REGULATORY CONSIDERATIONS IN THE DEVELOPMENT OF CLINICAL TRIALS

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Discussion

Clinical trials constitute a fundamental tool for public health systems, as they allow the identification of safe and effective therapies for treating diseases, as well as interventions for their prevention, including vaccines. The primary objective of this type of research is to address public health needs, improve quality of life, and enhance the well-being of not only clinical trial participants, but also the entire population, receiving products that eventually will reach the market (PAHO, 2026). Prior to their execution, *in vitro* testing and non-clinical studies using animal models are conducted to ensure safe use, and a secure transition to clinical phases involving human subjects. Clinical trials must be carried out with rigorous ethical principles, and regulatory systems that guarantee participant protection and quality of investigational data.

A clinical trial compares the effects of an experimental product against another product—either a placebo or a reference product—is always prospective, and requires the monitoring of participants throughout its entire execution (Friedman et al., 2015).

Individuals who participate in clinical trials do so voluntarily to test pharmaceuticals, biologics, biotechnological products, vaccines, and medical devices. It is worth noting that these studies require rigorous preparation from design to execution, carefully safeguarding both the integrity of the participants, and the data generated, which will be used subsequently to obtain marketing authorization from any national regulatory authority.

Keywords: preclinical, clinical, quality control, ethics

This article analyzes the regulatory aspects upon which clinical trials are based, drawing on available scientific evidence, covering non-clinical and clinical stages, quality control of investigational products, and the ethical dimension that must govern the development of all stages.

Non-Clinical Studies

Non-clinical studies constitute a fundamental stage in drug development, as they are conducted prior to administration in humans.

Their primary function is to generate scientific evidence regarding the safety, pharmacological action, and toxicity profile, of the molecule. All of the above contribute to identify potential risks related to toxicological data, and define strategies for the design of clinical trials in human subjects.

From a regulatory standpoint, non-clinical testing is a critical requirement for both ethics committees and regulatory authorities, as the data generated by this studies allow extrapolation to clinical trials involving humans. Non-clinical studies are generally developed through *in vitro* testing and/or *in vivo* studies using animal models. The International Council for Harmonisation (ICH, 1998) establishes the duration for chronic toxicity testing in animals: six months for rodent studies and nine months for non-rodent studies. Non-clinical studies include pharmacodynamic testing—which defines the molecule's mechanism of action and biological activity—, pharmacokinetic testing—aimed at determining absorption, distribution, metabolism, and excretion (ADME)—, and toxicity testing, which allows for the identification of adverse events based on the exposure level and treatment duration (ICH, 2009).

Non-clinical studies must comply with international standards that guarantee the integrity, traceability, and reliability, of the data generated; therefore, they must be conducted in accordance with Good Laboratory Practices (GLP). Currently, toxicity studies must be carried out following GLP principles established by the Organization for Economic Co-operation and Development (OECD, 1998).

It is worth noting that not all non-clinical studies are developed in the same manner, as factors such as product type or target population characteristics may demand additional regulatory considerations. This is the case of advanced therapies, which present specific implications regarding their mechanisms of action or immunological concerns; as well as products intended for populations with childbearing potential, which require the evaluation of reproductive effects (ICH, 2009).

The regulation of non-clinical studies continuously evolves based on accumulated experience in pharmaceutical development. An example of this is the implementation of the '3Rs' principle: Replacement, Reduction, and Refinement, in the use of laboratory animals. This strategy aims to decrease the use of experimental animals to the greatest extent possible, promoting research with alternative methodologies to substitute them, provided that the data generated remains reliable, with the purpose of minimizing the suffering of animals.

The toxicological safety data generated during non-clinical studies allow for the evaluation of the benefit-risk ratio, and support a safe transition to the clinical stages involving human subjects. Agencies such as the U.S. Food and Drug Administration (FDA) provide guidance documents for the industry, which direct the estimation of the maximum safe starting dose to be used in initial clinical trials involving healthy adult volunteers (FDA, 2005). This guidance outlines the factors for determining the starting dose; hence, non-clinical data is fundamental to protect clinical trial participants.

Clinical Development

The development of clinical studies involving human subjects is divided into Phases I, II, III, and IV, each with specific characteristics and requirements, pursuant to applicable ethical and regulatory frameworks. This stage is of paramount importance, as it represents the first time a new product is being tested in healthy or diseased participants—depending on the type of molecule under evaluation—in order to determine its safety and efficacy, this stage should be developed with Good Clinical Practices (GCP), which entails ensuring a risk-based design, rigorous execution, participant protection, and the integrity of the data generated from the intervention with the new product. Consequently, prior to its execution, every clinical trial must obtain approval from an ethics committee, and authorization from a national regulatory authority (ICH, 2025).

Phase I is the stage in which the product is administered to humans for the first time; its primary objective is to verify the safety and behavior of the product within the body. One of its distinctive characteristics is that the intervention group consists of a small number of participants.

Phase II aims primarily to evaluate the efficacy of the investigational product, and to determine the optimal dose; furthermore, safety continues to be assessed by identifying potential adverse events. The number of participants is larger compared to Phase I, and in some designs, a placebo or a comparator treatment is included.

Phase III is the confirmatory stage of the product's efficacy; it also monitors the occurrence of adverse events that were not identified during Phase II, given that the number of participants is considerably larger. It is fundamental to compile all obtained results to present them before national regulatory authorities (NRAs), to secure marketing authorization.

Subsequently, Phase IV studies are conducted with the objective of identifying rare adverse events that did not emerge during the developmental phases, thereby, completing information regarding the product's effectiveness under real-world conditions of use (Vera Carrasco, 2022).

Quality Control of Investigational Products

The quality of investigational products is fundamental in the development of pharmaceuticals, vaccines, biologics, biotechnological products, and advanced therapies. This process begins with the selection of the raw materials used to synthesize the active substance, which will be used throughout all developmental stages of the investigational product—namely, from the non-clinical to the clinical stage.

Similarly, it is necessary to ensure that the manufacturing sites of the active substance comply with proper manufacturing standards (ICH, 2000). The manufacturer of the finished product to be administered to clinical trial participants in a specific dosage form, must comply with Good

Manufacturing Practices (GMP) (ICH, 2025), which ensure that the investigational product satisfies the quality standards proposed by the manufacturer. The primary objective of quality control is to guarantee that products are safe, possess high purity, and maintain the necessary potency throughout all phases of the clinical trial.

The quality of investigational products should not represent an obstacle to the execution of a trial, but rather, be considered a guarantee that what is being administered to participants complies with the regulatory requirements mandated by national regulatory authorities (NRAs). The validity of the obtained results depends heavily on the quality of the administered product; therefore, the sponsor, in conjunction with the investigative team, must guarantee quality throughout the entire clinical trial: from manufacturing and distribution to the research site, to storage and dispensing (ICH, 2025).

The finished product must possess the necessary documentation to support its identity, quality, purity, potency, and, above all, its batch-to-batch consistency over time, and throughout the entire lifecycle of the investigational product (Ro, 2025).

In this regard, the ICH E6 (R3) Good Clinical Practice guideline, published in 2025, includes a section establishing that the sponsor is responsible for determining the storage conditions, and the shelf life of the investigational product.

Chemistry, Manufacturing, and Controls (CMC) documentation is fundamental in regulatory applications, as it allows regulatory authorities to evaluate whether the investigational product maintains the quality attributes for which it was designed throughout the duration of the clinical trial in each of its phases. Stringent regulatory authorities, such as the FDA, provide their regulated entities with guidance documents that define the CMC information required for Phase I clinical trials (FDA, 1995), and for Phase II and III clinical trials (FDA, 2003). These guidelines establish quality criteria for both the active substance and the medicinal product, as well as requirements for stability studies. The quality control of investigational products is essential for the development of clinical trials, given that proper implementation guarantees compliance with regulations and, fundamentally, protection of participant safety.

Ethical Aspects in the Development of Clinical Trials
In the conduct of clinical trials, ethical frameworks constitute a fundamental pillar, as they guarantee the protection of the rights, safety, well-being, and dignity of participants. Documents such as the Declaration of Helsinki establish the ethical principles and scientific requirements, that must be met by protocols developed for clinical trials involving human subjects. Among the key elements are the involvement of ethics committees in the approval of studies, the protection of participant data ensuring privacy and confidentiality, the signing of an informed consent, as a free and voluntary process, exempt from pressures of any kind, as well as the transparency of the results, whether positive or negative (World Medical Association [WMA], 2024).

The entire research team—including investigators, sub-investigators, and coordinators, among others—as well as the sponsors, must guarantee compliance with established ethical guidelines. Participants must be treated with respect, and receive clear and understandable information from those responsible for the research, regarding all activities and procedures to be performed, along with a detailed explanation of the potential benefits and risks entailed by their participation in the clinical trial (ICH, 2025).

Likewise, the Declaration of Helsinki (WMA, 2024) recommends that a benefit-risk assessment should be conducted, ensuring that the clinical trial possesses sufficient evidence and justification to demonstrate, that the benefits substantially outweigh the risks to which participants might be exposed.

Review by an ethics committee is of paramount importance for the correct application of ethical principles throughout all stages of the clinical trial—before, during, and upon completion—in order to safeguard participants at all times (ICH, 2025).

It is important to emphasize that, within the regulation of clinical trials, no single stage is more relevant than another; each serves a specific and indispensable function, from non-clinical testing (*in vitro* and using animal models) to clinical phases, quality control, and ethical stages. Therefore, each stage demands rigorous attention and oversight at the time of its execution, ensuring that the generated data maintain integrity and quality, and that, throughout the stages involving human subjects, their dignity and safety are respected at all times.

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