Key considerations and stages in the development of clinical trials with medical devices: Regulatory Approach

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Regulatory approach

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Abstract

Traditionally, clinical trials have primarily focused on the research of new drugs, leading to an abundance of pertinent information in the literature, far exceeding that available for medical device trials. This article delves into the essential definitions to fully understand medical device trials. It explores the general characteristics of medical devices, details the technical criteria and stages of studies, and highlights the key differences compared to drug trials. This is done by reflecting the perspective of the National Directorate of Medicines (DNM) of El Salvador, a regulatory agency, regarding these types of trials. The article also includes a description of the legal and regulatory frameworks, both local and international, supporting the regulatory work.

Keywords: Controlled Clinical Trial, Medical devices, Medical Device Legislation, Drug Development

Introduction

The development of new products, both pharmaceutical and medical devices, is carried out progressively, from the synthesis of a new molecule or the design of a device, until its marketing stage to the general public. This is a generally slow process that can last years, and involves preclinical studies, which provide prior information about the research product. In the case of medicines, information is sought on pharmacokinetics, pharmacodynamics, toxicity, stability, etc., while for medical devices performance or functioning tests are carried out in animal models, mathematical models, tests on organs or tissues in the laboratory and they carry out measurements of technical specifications according to the type of device investigated. Information collected in the preclinical stage supports the execution of a clinical trial.

Clinical trials are essential studies in the development of new products applied to human beings, because they allow us to verify that the safety and effectiveness of the new product does not put human health at an unacceptable risk. You should always ensure that the benefit of using the product is greater than the risk involved in using it.

A controlled clinical trial is a type of research that studies new tests and interventional treatments, and evaluates the effects on human health. People voluntarily participate in clinical trials that test medical interventions including drugs, cells and other biological products, surgical and radiological procedures, devices, behavioral treatments and preventive care (WHO, 2023a).

Although clinical trials have been developed throughout history, mainly on new pharmaceutical products, in recent decades, clinical trials of medical devices have become increasingly necessary. This is explainable due to the technological development of the last century and the undeniable need for medical devices in health care.

It becomes important, therefore, to know what a medical device is and how they differ from medications, to address the needs and particularities of clinical trials that study medical devices, both in their execution and in the regulatory aspects that apply are submitted.

Technical criteria for clinical trials of medical devices

Before addressing the particular aspects of medical device clinical trials, it is necessary to define what they are. A medical device is any instrument, apparatus, implement, machine, implant, reagent for in vitro use, software, material or other similar or related article intended by the manufacturer for use, alone or in combination, in human beings, and which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body for one or more specific medical purposes, including: diagnosis, prevention, monitoring, treatment or alleviation of diseases, among others (WHO, 2017).

Being such a broad definition, an important factor that influences both the evaluation criteria of clinical trials, as well as the subsequent regulatory requirements if they are marketed, is the risk classification of a medical device. This classification is based on the potential danger that the device could have for the patient, taking characteristics such as the intended purpose of use, degree of invasiveness (if any), energy release, the duration of contact with the body and any potential risk of its use; thus, a final classification is determined in the range of Class A, which represents the lowest risk, to Class D as the highest risk (GHTF, 2012).

As expected for devices with a Class A risk classification, it is most common that it is not necessary to carry out tests on humans and develop a clinical trial, due to the low associated risk. However, for devices with a greater threat, it is very likely that it will be essential to evaluate their safety through clinical trials, depending on the characteristics of each device and its combination of use with other technologies.

If the need for a clinical trial is determined, the so-called "essential documents" must be generated, which are those that allow a correct evaluation of the development of the trial and the data generated in it (ICH, 2016). Some of the main ones are described in Table 1.

Table 1. General documentation to evaluate clinical trials

Document	Description
Protocol	Document that establishes the justification, objectives, pre-specified design and analysis, methodology, organization, monitoring, implementation and record keeping of clinical research.
Researcher's Manual	Compilation of current relevant clinical and non-clinical information on investigational medical devices.
Informed consent	Process by which an individual voluntarily confirms his/her decision to participate in a particular clinical research, through a signed document, after having been informed of all relevant aspects to make the decision to participate.
Labelling	Research products must be labeled in such a way that indicates that their use is not commercial, but only for the study, as well as information that serves for traceability, storage and transportation conditions.
Final disposal plan	It is detailed that at the end of the study the products will be returned or destroyed, maintaining accounting of the products used.
Maintenance and calibration	The maintenance and calibration log of the equipment used in clinical research is verified.
Risk management report and plan	The reports identify, document and communicate potential risks to the research product. The management plan indicates how to prevent or minimize risks, the probability of their occurrence and the damage they could cause. For medical devices, ISO 14971 "Medical devices — Application of risk management to medical devices" is taken as a reference.

Source: Own elaboration based on ISO14155(ISO, 2020)

These documents are common for all clinical trials, but in the development of those that investigate medical devices, other particular information that depends on the nature and risk of the device also becomes necessary. Examples of these requirements are shown in Table 2.

Table 2. Technical documentation to evaluate clinical trials of medical devices

Document	Description
Certificate of Good Manufacturing Practices or Declaration of Conformity	Indicates compliance with good manufacturing practices ensuring all stages of the device construction process. If you do not have the certificate, a declaration of conformity is requested that details the regulations or standards implemented in the design, construction and conditioning.
Technical documentation	Documents provided by the manufacturer indicating the correct use of the device and information about its design and operation.
Test reports	Laboratory test reports that verify the performance and safety of the research product materials. They depend on the type of device.
Reports and/or certificates of sterility (when applicable)	Validation information of the sterilization method for the devices that will be used in the study, detailing the process and results, as well as the certificate that shows that the product met the process parameters.
Biocompatibility studies	Information on the biocompatibility of the medical device depends on its nature and is based on ISO 10993 "Biological evaluation of medical devices".

All this information allows us to verify that the research is carried out, throughout its development, in a safe manner for the participants, both due to the methodology to be implemented and the technical quality of the medical devices to be investigated.

Development Stages of Clinical Trials of Medical Devices

The development of clinical trials is influenced by different factors, including the type of research product, which leads to methodological differences between the study of medications and that of medical devices.

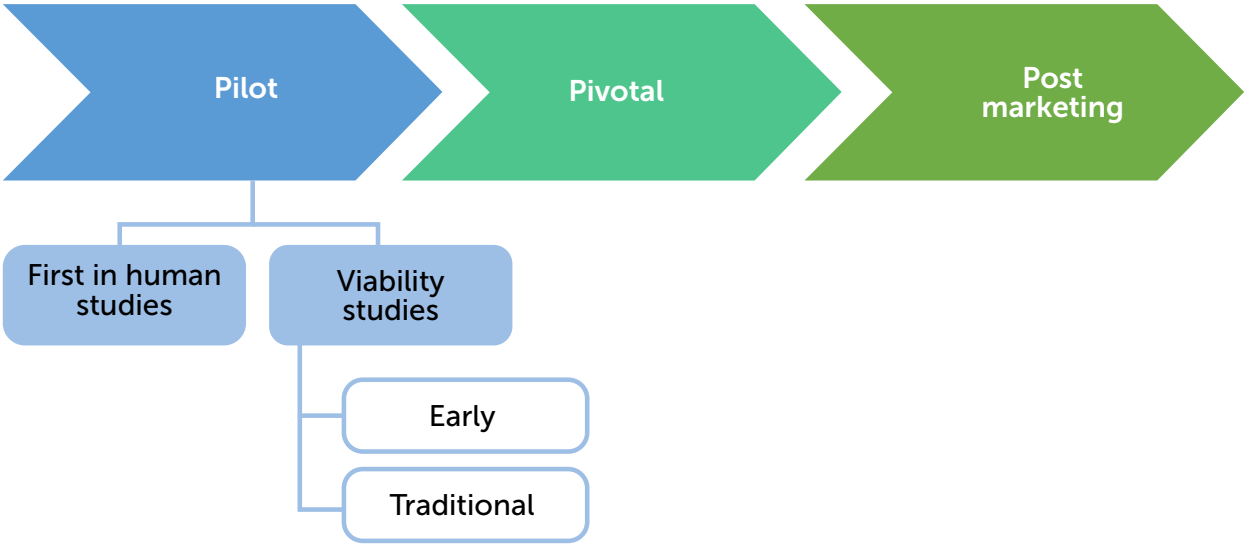
The main objective of clinical trials with investigational drugs is to evaluate their safety and effectiveness (AEMPS, 2019). Clinical trials that study new drugs are divided into four phases, the first three being necessary to achieve commercialization (Kerzberg, 2008). The classification with its main characteristics is summarized in Figure 1.

Figure 1. Drug clinical trial phases

Source: self made

On the other hand, clinical trials of medical devices are essential to ensure safety, effectiveness and clinical performance before marketing. These trials are divided into three stages (ISO, 2020), each with specific objectives and characteristics, as shown in Figure 2. Not all devices have to go through all stages, as it will depend on factors such as preclinical results, innovation and intention, clinical use of the device, as well as its design (FDA, 2013).

Figure 2. Stages of clinical trials with medical devices



Source: self made

The first stage, which is known as the pilot stage, is an exploratory study carried out with few participants. It is intended to obtain preliminary data on the design and development of the medical device and rely on the results to make necessary adjustments and improvements. They are not focused on testing a hypothesis or statistical data, they seek general information about safety and operation. They are used when more information is needed that preclinical studies can no longer provide, and it is at this stage that so-called first-in-human studies, as well as viability studies, are developed.

Viability studies can be classified into stages known as early viability or traditional viability. In early viability, the design concept is evaluated to obtain the first results on clinical safety and performance, as well as possible improvements that can be made to the device, since there is not yet a final design, they are generally made with less than 10 subjects (FDA, 2013). While those of traditional viability are carried out with more subjects, approximately between 20 to 30 (Santarelli, 2018), and are developed when there is already a finalized design (or very close to it) of the device, at the same time that there is much more preclinical information than in early viability studies; in this way, clinical and safety performance is evaluated more realistically.

The second stage is called the pivotal stage . This must be carried out with a sample that is statistically representative of the population for which the device is intended, generally there are approximately 100 participants (Santarelli, 2018), so a greater number of subjects are already participating compared to the pilot stage. A confirmatory study is developed to have definitive data on safety and effectiveness, and, therefore, it is necessary to carry it out with an established hypothesis and statistical methods that give reliability to the results. For this reason, the studies developed at this stage are those necessary for a research product to obtain marketing authorization.

Finally, the third stage is post-marketing, analogous to phase IV for drugs. It is done when the device is already commercially available. It aims to add research information that determines the clinical performance, safety and effectiveness of the medical device in a much larger number of participants. As part of this monitoring, surveillance is maintained for adverse effects, which, unlike medications, have more diverse natures. The design and/or operation of the device affects the category of adverse events, since they can be affected by inadequate maintenance or lack thereof, as well as

by errors associated with the use or incorrect applications of the device by users (Parvizi N, 2014).

Differences between clinical trials of medical devices and those of drugs

Although the purpose of clinical trials is the same: to verify the safety and efficacy of the research product in humans, there are differences in the execution of drug trials with those of medical devices, due to its nature. Some of the main differences are:

1. Nature of clinical trials. Randomized controlled clinical trials are considered the gold standard in clinical drug research. However, in the case of some medical devices, conducting them becomes impractical or unethical. This can be exemplified in the case of implantable devices, in which it would not be possible to develop a study with control or simulated treatments, since the risk that the participants would be subjected to would far exceed the benefit (Saha, 1988).

2. Scope of the test. Unlike medications, the study of medical devices does not always require large clinical trials. In many cases, clinical information is used primarily to confirm extensive theoretical studies, animal tests, and mathematical models. These previous studies are what provide the main evidence of safety and effectiveness of the device (Faris, 2017).

3. Primary source of valuation. Clinical trials are not always the primary source of information about the safety and effectiveness of a medical device. Given the diversity in the nature and applications of devices, sometimes technical aspects supported by robust mathematical models and validated in non-clinical studies may be more relevant. For example, a pacemaker designed to be used in magnetic resonance imaging (MRI) could focus on studies validating that specific function, rather than repeating trials on its overall safety and effectiveness (Faris, 2017).

4. Marketing authorization time. The authorization process for the marketing of medical devices is usually shorter than for medicines. While a drug can take on average 12 years to be authorized, a medical device can obtain authorization in a range of 3 to 7 years (Van Norman G, 2016).
5. Stages vs. Phases. Unlike drugs, where clinical trials are divided into phases, medical device clinical trials are divided into stages. This distinction reflects differences in the nature and purpose of testing between these two types of products.

6. Effect of the technique and/or procedure. The implementation and effective use of a medical device often depends on the skill and experience of the healthcare personnel using it. This means that the technique and/or procedure can significantly influence its results (Parvizi N, 2014), a factor that does not exist in the study of medications.

7. Design modifications. Medical devices may undergo changes in their design over time. Careful analysis is required as the effect of these changes on the risk-benefit ratio may affect the safety and effectiveness of the device (Parvizi N, 2014).

8. Evaluation time. The timing of a clinical trial for a medical device is crucial. It is important that the prototype of the medical device to be studied is sufficiently developed so that when evaluated in its corresponding study stage, it faithfully reflects its operation and results, as well as allowing sufficient time for the personnel who will use it to acquire the required experience and knowledge. If it is done too soon, there is a risk that the results will not be as expected and will be attributed to the device, when the design and application procedure really need to be further developed, or greater expertise in use is required (Neugebauer, 2017).

9. Monitoring of adverse events in medical devices vs. medicines. Medical devices present unique challenges regarding adverse events compared to medications. These events can arise from design defects, manufacturing failures, prolonged wear or user error. Unlike medications, where adverse events are often related to pharmacological effects or individual variations, devices have a much greater variety and are innovated more frequently. These differences require specific strategies in both pre-marketing and post-marketing surveillance (Parvizi N, 2014).
For example, in the causality analysis of adverse events, those associated with medical devices are evaluated not only in relation to the device itself, but also to the procedure in which they are used (Medical Device Coordination Group., 2022).

International guides, standards and norms

The main function of the regulatory authority in relation to clinical trials is to supervise them, verifying that clinical trials are carried out with strict compliance with what is established and authorized in the research protocol, and that they are recorded in accordance with good practices of documentation, issued by the World Health Organization (WHO, 2016); and which, in addition, are developed under ethical conduct framed in the Declaration of Helsinki (AMM, 2015), as well as the Good Clinical Practice standard.

The standard on Good Clinical Practices E6 R2 (GCP) is a process that establishes and integrates standards of scientific and ethical quality for the design, conduct, collection and reporting of clinical research that includes the participation of human subjects, detailing the role the parties involved must play in its development (ICH, 2016). GCP is par excellence the foundation on which any scientific research that is related to human subjects must be carried out.

There is a standard that is specific to medical device research, ISO 14155: 2020 Clinical Investigation of Medical Devices for Human Subjects (ISO, 2020). This addresses ethical considerations, protocol and what its content should be, the justification for the design of a clinical trial, monitoring plans, labeling of medical devices under investigation, the data monitoring committee, researcher manual and the management of risks of an investigational device, where the risks detected by the manufacturer due to use or misuse of the investigational medical device are taken into account.

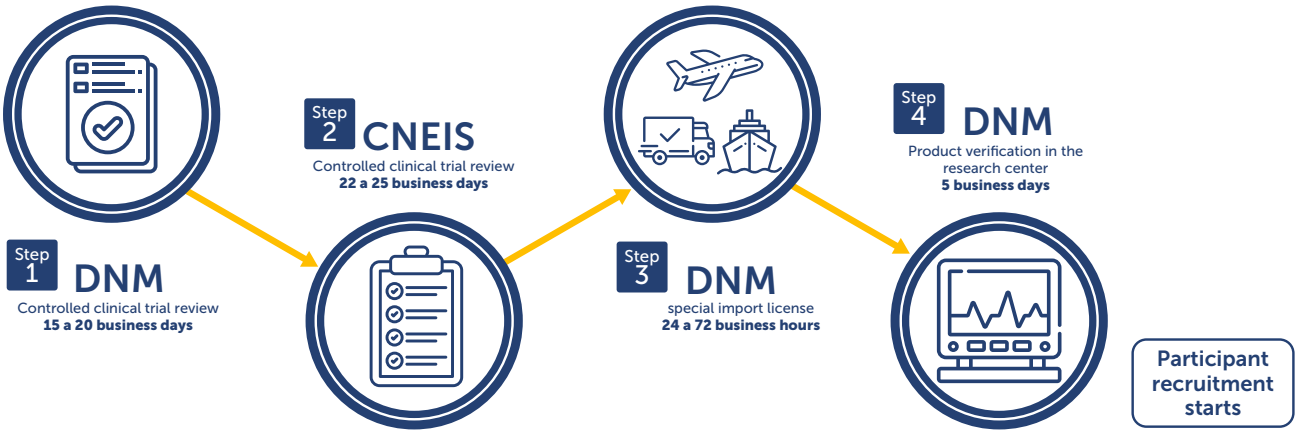
Risk management is so important that there is a specific standard for it, ISO 14971: Medical devices (MD) - Application of risk management to MDs, applicable to the entire life cycle of a medical device, from initial conception to withdrawal from service and final disposal (ISO, 2019). The documents mentioned here are part of the international bibliography that corresponds to the development of clinical trials with medical devices as research products. These are taken as references for national regulatory decisions, so that all evaluations are carried out from the same perspective, taking into account the nature and risk classification of the medical device.

Generalities of the national context

In addition to international guidelines, the evaluation of clinical trials in El Salvador is supported by its own legislation. Regarding national legal documents, the Medicines Law can be mentioned first, (Asamblea Legislativa - República de El Salvador, 2012) in addition to RTS 11.03.02:21 Medical Devices. Requirements for the health regulation of medical devices (OSARTEC, 2023). The efforts being made to strengthen national legislation and technical documentation are due to compliance with the requirements of the World Health Organization, in its document WHO Global Benchmarking Tool Plus Medical Devices (GBT+Medical Devices) for Evaluation of national Regulatory system Of Medical Products (WHO, 2023b), to evaluate the national regulatory systems of countries in the world.

The evaluation of a clinical trial using a medical device as a research product follows the process outlined in Figure 3, in which, together with the national regulatory agency, DNM, the National Health Research Ethics Committee (CNEIS) participates; so that, together, a favorable opinion is authorized and issued, respectively, on the conduct of a test in the national territory.

Figure 3. Clinical trial authorization process



Source: self-made

The DNM, as the national regulatory agency of El Salvador, and based on the aforementioned international and national guidelines, regulations and laws, is prepared to supervise clinical trials of medical devices. In this way, it supports research and innovation in technologies, allowing prototypes of medical devices developed in universities, businesses or industry. They are studied in an equitable and well-founded regulatory framework. Consequently, the quality and reliability of the results obtained in clinical research is ensured, which will make it possible to capitalize on the knowledge generated, while at the same time guaranteeing the health of the participants.

Bibliographic references

1. AEMPS. (2019,Jan 7). Clinical trials with drugs for human use . Retrieved on 11/03/2023, from the Spanish Agency for Medicines and Health Products: https://www.aemps.gob.es/medicamentos-de-uso-humano/investigacion_medicamentos/ensayosclinicos/
2. AMM. (2015). WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects . Retrieved on October 18, 2023, from the World Medical Association: https://www.wma.net/es/policies-post/declaracion-de-helsinki-de-la-amm-principios-eticos-para-las-investigaciones -medical-in-human-beings/
3. Asamblea legislativa - República de El Salvador. (2012). Medicines Law . Retrieved on October 18, 2023, from the Legislative Assembly - Republic of El Salvador: http://cssp.gob.sv/wp-content/uploads/2016/05/Ley-de-Medicamentos.pdf
4. Asamblea legislativa - República de El Salvador. (2012). General Regulations of the Medicines Law . Retrieved on October 19, 2023, from the Legislative Assembly - Republic of El Salvador: https://www.medicamentos.gob.sv/wp-content/uploads/2022/09/REGLAMENTO-GENERAL-DE-LA-LEY-DE-MEDICATIONS.pdf
5. Faris, O. &. (2017). An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials. New England Journal of Medicine (14). Retrieved from https://www.nejm.org/doi/full/10.1056/nejmra1512592
6. FDA, F. A. (2013). Investigational Device Exemptions (IDEs) for Early viability Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies. Guidance for Industry and Food and Drug Administration Staff. Obtenido de https://www.fda.gov/media/81784/download?attachment
7. GHTF. (2012). Principles of Medical Devices Classification. Recuperado el 11 de 2023, de

https://www.imdrf.org/sites/default/files/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n77-2012-principles-medical-devices-classification-121102.pdf
8. ICH. (2016). Integrated Addendum to ICH E6(R1): Guideline For Good Clinical Practice E6(R2). Recuperado el 8 de octubre de 2023, de ICH: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
9. ISO. (2019). Medical devices/medical products (MD) - Application of risk management to MDs . Retrieved October 18, 2023, from International Standard Organization.
10. ISO. (2020). Clinical investigation of medical devices for human subjects - Good Clinical Practice . Retrieved from International Standard Organization.
11. Kerzberg, E. (2008). Manual of clinical and pharmacological investigations. Rosario, Argentina: Corpus Editorial. Obtained from https://elibro.net/es/ereader/bibliotecaudb/67149?page=1.
12. Medical Device Coordination Group. (October 2022). Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745. Obtained from European Commission: https://ec.europa.eu/docsroom/documents/41183?locale=en.
13. Neugebauer, E.R. (2017). Specific barriers to the conduct of randomized clinical trials on medical devices. Trials, 18 (427). Retrieved from https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2168-0#citeas
14. OSARTEC. (2023). RTS 11.03.02:21 Medical Devices. Requirements for the Health Regulation of Medical Devices . Retrieved on October 18, 2023, from OSARTEC: https://www.medicamentos.gob.sv/wp-content/uploads/2022/09/RTS-dos-documentos23-08-2022.pdf
15. Parvizi N, W. K. (Febrero de 2014). Regulation of medicines and medical devices: contrasts and similarities. Clinical Medicine, 14(1), 6-12. Obtenido de https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873624/pdf/clinmed-14-1-6.pdf
16. Saha, P. S. (June de 1988). Clinical trials of medical devices and implants: ethical concerns. EEE Engineering in Medicine and Biology Magazine, 7(2), 85-87. doi:10.1109/51.1982
17. Santarelli, D. (05 de Septiembre de 2018). Clinical Trials - Meical Device Trials. Obtenido de Genesis Research Services: https://genesisresearchservices.com/clinical-trials-medical-device-trials/#
18. Van Norman G, e. a. (2016). Drugs, Devices, and the FDA: Part 2. Journals of the American College of Cardiology, 1(4). Obtenido de https://www.jacc.org/doi/epdf/10.1016/j.jacbts.2016.03.009
19.WHO. (2016). Guidance on good data and record management practices - Annex 5. Recuperado el 18 de octubre de 2023, de World Health Organization - Technical Report Series N°996: https://www.gmp-compliance.org/files/guidemgr/WHO_TRS_996_annex05.pdf
20.WHO. (2017). WHO Global Model Regulatory Framework for Medical Devices Including in Vitro Diagnostic Medical Devices. Obtenido de WHO Medical Device Technical Series: https://iris.who.int/bitstream/handle/10665/255177/9789241512350-eng.pdf?isAllowed=y&sequence=1
21.WHO. (2023). Clinical Trials. Recuperado el 15 de noviembre de 2023, de World Health Organization: https://www.who.int/health-topics/clinical-trials#tab=tab_1
22.WHO. (2023). WHO Global Benchmarking Tool Plus Medical Devices (GBT+Medical Devices) for Evaluation of National Regulatory Systems of Medical Products. Obtenido de World Health Organization: https://www.who.int/publications/m/item/08-GBT-MD-rev-VI-MD-ver-1-CT