the responsible EC and national law:

- Serious adverse events and device deficiencies
- Changes to any of the above-mentioned documents (e.g., amendments) are to be submitted and approved
- Deviations, if any, from clinical investigator plan (CIP) affecting subjects' rights, safety and well-being or the scientific integrity of the clinical investigation

Should the regulatory authority plan to inspect your site or if an auditor plans to review the study documentation, make sure that the authorized personnel have access to all study-related documentation.

Ensure you are always prepared for an audit or inspection.

Only when the documents have been approved by the ec and, if required, by the national regulatory authority, can the clinical study be initiated.

Reference | ISO 14155:2011 | 4 Ethical considerations, 4.1 General, 4.5 Communication with the ethics committee, 6.7 Subject privacy and confidentiality of data, 6.11 Auditing, 8.2.2 Preparation of documents and materials, 8.2.5 Safety evaluation and reporting, 8.4 Communication with regulatory authorities, 9.8 Safety reporting

Informed consent process

- It is mandatory to have a signed and dated informed consent form (ICF) for each subject (screened or enrolled) before any study procedures are performed.
- Only ICF versions that have been approved by the study's ethics committee are to be used, signed and dated by a subject.
- Alternative therapies as well as risks associated with the clinical investigation are to be discussed with the subject.
- The subjects need to have sufficient time to understand the purpose of the study and to consider their agreement to participate in the study.
- All of the subjects' questions should have been answered prior to study start.
- The subjects should be informed that they can withdraw from the study without any recourse. Subjects need not mention the withdrawal reason if asked.
- A signed ICF, from a legally authorized representative (LAR) is also needed in case of an emergency treatment if the subject is unable to sign. The conditions for this are to be described in the CIP.
- In the case of a life-threatening situation where the subject may benefit from the use of the medical device and the LAR cannot be reached, a subject may be enrolled without the consent of the subject/LAR. The conditions for this are also to be described in the CIP.
- Obtain informed consent from the subject immediately after recovery; the subject must be excluded from the study if not willing to participate any longer.

If it isn't documented, it doesn't exist | Make sure that:

- The IC process is documented in the hospital record
- A copy of the ICF has been given to the subject
- The original ICF has been filed in the investigator file
- An ICF log is maintained

Reference | ISO 14155:2011 | 4 Ethical considerations, 4.1 General, 4.5 Communication with the ethics committee, 6.7 Subject privacy and confidentiality of data, 6.11 Auditing, 8.2.2 Preparation of documents and materials, 8.2.5 Safety evaluation and reporting, 8.4 Communication with regulatory authorities, 9.8 Safety reporting

CIP Complicance

Compliance with the clinical investigator plan (CIP) is a very important topic. If there are any concerns with the CIP, they should be discussed prior to study start with the sponsor.

- Compliance with the CIP is to be confirmed in writing by the investigator (CIP signature page).
- By giving this confirmation, the investigator agrees to conduct the clinical study in accordance with the CIP. This means that the CIP needs to be:
  - Read
  - Understood
  - Followed by the whole study team
- In the event of an emergency, you may take action without any prior approval of the study's ethics committee or sponsor if necessary to protect the rights, safety and well-being of the subject. However, those deviations are to be documented and reported to the sponsor and the ethics committee as soon as possible.
- Make sure that the assigned study team has constant access to the CIP and applicable approved amendments.
- Ensure complete confidentiality of the study documentation within your team.
- The CIP and its amendments should always be filed in the study-specific investigator site file.
- Versions that have been superseded should clearly be marked as "outdated" versions.
- Old CIP versions should be collected from the study team and exchanged with the current version.
- Only start the clinical trial once the regulatory and ethics committee approval is complete.
- Only authorized investigators – as outlined on the site designation log – should use the investigational medical device as defined in the instruction for use and the CIP.
- Keep in mind that non-compliance with the CIP might have a big impact on the outcome of the clinical investigation.
- Changes to the CIP are only allowed after an amendment has been approved by the ethics committee and regulatory authority.

Refernece | ISO 14155:2011 | 6.2 Investigation site initiation, 8.2.1 Selection of clinical personnel, 9.4 Communication with the EC, 9.6 Compliance with the CIP

Resources

We all know that the conduct of a clinical study is managed by a large team of experts. Everybody involved in the clinical research needs to be aware of the time and capacities needed.

- Time is needed to prepare the submissions for the documents to the ECs and regulatory authorities.
- Before the study activities can start, you and the study team need to be available for a site initiation visit. Often there is also an investigator meeting planned to train the entire study team.
- Filing of documents and maintenance of the investigator file costs time and requires adequate resources on-site.
- Description of the study-related procedures, risks, benefits (if any), handling of the device, study visits and all ICF related processes require an investigator's time.
- The study-specific examinations, as requested in the CIP, are to be conducted, and qualified site personnel need to have the capacities to perform them as outlined in the CIP.
- The results of the clinical study are to be documented in the clinical records. Therefore, resources are needed for source data documentation.
- Timely documentation of the study-related data into the CRF is requested. The study team needs to make sure that they have adequate time for this process.
- Also during routine monitoring visits, the assigned study team needs to make sure they are available for the monitor.
- In addition, time needs to be included for study-specific training.

- AE/SAE/SADE documentation and reporting in compliance with the CIP and national requirements is another important topic that needs adequate attention from the assigned study team.
- The time involved to communicate internally with the study team, and to communicate externally with the sponsor, the monitor, EC and regulatory authority should be calculated when conducting a clinical study.
- Audits and inspections require time for preparation, attendance and follow-up.
- Documenting the device accountability is also a priority.

Refernece | ISO 14155:2011 | 4.7 Informed consent, 4.7.2 Process of obtaining informed consent, 4.7.3 Special circumstances for informed consent, 4.7.4 Information to be provided to the subject, 4.7.5 Informed consent signature, 6 Clinical investigation conduct, 8.2.4.5 Routine on-site monitoring visits, 9.4 Communication with the EC, 9.5 Informed consent process, 9.6 Compliance with the CIP, 9.7 Medical care of subjects, 9.8 Safety reporting

Training

Before a clinical study can begin, training needs to be performed for all involved parties. Some of the topics mentioned below are presented during the site initiation visit or during the investigator meeting, and some will be repeated during the course of the study based upon the requirements.

In each case there needs to be evidence that each of the involved members are trained on the material below:

- Clinical investigation plan
- Investigator's brochure
- Instruction for use
- IC process and other documents handed to the subjects (e.g., subject card, subject diary)
- Device handling
- Device accountability
- CRFs and instructions for completion
- SAE/SADE/DD documentation and reporting
- International Standards (ISO) and national regulations

A training log or equivalent documentation is to be maintained. This log will serve as evidence of training completed during the course of the clinical trial. The investigator and site staff need to be trained on all study-related documentation and procedures.

Reference | ISO 14155:2011 | 5 Clinical investigation planning, 5.1 General, 6.3 Investigation site monitoring, 6.6 Additional members of the investigation site team, 8.2.1 Selection of clinical personnel, 9.2 Qualification of the principal investigator, A.2 Identification and description of the investigational device

Device Accountability

During a clinical study, documentation of the receipt, use and return of the medical device is a mandatory process. As soon as the sponsor delivers the investigational medical devices, the shipping receipt should be acknowledged.

- The investigational device needs to be identified for each subject; therefore, the batch number/serial number needs to be documented in a device accountability log or other document as provided by the sponsor.
- Also in a case where a device has been returned or explanted, documentation is needed.
- Last but not least, the return of medical devices to the sponsor (used, unused, expired, malfunctioning) must be fully documented.

If it isn't documented, it doesn't exist

At each stage of the clinical study, it should be known where each medical device associated with the clinical study is.

Ensure that access to the medical device is controlled; this means that only authorized staff have access to the securely stored medical device and that it is only used for the clinical study.

Reference | ISO 14155:2011 | 6.9 Investigational device accountability, 8.2.2 Preparation of documents and materials, 8.2.4.5 Routine on-site monitoring visits

Documentaion

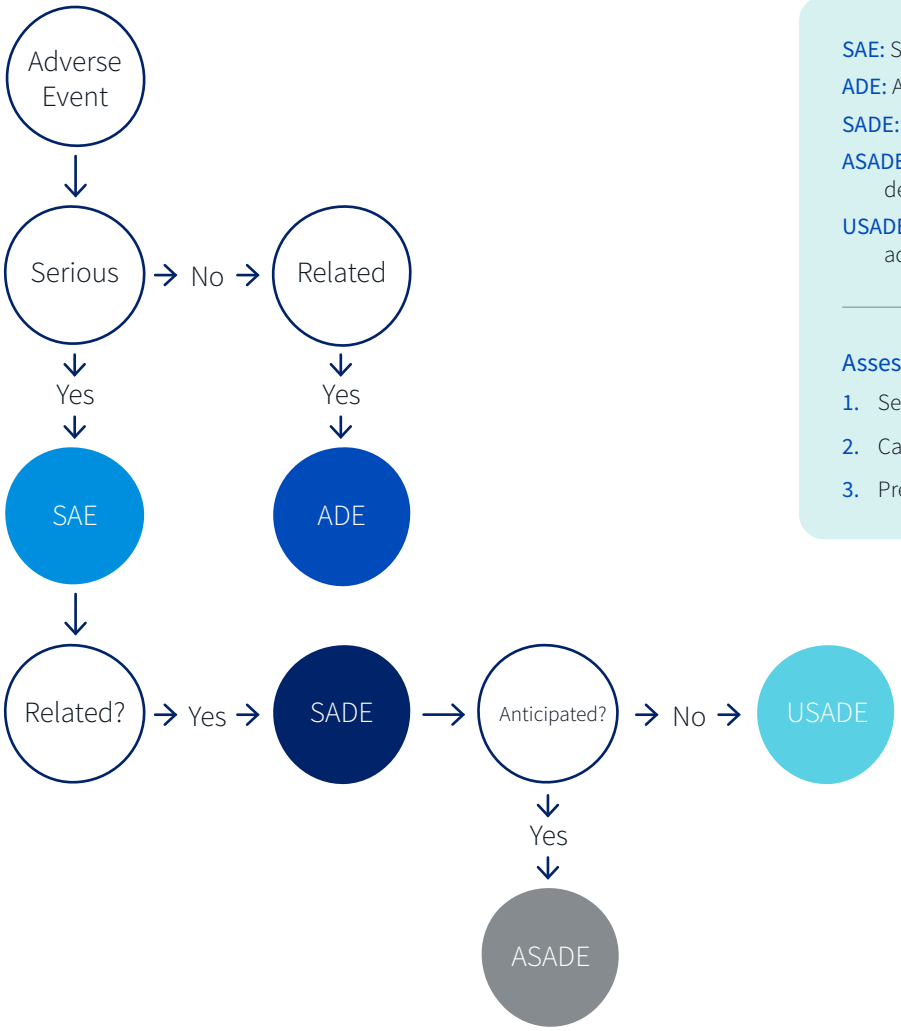
If it isn't documented, it doesn't exist

- Case report forms (CRFs) must be completed thoroughly, legibly, accurately and in a timely manner.
- Source documents (e.g., hospital records, laboratory notes, device accountability records, images) are to be created and maintained throughout the entire study. They must be made available to the monitors, sponsors and inspectors during monitoring visits or inspections/audits.
- In case you need copies of the original documents, make sure that they are signed and dated by one of the authorized study members. This confirms that the document is a true copy of the original document.
- Source documents and all data entered into the CRFs need to be consistent. Any discrepancies must be explained in writing.
- All study-related documentation is to be filed in the investigator's file. The documents are to be retained as required by the applicable regulatory requirements and local laws.
- Should the site staff need to correct any data in the CRF or any other document, they must cross through the incorrect data, write the correct data and initial and date all changes. (Never use any correction fluid or tape!)

During the course of the clinical study, there are several logs that must be maintained:

- Designation log of responsibilities: this log documents the delegation of the roles and responsibilities of the site staff including titles, names, initials and signatures.
- Subject screening log or subject identification log: this log documents all subjects screened/enrolled for this study. This log is to be maintained in the site file. Due to data protection, a copy should not be sent to the sponsor.
- Device accountability log: this log documents the devices used on site for each subject. It should be reconciled against the device shipping and return forms, the CRFs and the source documents.
- Training log/documentation: this log should serve as evidence of training delivered during the course of the clinical trial. The investigator and site staff need to be trained on all study-related documentation and processes.

Safety Reporting



SAE: Serious adverse event

ADE: Adverse device effect

SADE: Serious adverse device effect

ASADE: Anticipated serious adverse device effect

USADE: Unanticipated serious adverse device effect

Assessments:

1. Seriousness
2. Causality
3. Previously Unidentified

Timely safety reporting and documentation of any adverse events or device deficiencies need to be a high priority throughout the entire study.

In the following section you will find the definitions of an adverse event, a serious adverse event and a device deficiency:

- An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, other persons or users, whether or not it is considered to be related to the investigational medical device.
- If the relationship is considered to be related to the device, it is referred to as an **adverse device effect** (ADE).

- A **serious adverse event (SAE)** is defined as an AE that:
  A. Led to death
  B. Led to serious deterioration in the health of the subject, that resulted in:
     - A life-threatening illness or injury
     - A permanent impairment of a body structure or body function
     - Inpatient or prolonged hospitalization
     - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment
  C. Led to fetal distress, fetal death or a congenital abnormality or birth defect
- If the relationship is considered to be related to the device, it is referred to as a **serious adverse device effect** (SADE).
- A **device deficiency** is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

SAEs and device deficiencies that could have led to a serious adverse device effect (SADE) are to be reported by the investigator to the sponsor immediately, and if required by the national law, to the ethics committee and/or regulatory authority.

- The safety reporting process and responsibilities, as well as all definitions, should have been provided in writing by the sponsor.
- All device deficiencies should also be documented with regard to their identity, quality, durability, reliability, safety and performance.
- In addition to this, ensure compliance with your local and national regulations.

Reference | ISO 14155:2011 | 3 Terms and definitions, 4.5.4 Continuing communication with the EC, 6.4 Adverse events and device deficiencies, 8.2.5 Safety evaluation and reporting, 9.4 Communication with the EC, 9.8 Safety reporting, annex F

Device Development History

- Labcorp works with medical device and diagnostic firms to build a strategic and regulatory driven plan that covers development goals across the full product life cycle. This specialized and flexible approach enables device manufacturers to manage their overall development portfolio holistically – from preclinical testing and conducting clinical trials, to regulatory submissions and post-market surveillance.
- The Labcorp team is deeply experienced, having conducted medical device trials since 1985. Recent experience includes more than 500 MDD studies, with over 5,000 investigative sites, reaching an estimated 110,000 patients in the past 5 years alone.
- Labcorp's dedicated Medical Device and Diagnostic Solutions group combines deep expertise in the medical device and diagnostic industry, with Labcorp and LabCorp core competencies in development and diagnostics. The company's recent medical device mergers and acquisitions activity includes Chiltern (including the device-focused business of Theorem), PMI (device preclinical and surgical solutions), Regulatory and Clinical Research Institute or RCRI (a clinical/regulatory team dedicated to medical device and diagnostic development) and assets from ENVIGO (preclinical device testing).

Learn more at medtech.labcorp.com

labcorp