

SAFETY ANALYSIS INSIGHT

Safety Strategies and Considerations in Early Clinical Drug Development

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Early clinical drug development forms the foundation for assessing the drug's impact throughout its development lifecycle. Uncertainty may arise from particular knowledge, or lack thereof, regarding the mode of action of the IMP, the presence or absence of biomarkers, the nature of the target, the relevance of available animal models and/or findings in non-clinical safety studies. In addition, risks may derive from the characteristics of the population to be studied, whether healthy volunteers or patients, including potential genetic and phenotypic polymorphisms influencing PD and PK (i.e. in the intended target or in enzymes and organ functions influencing PK).¹ Implementing effective safety strategies is essential to support identification, evaluation and management of risks associated with a new pharmaceutical product. The implementation of safety strategies from the beginning, promotes both the efficacy and safety of the drug in subsequent phases of development.

Preclinical Safety Assessments

Preclinical safety studies play a vital role in the pharmaceutical development process, serving not only to evaluate pharmacological and toxicological effects before human trials begin, but also throughout the clinical development phase. These studies involve a comprehensive characterization of the drug, which includes both in vitro (lab-based) and in vivo (animal-based) tests. Preclinical safety testing should consider: 1) selection of the relevant animal species; 2) age; 3) physiological state; 4) the manner of delivery, including dose, route of administration, and treatment regimen; and 5) stability of the test material under the conditions of use.²

Toxicity-testing approaches are integral, providing data on potential toxic effects and the dose-response relationship, and traditionally have been based on studies in experimental animals. However, in the last 20 years, there has been increasing concern regarding the sustainability of these methodologies.³ New approach methodologies are being considered globally with various initiatives initiated to address this need.

First-in-Human (FIH) Trials

FIH trials, often phase I clinical trials, are designed with the primary goal of assessing the drug's safety profile in a small number of participants. Phase I trials provide a bridge between preclinical findings to human exposure, with safety monitoring continuing in the guise of adverse event monitoring, vital signs, blood tests, and other biomarkers, all scheduled as per the approved protocol design. The design of these trials often includes a dose-escalation study, where doses are increased gradually among different cohorts until a maximum tolerated dose is identified. The trial design should provide a specific plan for monitoring for adverse events or adverse reactions. The mode of action of the investigational medicinal product, findings in the non-clinical toxicity studies and any anticipated responses should be used to identify likely adverse reactions.¹

Ethical Considerations

Ethical guidelines are established for clinical research to protect healthy volunteers, patients, and to preserve the integrity of the science. The ethical guidelines in place today were primarily a response to past abuses, examples of which include 'The Tuskegee experiment', which occurred in Alabama, USA, where available treatment was withheld from 400 African American men with syphilis so that scientists could study the course of the disease. It has been found that disclosure of the study in 1972 is correlated with increases in medical mistrust and mortality and decreases in both outpatient and inpatient physician interactions for older black men.⁴ Some of the influential codes of ethics and regulations that guide ethical clinical research have been developed in response to such examples. These include: Nuremberg Code (1947), Declaration of Helsinki (2000), Belmont Report (1979), CIOMS (2002), U.S. Common Rule (1991).

Ethical guidelines include obtaining informed consent from participants, who must be fully aware of the potential risks and benefits of the trial, and obligations of sponsors and investigators. The global distribution of clinical trials is changing. Trials are shifting to low-income and middle-income countries (LMICs), where markets are expanding; participants are easily recruited; and research costs remain low.⁵ Therefore, clear guidelines need to be in place to protect vulnerable populations, including children and pregnant women, as well as an equitable distribution of burdens and benefits in the selection of groups of subjects. Research in populations and communities with limited resources should be considered. The rights of injured subjects to treatment and compensation are critical too, as past examples such as the 'Elephant Man trial', where six healthy young men were treated for organ failure after experiencing a serious reaction within hours of taking the drug TGN1412 in a clinical trial, were told they would be likely to develop cancers or auto-immune diseases as a result of their exposure to the drug. However, strict protections can negatively impact LMICs. For example, in 2012, following a ruling in India that required sponsors to provide free clinical care to participants injured during a trial, whether or not the injury was research-related, clinical trial registrations fell sharply after the new protections were introduced.⁶

The independence of ethics committees or institutional review boards is mandatory to safeguard the rights and welfare of the participants and ensure that the risk-benefit ratio remains favourable.

Regulatory Framework

Countries and regions have adopted a variety of strategies and regulatory measures to streamline and support the approval process for clinical trials. Many regions adhere to harmonized guidelines such as those provided by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). These standards help ensure that safety, quality, and efficacy data are reliable and consistent across international borders. Considerations need to be made regarding the differing approval processes available to companies, such as the centralized approval in the European Union which allows for a single application to secure approval across multiple EU member states and those in the USA, where the FDA offers expedited pathways for certain drugs, including Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review, designed to facilitate the development and hasten the review of drugs that meet significant unmet medical needs.

Regulatory agencies are also increasingly supportive of adaptive trial designs that permit modifications to the trial based on interim results. Adaptive design trials have been shown to increase the efficiency of traditional clinical trials by facilitating the selection of the dose, reducing the number of patients exposed to ineffective or potentially toxic doses, aiding the precise calculation of sample size and reducing the duration and costs of clinical development. These new designs in early drug development enable the integration of preclinical data, the incorporation of information beyond the traditional dose-limiting toxicity period, findings from other trials and emerging safety data, thereby increasing the likelihood of accurately determining any benefit of a new treatment and complying more quickly with regulatory requirements for efficacy and safety.⁷

This flexibility can lead to faster and more efficient trials as well as identifying safety issues early and adjusting doses or protocols to mitigate any risks to participants without compromising the integrity of the study. Having a system in place or access to global regulatory intelligence ensures compliance with regulatory guidelines and therefore upholds safety and efficacy standards.

Risk Management

Risk management is a term used throughout ICH Guideline for Good Clinical Practice, and has many differing connotations such as risk based monitoring, risk assessments, and risk to critical trial processes, but in the context of safety in early drug development, risks should be captured in the Investigator Brochure (IB). The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).⁸

The **Development Core Safety Information (DCSI)** plays a crucial role in risk communication during clinical trials. It serves as an independent section within the Investigator's Brochure (IB), mirroring the Company Core Safety Information (CCSI). The DCSI provides a standardized summary of all relevant safety data described in more detail elsewhere in the IB. By including safety information in the DCSI, researchers ensure consistent risk communication to study participants, regulatory authorities, and other stakeholders. Additionally, the DCSI facilitates efficient safety monitoring, timely identification of adverse events, and compliance with regulatory requirements. As trials gather accumulating safety data, regular updates contribute to the overall safety assessment of the investigational product.

Patient Selection and Biomarkers

Careful selection of trial participants and the use of biomarkers can also play significant roles in safety strategies. Selecting the right patient population with characteristics that match the intended demographic for the drug or treatment, can more accurately determine how safe and effective the treatment is within that group. A safety biomarker can broadly be defined as “a biomarker that is measured before or after an exposure to a medical product or environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect”.⁹

Biomarkers are an increasingly important drug development tool for monitoring and potentially predicting the safety and efficacy of novel therapeutics in both nonclinical and clinical environments and have the promise to accelerate and improve the drug development process.¹⁰

To understand the value of a biomarker, it is necessary to know the pathophysiological relationship between the biomarker and the relevant clinical endpoint. Good biomarkers should be measurable with little or no variability, should have a sizeable signal to noise ratio, and should change promptly and reliably in response to changes in the condition or its therapy. Biomarkers can be used to monitor and predict safety outcomes, providing an additional layer of safety monitoring that can help in making real-time decisions about the trial's continuation.¹¹

As we look to the future, considerations need to be made about how different clinical trial designs are likely to be and the impact of those difference on safety strategies. Patient recruitment methods will be impacted based on wearables, diagnostics and implantable devices. Will these new technologies and the ability to precisely and easily extract real time data support safety strategies, and adaptive trial design? As more new approach methodologies are being evaluated globally eliminating the need for animal studies, elements of pre-clinical assessment may change, with more preclinical modelling being utilised. Will this support faster pharmacological and toxicological data analysis? In conclusion, safety strategies in early clinical drug development require an integrative approach combining scientific, ethical, and regulatory principles, but need to shift gear periodically to keep up with the technology, complexity, and customization of future clinical trials.

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