ASPHALION MedTech

Clinical testing under Regulations (EU) 2017/745 and 2017/746

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1. Introduction

Clinical testing is essential for the demonstration of safety and performance of medical devices and in vitro diagnostic devices (IVDs) under EU Regulations (EU) 2017/745 and (EU) 2017/746, respectively. Resulting data from this studies support conformity assessments and play a critical role in generating clinical evidence, as required by the new regulatory frameworks.

This document explains **key elements** regarding the **clinical development stages**, **regulatory pathway**, and **sample size** determination for both clinical investigations and clinical performance studies.

2. General concepts, regulatory frameworks and definitions

Clinical testing is the final step before a medical device can apply for registration and enter the market. It is essential for confirming the device's safety and performance under real clinical conditions.

The term *clinical study* may refer to research involving humans conducted in a medical context. This includes **clinical investigations** of medical devices, **clinical performance** studies of in vitro diagnostic devices (IVDs), clinical trials with medicines, and other types of studies carried out in clinical settings.

Clinical studies are essential for the demonstration of safety and performance of medical devices and in vitro diagnostic devices (IVDs) under EU Regulations (EU) 2017/745 (MDR) [1] and EU 2017/746 (IVDR) [2]. These investigations support conformity assessments and play a critical role in generating clinical evidence.

A clinical investigation plan (CIP) for medical devices under MDR or a clinical performance study plan (CPSP) for an IVD under IVDR can be considered early in product development to meet ethical requirements and follow good clinical practice (GCP).

2.1. Good clinical practice and good study practice

Clinical testing of devices, shall be conducted in accordance with the ethical principles that originated from the Declaration of Helsinki. These principles protect the rights, safety, and well-being of human subjects, which are the most important considerations and shall prevail over interests of science and society.

These principles must be understood, observed, and applied at every step in the clinical investigation. The international standard that set the framework for good clinical practice for medical devices is ISO 14155:2020 (EN ISO 14155:2020/A11:2024), [3]. Similarly, the principles of good study practice for clinical performance studies with IVDs are established in ISO 20916:2019 (EN ISO 20916:2024), [4].

2.2. Clinical investigations under regulation (EU) 2017/745

Key definitions of terms related to clinical investigations under MDR are summarized in **Table 1**.

Term	Definition	Where in Regulation (EU) 2017/745?
Clinical evidence	'Clinical evidence' means clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.	Article 2 (51)

Clinical investigation	'Clinical investigation' means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.	Article 2 (45)
Investigational device	'Investigational device' means a device that is assessed in a clinical investigation.	Article 2 (46)
Clinical investigation plan	'Clinical investigation plan' means a document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation.	Article 2 (47)
Clinical data	'Clinical data' means information concerning safety or performance that is generated from the use of a device and is sourced from the following: clinical investigation(s) of the device concerned, clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated, reports published in peer-reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated, clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up.	Article 2 (48)

Table 1. Key definitions in MDR

2.3. Clinical performance studies under regulation (EU) 2017/746

Key definitions of terms related to clinical performance studies under IVDR are summarized in **Table 2**.

Term	Definition	Where in Regulation (EU) 2017/745?
Clinical evidence	'Clinical evidence' means clinical data and performance evaluation results, pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.	Article 2 (36)

Performance study	'Performance study' means a study undertaken to establish or confirm the analytical or clinical performance of a device.	Article 2 (42)
Scientific validity	'Scientific validity of an analyte' means the association of an analyte with a clinical condition or a physiological state.	Article 2 (38)
Analytical performance	'Analytical performance' means the ability of a device to correctly detect or measure a particular analyte.	Article 2 (40)
Clinical performance	'Clinical performance' means the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user.	Article 2 (41)
Performance study plan	'Performance study plan' means a document that describes the rationale, objectives, design methodology, monitoring, statistical considerations, organisation and conduct of a performance study.	Article 2 (43)
Device for performance study	A device intended by the manufacturer to be used in a performance study. A device intended to be used for research purposes, without any medical objective, shall not be deemed to be a device for performance study.	Article 2 (45)

Table 2. Key definitions in IVDR

3. Clinical development of a medical devices

A clinical pathway should typically be established early in the medical device development process, followed by a well-defined clinical investigation strategy and clinical validation before product launch.

Clinical development stages of medical devices are addressed in Annex I of ISO 14155:2020.

Medical device clinical development typically follows three phases, determined by the device's risk assessment. Thorough evaluations during each phase can simplify the requirements of subsequent phases. The study population may vary by phase; for example, the pilot phase often includes a smaller subset of the intended patient group, while the pivotal phase should involve participants who better reflect the broader target population.

Pilot stage

Pilot-stage clinical investigations are early-stage studies with the following attributes:

- First in human / Early feasibility clinical investigation (proof-of-concept investigation) / Traditional feasibility clinical investigation
- An early-phase exploratory clinical investigation to determine the device's strengths, limitations, and gather initial data for design, development, and validation.
- Information from these investigations guides subsequent steps, such as design modifications and pivotal study parameters.
- They enrol a small number of subjects (often from a single site) to evaluate a device at an early development stage, focusing primarily on initial clinical safety (with performance also examined).
- Pilot studies also gather preliminary data on the device's learning curve, generate effect size and variance estimates for sample size calculations, and refine pivotal investigation procedures.

Pivotal stage

Clinical investigations conducted during the pivotal stage are characterized for being confirmatory conducted to provide the information necessary to evaluate performance and safety of the investigational device.

A confirmatory clinical investigation should include a clear, predefined hypothesis for the primary endpoint(s) and a robust, pre-specified statistical method in the CIP.

Post-market stage

Clinical investigations performed during the post-marketing stage may include confirmatory clinical investigations or other types of clinical studies to evaluate, confirm or monitor specific aspects of safety and/or performance of the device.

According to Annex XIV of the MDR, the **clinical development plan** of a medical device contains the information regarding progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a post-market clinical follow-up (PMCF) with an indication of milestones and a description of potential acceptance criteria and is part of the **clinical evaluation plan**.

This paper will focus mostly on **pre-market clinical investigations**, i.e., a clinical investigation carried out **before market approval** of the investigational device.

4. Clinical regulatory pathways under MDR and IVDR

4.1. MDR

When a **sponsor** plans to gather clinical data for use in the conformity assessment of a medical device, they must follow the relevant regulatory pathway as outlined in the MDR (i.e., it is the sponsor who is responsible for determining the correct regulatory pathway for a clinical investigation).

Article 61 establishes the requirement to perform a clinical evaluation and compile sufficient clinical data, ensuring the device meets the general safety and performance criteria.

Article 62 of the MDR sets out general requirements for clinical investigations to demonstrate device conformity. Under Article 62(1), any investigation conducted as part of a clinical evaluation for conformity assessment must be designed, authorized, conducted, recorded, and reported in compliance with Articles 62–81 of the MDR.

These investigations can have multiple objectives, such as verifying or confirming device performance, clinical benefits, safety, or potential side effects. They may involve devices without a CE mark or CE-marked devices used outside their approved indications.

Article 63 covers informed consent, emphasizing clear risk-benefit communication, while Articles 64–67 address additional requirements for certain investigations, modifications to ongoing studies, and the coordinated assessment procedure among Member States.

For a medical device without CE marking, where a clinical investigation is conducted to generate data for conformity assessment (with the objective of obtaining CE marking), **the regulatory pathway follows Article 62 of the MDR**.

The regulatory pathway for a clinical investigation to generate data for the CE-mark of the medical device is summarized in **Figure 1**.

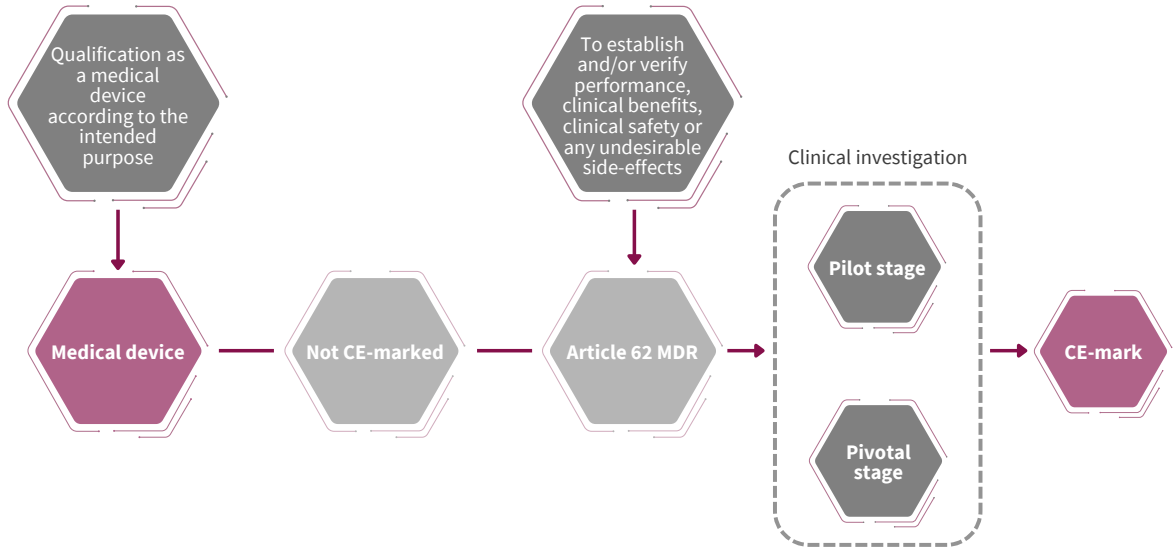

Figure 1. Regulatory pathway for a clinical investigation to generate data for the CE-mark of the medical device

Annex XV of the MDR provides detailed requirements for clinical investigations, including the clinical investigation plan, and the investigator's brochure, along with other important areas to have into consideration.

The CIP for a medical device clinical investigation must be reviewed by an Ethics Committee (EC). Once the EC issues a favourable opinion, the sponsor may then submit an application to the Competent Authority for official authorization to carry out the investigation.

4.2. IVDR

For IVDs, it must be determined whether the clinical performance study follows Article 57 ("General requirements regarding performance studies") or Article 58 ("Additional requirements for certain performance studies") of the IVDR. Studies falling under Article 57 do not require authorization from the competent authority and may not require notification, although this can depend on specific provisions of individual Member States.

The clinical performance study plan must be reviewed by an Ethics Committee (EC). Once the EC issues a favourable opinion, the sponsor may then submit an application or notification to the Competent Authority -if required- for official authorization to carry out the clinical performance study.

The following describe the clinical performance studies which follow **Article 57 of IVDR**.

- **IVDs without CE marking when**:
  - Samples have not been obtained through a surgically invasive procedure performed exclusively for the study.
  - The study is not a clinical investigation as defined in Article 2(46).
  - The study does not involve additional invasive procedures or other risks to participants.

- **IVDs with CE marking when**:
  - The IVD is used in accordance with its intended purpose.
  - No additional or burdensome procedures are performed on participants during the study.

The following describe the clinical performance studies which follow **Article 58 of IVDR**.

- **IVDs without CE marking when:**
  - Samples have been obtained through a surgically invasive procedure performed exclusively for the study.
  - The study is a clinical investigation as defined in Article 2(46).
  - The study involves additional invasive procedures or other risks to participants.
  - The IVD is a companion diagnostic:
    - If it uses left-over samples, notification is required.
    - In all other cases, authorization is required.

- **IVDs with CE marking when:**
  - The IVD is used outside its intended purpose.

Finally, for studies using CE-marked IVDs in accordance with their intended purpose but involving additional or burdensome procedures for participants, **Article 70(1) applies**, requiring notification.

According to Annex XIII of the IVDR, the **performance evaluation plan** of an IVD contains an outline of the different development phases including the sequence and means of determination of the scientific validity, the analytical and clinical performance, including an indication of milestones and a description of potential acceptance criteria.

The regulatory pathway for a clinical performance study to generate data for the CE-mark of the IVD is summarized in **Figure 2**.

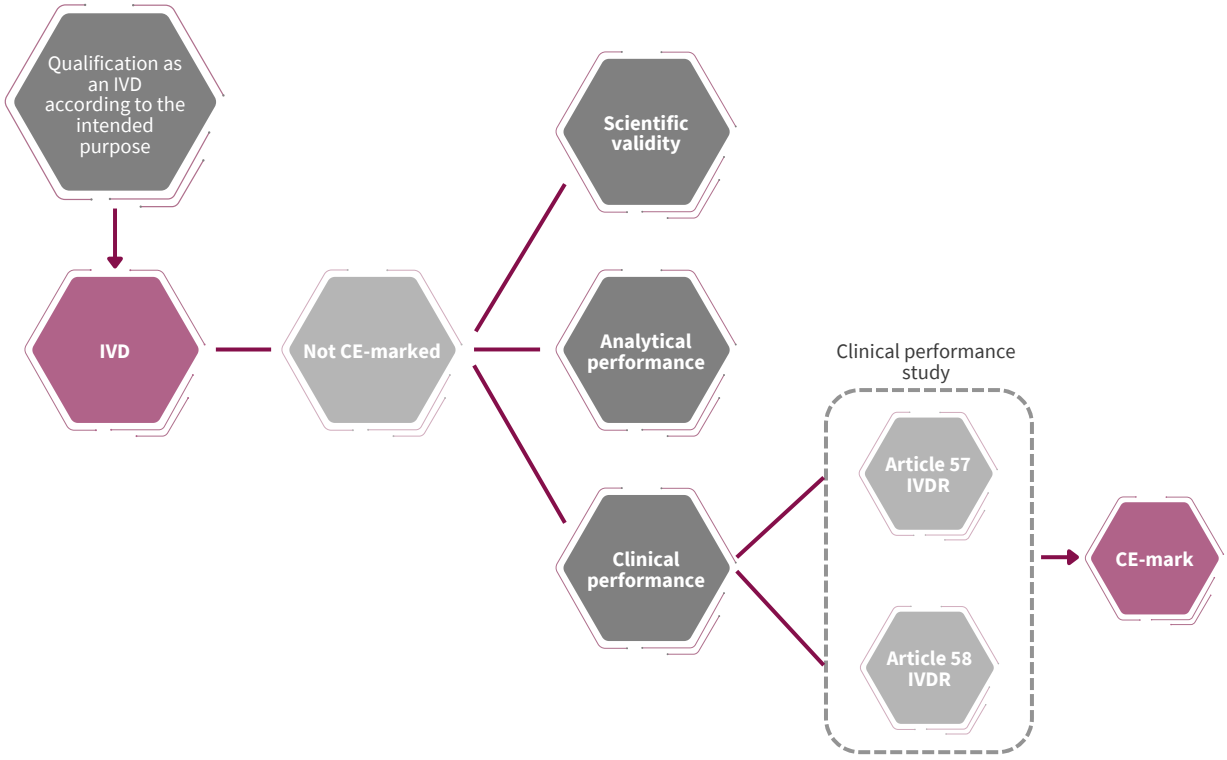

Figure 2. Regulatory pathway for a clinical performance study to generate data for the CE-mark of the IVD

5. Design of clinical studies

According to **Article 62 (3)** of the MDR, **clinical investigations** shall be designed and conducted in such a way that the rights, safety, dignity, and well-being of the subjects participating in a clinical investigation are protected and prevail over all other interests, and the **clinical data** generated are scientifically valid, reliable, and robust.

According to the General requirements of Clinical Investigations set in Annex XV of MDR:

Clinical investigations *shall be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims regarding the safety, performance and aspects relating to benefit-risk of devices as referred to in Article 62(1); the clinical investigations shall include an adequate number of observations to guarantee the scientific validity of the conclusions.*

The content of the clinical investigation plan is specified in Section 3 of Annex XV of MDR and in Annex I of ISO 14155:2020.

Similarly, **Article 57 (3)** of the IVDR states *that **performance studies** shall be designed and conducted in such a way that the rights, safety, dignity and well-being of the subjects participating in such performance studies are protected and prevail over all other interests and the data generated are scientifically valid, reliable and robust.*

Clinical performance studies shall be performed on the basis of a **clinical performance study plan**, whose content is specified in Section 2.3.2 of Annex XIII of IVDR and in Annex B of ISO 20916:2019.

To design a clinical study, it is essential to clearly define the study objective, select appropriate endpoints and outcome variables, identify the comparator or control group, develop a plan for data analyses, and determine the sample size (**Figure 3**).

Figure 3. Essential steps in the design of clinical studies

Among these steps, the one that often causes confusion is deciding how many participants are needed for the study. This involves balancing things like the size of the effect you expect to find, ethical concerns, and practical limitations. Typically, the clinical testing cost may be the highest in the whole chain of developing a medical device, and the budget for clinical testing is closely related to clinical study size.

When addressing the estimation of sample size for a clinical study, it is essential to understand the concept of **statistical inference**. When there is information that we would like to know about the large population, a small representative subset is taken in a clinical study to perform observations and calculate measures, which then we refer back to the whole population with some degree of uncertainty. The aim of statistical inference is to quantify that uncertainty.

5.1. Null hypothesis and alternative hypothesis

Establishing the **null hypothesis (H_0)** and **alternative hypothesis (H_1)** are key components of statistical testing used to evaluate the performance and/or safety of a device.

H_0 represents the assumption that there is no effect, no difference or no improvement due to the device. If data show a statistically significant result, H_0 is rejected in favor of the alternative.

p-values give the probability that the observed effect could have arisen by chance (when the null hypothesis is true).

A low p-value (typically <0.05) suggest that observed results are unlikely under $H_0$and provides evidence against the null hypothesis.

A high p-value means the observed data are consistent with H_0, thus, we fail to reject the null.

5.2. Type I and Type II errors

Type I error (α): The null hypothesis is rejected when it is actually true. The clinical study falsely conclude that the device is effective or safe when it is not. Type I error is usually set at 0.05 (significance level).

Type II error (β): The null hypothesis is not rejected. A real effect is missed, i.e., the device is safe and/or effective but it is concluded that it is not. Type II error is usually set at 0.2. The power of a clinical study is 1-β, i.e., the probability of correctly rejecting the null hypothesis.

5.3. Key input parameters for sample size estimation

Sample size estimation along with the specific methos used for such estimation shall be included in the clinical investigation plan or the clinical performance study plan.

Although sample size estimation method depends on the type of comparison of the investigational device with the comparator or control, type of outcome variables and endpoints of the clinical study (among others), the following parameters are often used as inputs:

- Significance level (usually 0.05)
- Power (usually 80%-90%)
- Statistical Test type, which depends on the endpoints of the clinical study
- Effect size (clinically meaningful difference)
- Outcome variability (e.g., standard deviation)

Estimating effect size reflects the expected difference or magnitude of change, and it shall be clinically meaningful. Outcome variability determines the dispersion of the data, directly impacting how large a sample is needed to detect an effect. The source of theses parameters is often **pilot studies**, but eventually may also be published literature.

Underpowering (not enough participants included) and overpowering (including more participants that necessary) a clinical study are pitfalls that can affect the validity and ethical integrity of a clinical investigation.

Hence, a proper sample size estimation avoids unnecessary costs, time and patient exposure while meeting regulatory and ethical standards.

6. Conclusions

Clinical testing under the Regulations (EU) 2017/745 (MDR) and (EU) 2017/746 (IVDR), is the step for confirming that the device meets the required standards of safety and performance in actual clinical settings. These clinical studies may encompass various research activities involving human subjects, including clinical investigations for medical devices or clinical performance studies for IVDs.

Adherence to good clinical practice (GCP) ensures that clinical testing is performed ethically, respecting participants' rights, safety, and well-being above all else. The use of a clinical investigation plan (CIP) under

MDR or a clinical performance study plan (CPSP) under IVDR helps sponsors systematically outline the study rationale, objectives, and methodology.

By evaluating the pilot, pivotal, and post-market stages of device development, manufacturers can gather robust data to underpin the benefit-risk profile of a new medical product. Properly powered clinical studies further reinforce this process by balancing scientific validity, cost-efficiency, and ethical considerations.

7. References

[1] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.
https://eur-lex.europa.eu/eli/reg/2017/745/oj/eng

[2] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU
https://eur-lex.europa.eu/eli/reg/2017/746/oj/eng

[3] ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice (EN ISO 14155:2020/A11:2024)

[4] ISO 20916:2019 In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice (EN ISO 20916:2024)

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