Regulatory, quality and clinical affairs

NX-451 – What to know when working with medical devices

Session 11

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Clinical Investigation – Introduction

MDR article 2(45) defines 'clinical investigation' as:

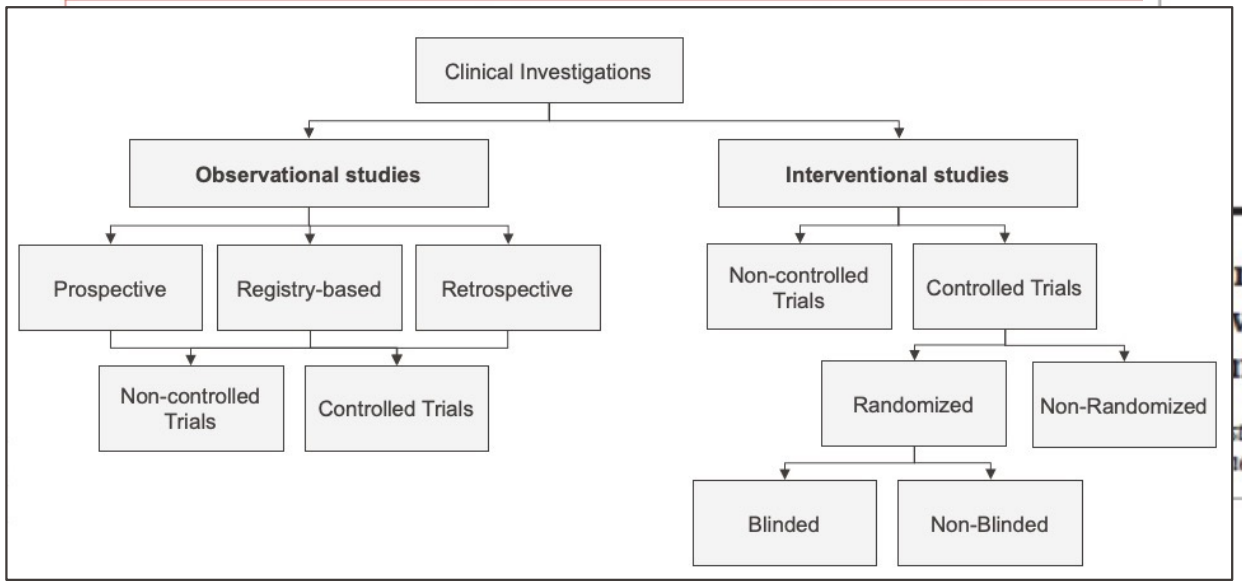
'any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.'

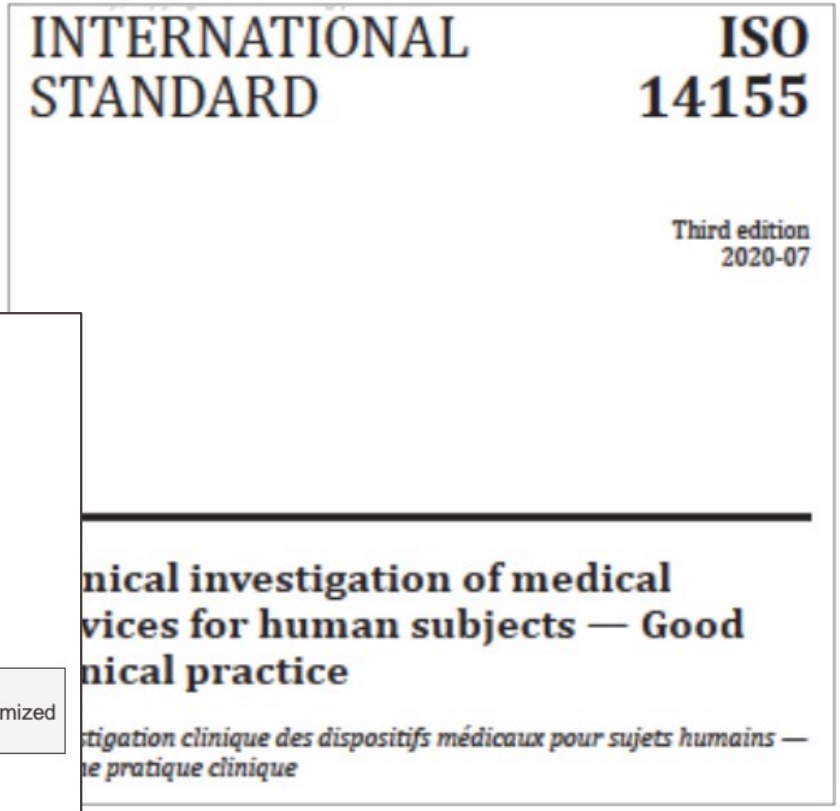
- In the medical device field, a clinical study aims at collecting relevant data that will be used in the Clinical Evaluation to demonstrate the clinical benefit.

Clinical Investigation – Definitions

Clinical Investigation are to be based on strong regulatory, scientific and good practices

MDR Art	Description
62-81	General requirements regarding clinical investigations conducted to demon conformity of devices - approval from CA - approval from EC - GCP principles - medical device confirms with GSPRs - according to requirements of Annex XV , Art 62-81




INTERNATIONAL STANDARD

ISO 14155

Third edition
2020-07

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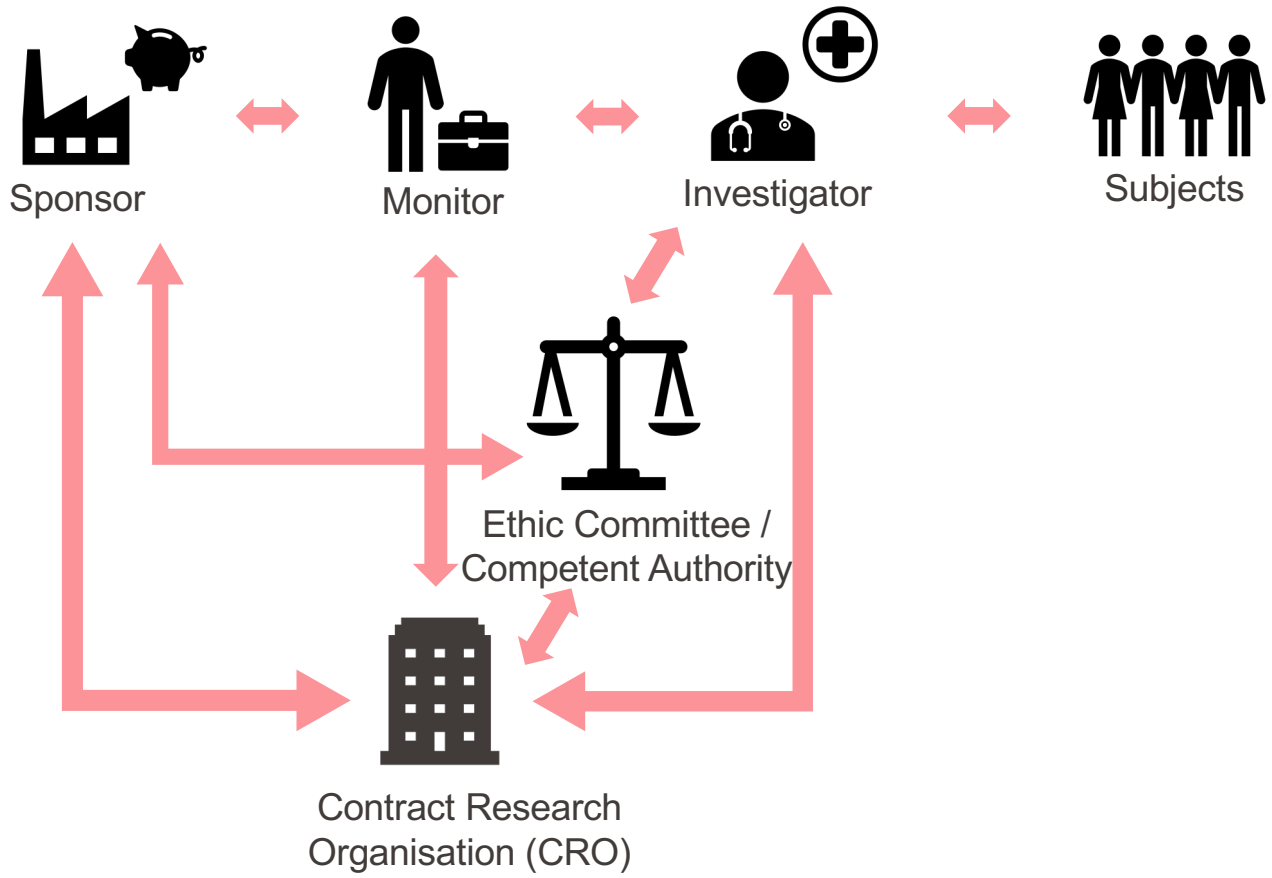
Clinical Investigation – Stakeholders



Clinical Investigation – Stakeholders

The Sponsor

- Individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation. They are responsible for the clinical investigation planning and conduct.
- Usually, the manufacturer of a device but it can be the Principal Investigator (Self Sponsored study) or any other research organisation.
- Often the Sponsor is the direct beneficiary of the clinical investigation outcome, for instance when data are collected to demonstrate safety and/or performance of a device. But it can also be to address a research question for scientific purpose.

The (Principal) investigator (PI)

- Individual member of the investigation site team designated at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical-investigation-related decisions.
- The PI must conduct the study in accordance with the approved protocol, Good Clinical Practices (e.g., ISO 14155), obtain informed consent, and protect participants' safety and rights.
- He or she is responsible for supervising qualified staff, ensuring accurate data collection, maintaining complete documentation throughout the investigation and reporting as necessary.

Clinical Investigation – Stakeholders

The Monitor

- Verify the study is conducted according to the approved protocol, ethical standards, and applicable regulations, including confirming proper informed consent.
- Monitor the accuracy and completeness of data (source data verification), ensure proper documentation of adverse events, and confirm participant rights are adequately preserved.
- Provide training and guidance to site staff, verify investigational device handling, document monitoring visits, and act as the key link between the sponsor and the site.

The Clinical Research Organization

- Person or organization contracted by the sponsor to perform one or more of the sponsor's clinical investigation-related duties and functions.
- Typically plans, initiates, monitors, and manages clinical investigations on behalf of sponsors, following regulatory and GCP standards.
- They provide expertise in study design, regulatory submissions, data management, biostatistics, safety monitoring, and medical writing.

Clinical Investigation – Stakeholders

The Ethical Committee (EC)

- Independent body whose responsibility is to review and approve study protocols. It evaluates the ethical and scientific aspects of the investigation to ensure compliance with applicable laws, GCP, and ethical standards before and during the study.
- The Ethics Committee ensures that clinical investigations prioritize the dignity, rights, and well-being of human subjects, with special attention to risk-benefit balance, scientific relevance and informed consent.

The Ethical Committee typically verifies:

- Ethical acceptability and scientific validity of the clinical investigation plan (CIP), ensuring the rights, safety, and well-being of participants are protected.
- Informed consent process and documentation, ensuring clarity, voluntariness, and comprehension by participants.
- Qualifications of investigators and adequacy of study sites to safely conduct the investigation.
- Risk–benefit assessment, verifying that anticipated benefits justify the risks.
- Participant recruitment materials, including advertisements and information sheets, for accuracy and appropriateness.

Clinical Investigation – Stakeholders

The Competent Authority (CA)

- A national regulatory body responsible for authorizing and overseeing clinical investigations to ensure they comply with applicable legal and safety requirements. It assesses the safety of the investigational device, and regulatory compliance before the investigation can begin.

The Competent Authority typically verifies:

- Regulatory compliance and device safety: Ensures the investigational device and clinical investigation plan comply with applicable laws (e.g., EU MDR, ISO 14155) and do not present undue risk to participants.
- Scientific and technical validity: Evaluates whether the study has a solid scientific basis, appropriate methodology, and adequate preclinical or prior clinical data to justify human involvement.
- Oversight through inspections: May conduct inspections of sponsors, investigators, and study sites to ensure ongoing compliance with regulatory and ethical requirements throughout the investigation.

Clinical Investigation – Stakeholders

The subjects

- The subject is an individual who participates in a clinical investigation. A subject can be either a healthy volunteer or a patient.
- Participants to clinical investigation may be anyone:
  - Adult healthy person
  - Adult person with a specific medical condition
  - Deceased persons
  - Paediatric (Children, Adolescents)
  - Adult lacking capacity
  - Pregnant Women
  - Embryos and Foetuses
  - Prisoner

Vulnerable population

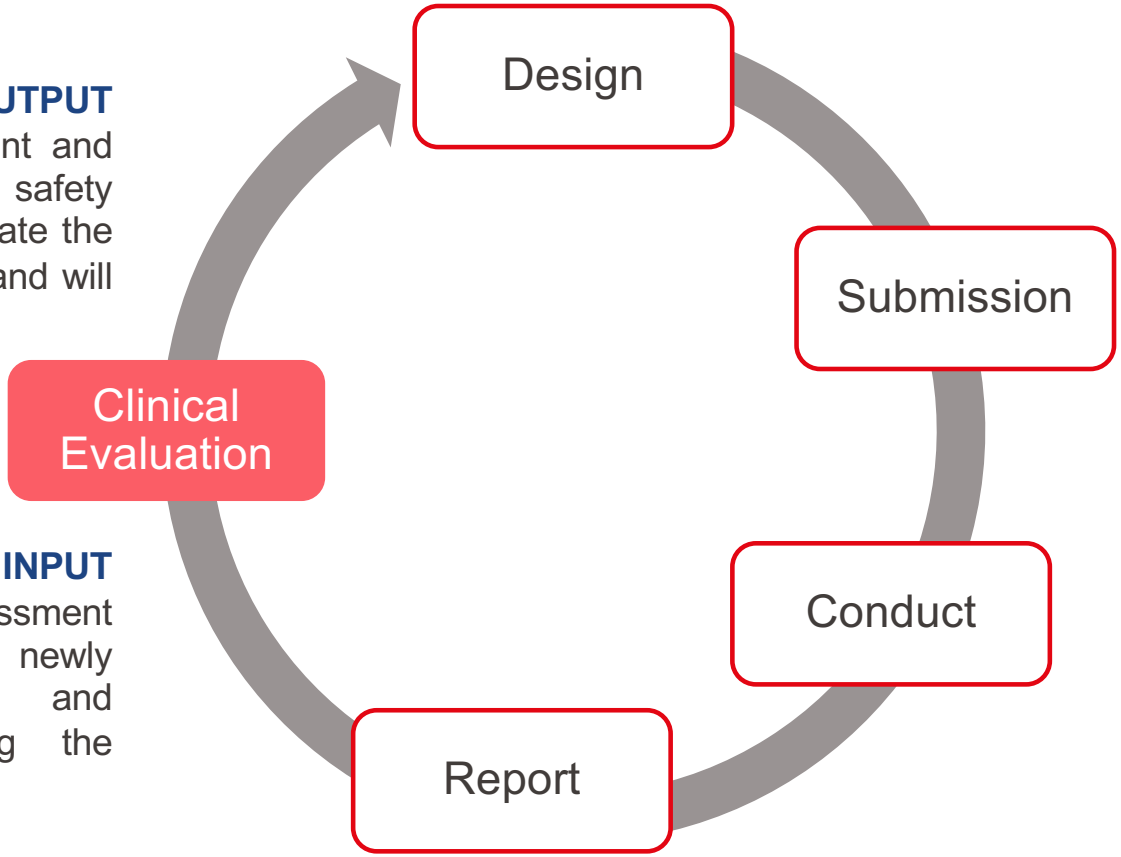
Clinical Investigation – Overall process

OUTPUT

The benefit-risk ratio assessment and appraisal of external or internal safety and performance data may indicate the need for a clinical investigation and will help define the relevant design.

INPUT

The benefit-risk ratio assessment should be updated to reflect newly available data on safety and performance acquired during the clinical investigation.



Clinical Investigation – Design Stage

The design stage of a clinical investigation involves preparing and structuring the study by defining objectives, selecting methods, determining sample size, planning data collection and analysis strategies, and ensuring ethical considerations are in place to guarantee reliable outcomes.

Typical activities will include:

- Defining objectives and endpoints of the study - what is the hypothesis to be demonstrated
- Determine study design – what is the type of study that must be conducted
- Define inclusion/exclusion Criteria – what is the characteristics of the needed study population
- Set data collection methodology and statistical plan – what data we collect and how to analyse it
- Identify and contract study site(s), investigator(s) and eventually a CRO.
- Prepare the complete Clinical Trial Application, the set of documentation that must be assembled.

The justification for the design of the clinical investigation shall be based on the evaluation of pre-clinical data and the results of a clinical evaluation and shall be aligned with the results of the risk assessment (ISO 14155, art 6.3)

Clinical Investigation – Design Stage

A clinical trial file (CTF) is a comprehensive collection of documents and records related to a clinical trial, used to ensure compliance with regulatory requirements, ethical standards, and good clinical practice. It start with the clinical trial application which is the dossier submitted to the Ethical Committee and the Competent Authority to seek approval to conduct a clinical trial.

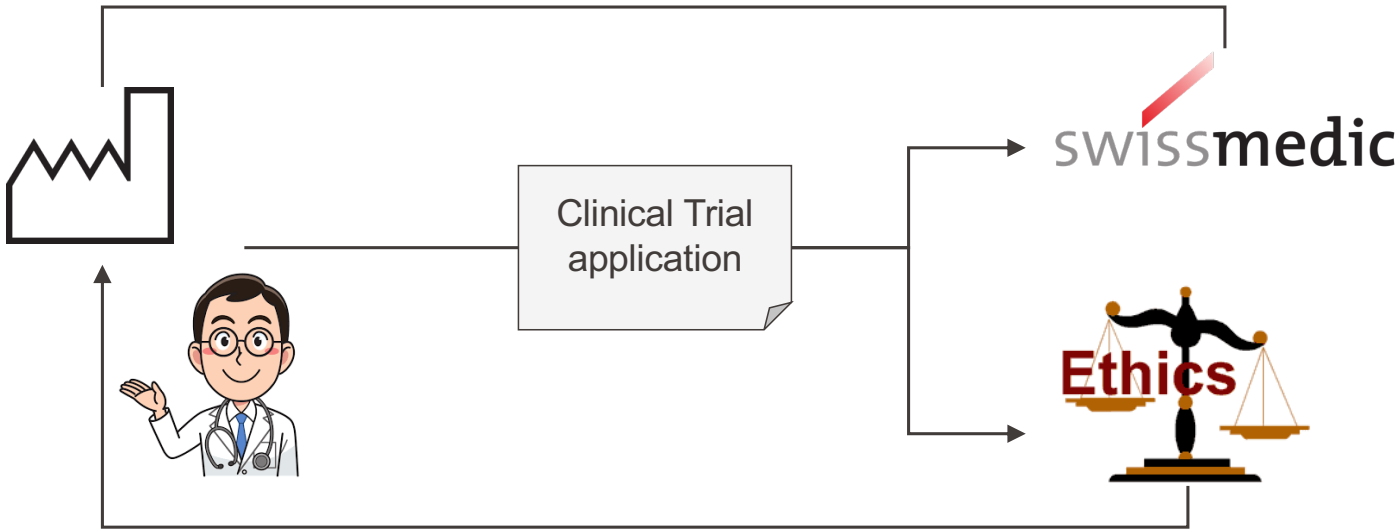
The CTA includes:

- Clinical Investigation Plan (CIP) – The detailed protocol for the clinical investigation, outlining objectives, design, methodology, data collection, and statistical analysis.
- Patient information Sheet (PIS) and Informed Consent Form (ICF) – A document that provides participants with all the necessary information about the investigation to make an informed decision about their participation.
- Investigator's Brochure (IB) – A comprehensive document providing the clinical and preclinical data related to the medical device being tested, designed to inform investigators of the potential risks and benefits.
- Case Report Forms (CRF) – Forms used to collect data from each participant in the trial, including clinical and demographic information.
- Investigator and Study Staff Qualifications – Documentation showing the qualifications and training of the investigator and other key personnel involved in the clinical investigation

Clinical Investigation – Submission / Authorization

Any clinical investigation MUST be authorized BEFORE starting. Depending on the design of the study, the Ethical Committee and the Competent Authority shall give their authorisation for the study to take place. Other agencies may have to be consulted (i.e. OFSP in Switzerland).

The clinical trial application (CTA) is prepared by the Sponsor (or the CRO) with the support of the investigator. Once ready, it is sent to the Competent Authority and the Ethical Committee for review and approval.



⇨ **Both Authorities must approve the study before it may start !**

Clinical Investigation – Submission / Authorization

Some feedbacks from the Ethical Committee on a submission:

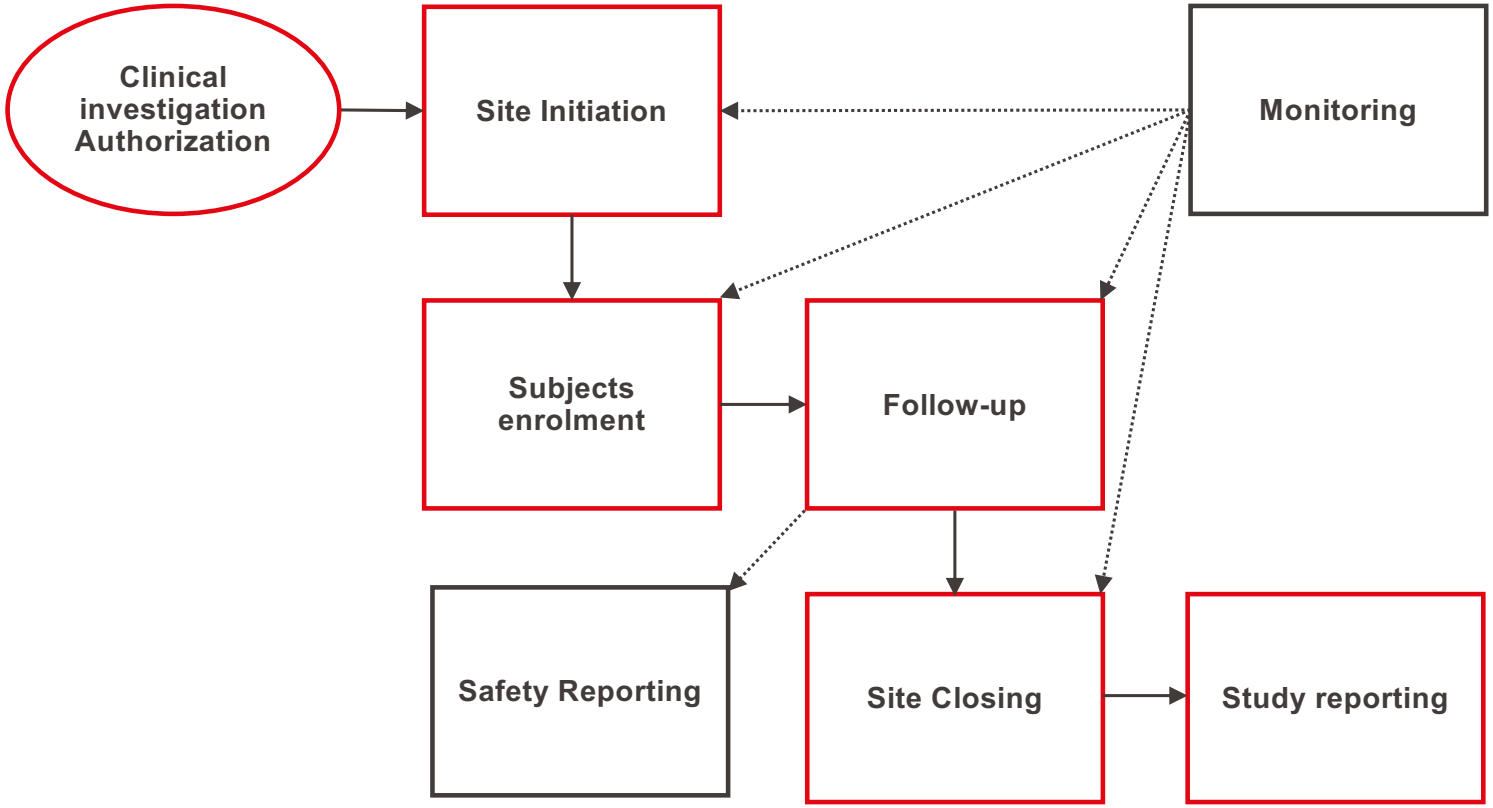
- The number of patients (n=15) seems low to validate your hypotheses. Could you please justify this choice in a few sentences?
- "*The Principal Investigator will directly invite some of his patients to participate in this investigation; no particular form of marketing will be performed*." This statement indicates that participant selection is non-random and based on personal judgment, which could introduce selection bias. What potential impact could these choices have on the study results in terms of selection bias?
- Given the study's methodology, we suggest modifying the title by replacing the term evaluation with feasibility, which appears to be more appropriate.
- Please provide the monitoring plan contract between the CRO and the sponsor.
- Inclusion criteria – "*Able to demonstrate a good capacity in managing their diabetes*". By limiting the study to participants who are experienced and have good diabetes management, your protocol aims to reduce variability. However, will you be conducting an analysis of inter-individual variability?

Clinical Investigation – Submission / Authorization

Some feedbacks from the Competent Authority on a submission:

- The investigator brochure is insufficient. Summaries of many preclinical tests are missing. Instead, we only found general statements (e.g., "*The adjustability and the reproducibility of the implant has been demonstrated and validated with appropriately designed functional tests*"). The summaries should briefly describe what was done, why it was done, how it was done, the objectives, and the results.
- Risk management, learning curve: The CIP lacks a description of the type of training or introduction that will be provided to the investigator physicians—e.g., "proctoring" involving the presence of an appropriate representative from the manufacturer during the first procedures.
- Anonymization: In addition to an identification code, the sponsor is requesting in the CRFs the patients' initials and full dates of birth. This level of anonymization is insufficient. For example, the sponsor could omit the initials or limit the date of birth to the year only.
- The case report form does not allow the sponsor to meet its responsibilities for risk management and safety reporting concerning adverse events (AEs) and device deficiencies (DDs).
- Please add the software version or number of the investigational device to the Clinical Investigation Plan (CIP), Investigator's Brochure (IB), and the manufacturer's statement.

Clinical Investigation – study conduct



Clinical Investigation – study conduct

Site initiation

- An initiation visit shall be performed at each study site before the first patient is being processed.
- During the visit the sponsor will verify that:
  - The documentation is available on-site and is compliant
  - The investigator and study personnel have been properly trained or are trained (on the device and on the study)
  - The investigational devices are available and correctly managed / maintained
  - Data collection and management process is in place
- The visit is documented and the participants to the study are identified as part of the investigation site team.

Subjects' enrolment

- The enrolment of subject is the formal inclusion of patient in the study. Usually, investigators have screened their patient's database and invite them to participate in the clinical investigation
- Patient selection must be made based on the inclusion and exclusion criteria
- During the enrolment, the investigator will inform the patient about the study and collect the informed consent of the patient. The patient may go through specific clinical exam before the formal enrolment
- Enrolment may start ONLY when positive response from EC is obtained.

Clinical Investigation – study conduct

Visits / Follow-up's

- Once after the initial intervention has taken place or if repeated interventions are necessary, the patient will be followed-up (study visits)
- During follow-up visit, assessment of the patients' conditions will be made to assess safety and efficacy of the treatment
- Overall medical examination may typically take place and study-specific assessments will be performed
- During follow-up visit undesired adverse events will be recorded if any
- At each study visit, the investigator will assess if the patients may continue participating in the study
- Follow-up visits may take place during a period from a couple of days to multiple years depending on the study design
- Data are collected and formalized in the case report form (CRF)

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Clinical Investigation – Submission / Authorization

Clinical investigation plan overview

Study Period / Activities	Screening	Baseline	Surgery	Day 1	Day 7	Day 14	Day 28	M 2	M 3	M 6	M 12	M 18	M 24
Consent/Authorization	X												
Inclusion/Exclusion Criteria	X												
Demographics		X											
Medical history		X											
Concomitant anti-glaucoma medications		X											
Clinical eye evaluation		X											
Surgery			X										
Biomicroscopy examination		X		X	X	X	X	X	X	X	X	X	X
IOP measurement and, if necessary, adjustment of Device		X		X	X	X	X	X	X	X	X	X	X
Type and number of anti-glaucoma medication				X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X	X	X
Subjective refraction		X			X	X	X	X	X	X	X	X	X
Pachymetry		X					X		X		X		X
Funduscopy		X			X	X	X	X	X	X	X	X	X
Gonioscopy assessement		X			X		X		X	X	X	X	X
Visual field evaluation		X									X		X

Clinical Investigation – study conduct

Monitoring

- The conduct of a clinical investigation shall be monitored. The monitoring aims at ensuring the study is compliant with the protocol and GCP.
- During monitoring visit, the monitor will typically verify that:
  - Informed consent has been obtained
  - Case report forms are properly and accurately completed. Data privacy is maintained
  - Planned visits and interventions are properly performed
  - The documentation used is appropriate
  - The safety reporting is correctly performed
  - The personnel performing the study remain appropriate (training, practices), the infrastructure remain appropriate
  - Investigational devices are correctly accounted and used
  - Deviations to protocol are identified and reported
- The visits are based on a Monitoring plan, and they are systematically documented shall be documented.

Clinical Investigation – study conduct

Safety reporting

- Sponsor and investigator have the obligation to report to the competent authorities on safety aspects of the study in two ways:
  - A yearly report on the study shall be provided to the authorities. This report shall include data related to efficacy and safety of the treatment, observed adverse events, deviation to protocol, etc.
  - If Serious Adverse events occur they shall be reported from the investigator to the sponsor and then to the Competent authorities.

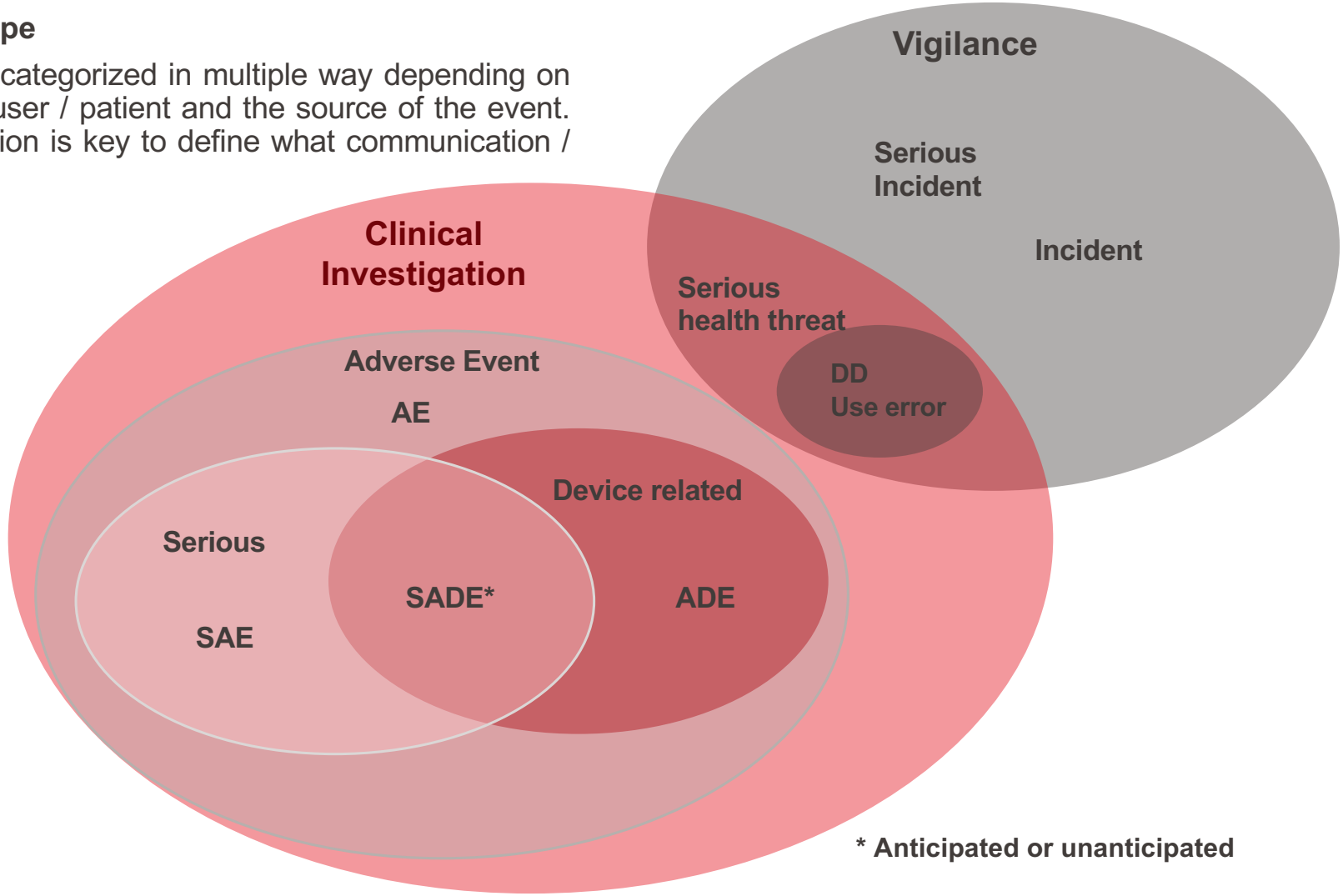
Adverse events

- Adverse event (AE) - Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.
- Serious adverse event (SAE)- Any adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject (life-threatening illness or injury, permanent impairment of a body structure or a body function, hospitalisation or prolongation of patient hospitalization, medical or surgical intervention to prevent life-threatening illness or injury or permanent, impairment to a body structure or a body function, c) chronic disease, foetal distress, foetal death or a congenital physical or mental impairment or birth defect.
- (Serious) Adverse device effect (ADE): Adverse event related to the use of an investigational medical device

Clinical Investigation – study conduct

Adverse events type

Averse events are categorized in multiple way depending on the impact on the user / patient and the source of the event. Correct categorization is key to define what communication / action is needed



* Anticipated or unanticipated

Clinical Investigation – study conduct

Site closing

- Once the study has been completed, the study needs to be formally closed-out. During close-out the following activities are typically performed:
  - Verification of all documents to ensure they are completed and correct
  - All outstanding queries are resolved
  - All adverse events have been properly documented and followed-up
  - Proper arrangements have been made to store and archive the data
  - All patients have been properly discharged
  - All Notification to Ethical Committee and Competent Authorities have been made
  - Investigational device have been retrieved / decommissioned as relevant
- The study is the finalized through the clinical investigation report which is sent to the authorities.

Clinical Investigation – study conduct

Study reporting

- Once the study is closed, usually the sponsor ends up with raw data (i.e. content of the CRF). Analysis and reporting of the data needs to be done to assess how endpoints have been achieved.
- Usually, the data analysis is performed jointly between the investigator and the sponsor. But it can be also performed by an independent body.
- The clinical investigation report shall take into account the data from each investigation site and for all subjects.
- The clinical investigation report shall be submitted to the competent authority and the ethical committee.
- Eventually, the report is used for publication i.e. in a peer review journal and/or as primary inputs for the clinical evaluation report.
- The clinical investigation report will mainly address:
  - How the study was conducted, including participant enrolment, procedures followed, and any significant deviations or challenges encountered.
  - Presents analysed data on safety, performance, and any adverse events observed during the study.
  - Summarizes the overall findings and provides recommendations for regulatory approval or further research.

Clinical Investigation – Key design aspects

Study objectives

Why do you want to conduct a clinical investigation ?

What do you want to demonstrate with the investigation ?

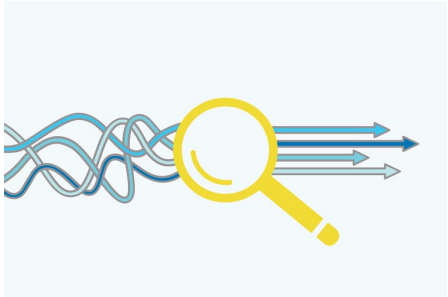
Which claims/clinical benefits need to be verified ?

Controlled investigation : Superiority, non-inferiority, equivalence

Directly related to the hypotheses

Identifying the claims/clinical benefits to be verified typically comes from the Clinical Evaluation

Study endpoints



What do you need to measure to reach your objectives / to prove your hypotheses ?

Target outcome measure / indicator of performance, effectiveness or safety

Primary endpoint : endpoint for which the investigation is powered (sample size)

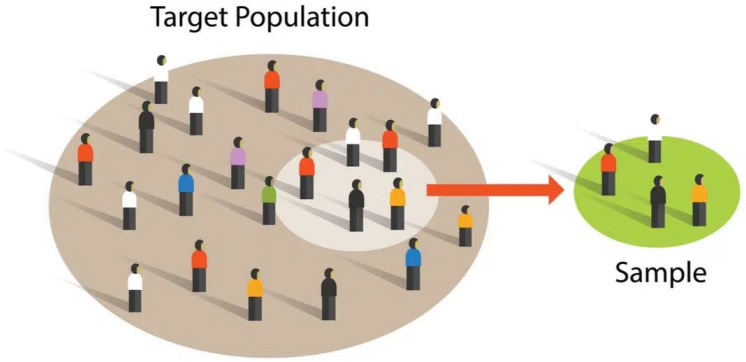
Clinical Investigation – Key design aspects

Eligibility Criteria
(inclusion / exclusion criteria)

- Should correspond to the objective and the intended use of the device
- Restrictions should be justified

Sample Size

- Calculated with sufficient power to demonstrate clinically important difference
- Based on the hypotheses
- Based on statistical parameters
- In exploratory/observational investigations, it should be justified “qualitatively” (scientific rationale)
- Methods and assumptions used to calculate sample size must be described in the CIP

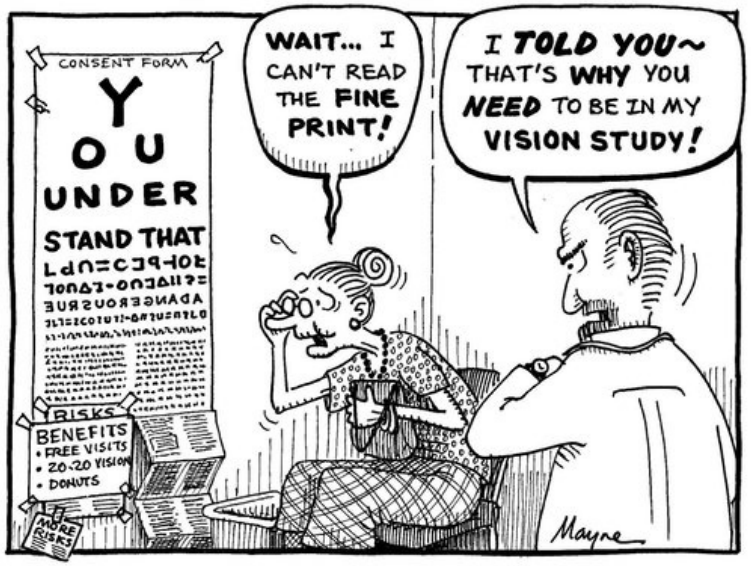


Clinical Investigation – Key design aspects

Informed Consent Process

PATIENTS MUST:

- Receive pertinent **information**
- **Understand** this information
- Be **capable of making** a choice
- Choose **freely**

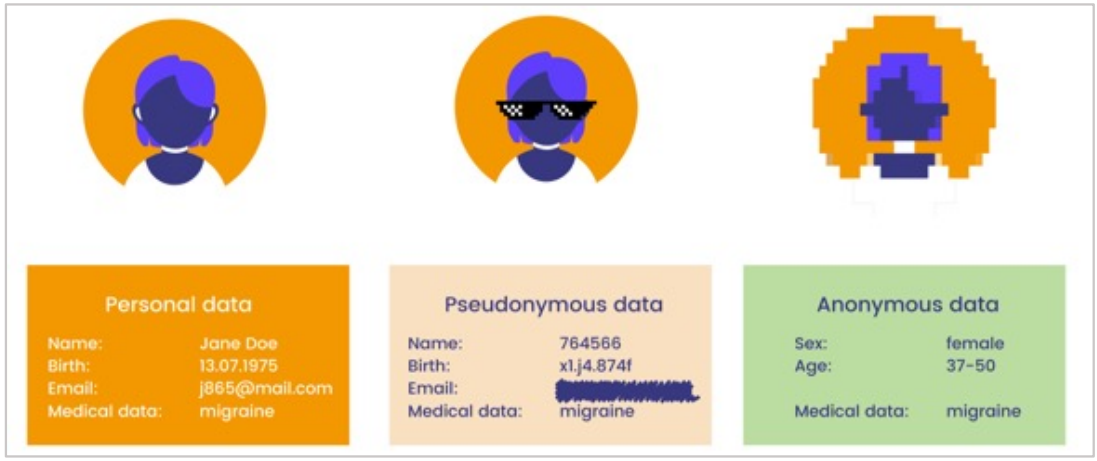


- Explain **all aspects of the clinical investigation** that are relevant to the subject's decision to participate throughout the clinical investigation;
- **Avoid** any coercion or undue **improper influence** on, or inducement of, the subject to participate;
- Not waive or appear to waive the **subject's legal rights**;
- Use **native non-technical language** understandable to the subject;
- Provide ample **time for the subject** to read and understand the ICF and to consider participation in the clinical investigation;
- Ensure personally dated **signatures** of the subject and the principal investigator or authorized designee;
- Provide the subject with a **copy** of the signed and dated ICF;
- Keep **records** of signed ICF;
- Know how informed consent is obtained and recorded when the subject is **unable to provide it** him- or herself;
- Ensure important **new information** is provided to new and existing subjects throughout the clinical investigation, which may relate to the subject's willingness to continue participation in the clinical investigation.

Clinical Investigation – Key design aspects

Preservation of Privacy

Preservation of privacy during a clinical study is critical to protect the rights and confidentiality of participants. It involves a combination of ethical principles, legal compliance, and technical safeguards.



'**Pseudonymisation**' means the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person;

'**Anonymization**' means information which does not relate to an identified or identifiable natural person or to personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable

Clinical Investigation – Key design aspects

Site Selection

Site selection in a clinical investigation is a critical step that directly influences the quality, efficiency, regulatory compliance, and success of the study..

“The investigation site’s facilities should be similar to the facilities required for the intended use of the investigational device(s), although additional equipment and capabilities may be needed at investigation sites during the clinical investigation to ensure that the necessary safety precautions are available.”
ISO 14155, clause 6.8

Key activities

- **Conduct feasibility assessments** to evaluate site suitability based on patient access, infrastructure, and experience.
- **Verify investigator qualifications** and ensure the site complies with regulatory and ethical standards.
- **Assess operational capabilities** including staffing, equipment, and data systems.
- **Review recruitment potential** and initiate budget, contract, and regulatory preparations.
- **Perform site qualification visits** and finalize site selection based on predefined criteria.

Q&A