Written by Alexandra Argyraki,
Excelya PV & Safety Department

Pharmacovigilance challenges in early phase clinical trials

INTRODUCTION

Early phase clinical trials have their own unique challenges, as they play a vital role in drug development. During early trials we aim to evaluate the safety, tolerability, and pharmacokinetics of investigational compounds in human subjects. These trials often involve small participant populations, novel therapies, and limited exposure data. Consequently, identifying and managing potential risks become paramount in ensuring the safety and well-being of trial participants.

This whitepaper delves into the multifaceted challenges faced by sponsors, investigators, and regulatory bodies in pharmacovigilance during early phase clinical trials. We aim to provide a comprehensive overview of the key areas that demand heightened attention and proactive measures in the context of safety monitoring and adverse event reporting.

Authorities such as the World Health organisation have guidelines and tools to help us achieve this, and regulatory boards help us keep in check with providing optimal patient care.

We hope to help you navigate this process, and provide some background knowledge of how you can best find solutions to these unique challenges.

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EARLY PHASE CLINICAL TRIAL CHALLENGES

Early phase clinical trials serve as the crucial foundation for advancing medical knowledge and identifying promising investigational compounds. By assessing safety, pharmacokinetics, and early efficacy signals, these trials provide critical insights that shape subsequent phases of clinical development. Rigorous study design, ethical considerations, and regulatory oversight are paramount to ensure participant safety and the validity of trial outcomes. Through the implementation of robust early phase trials, researchers and healthcare professionals pave the way for the development of safe and effective therapies that address unmet medical needs.

Excelya's Pharmacovigilance experts have extensive practical experience in handling studies of this kind, across multiple geographies and therapeutic areas. For more information about the services we offer, or to see a brochure or case study, please contact marketing@excelya.com

TYPES OF EARLY PHASE TRIALS

Phase I (First in Humans, Dose Escalation):

The first time a new drug is tested in Healthy Volunteers or Patients, the aim is to assess the safety/toxicity of the drug and find the Maximum Tolerated Dosage (MTD) and the Recommended Dosage for Phase II (RP2D).

These trials are conducted open-label with dosage cohorts and a small number of participants.

Phase II (Proof of Concept):

Phase II studies are usually randomized studies evaluating the safety (short-term adverse events) and efficacy of a drug with a larger number of participants.

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EARLY PHASE CLINICAL TRIALS REASONS FOR FAILURE

Early phase clinical trial failures can occur due to a combination of factors, ranging from safety concerns and efficacy shortcomings to study design limitations, technical challenges, regulatory compliance issues, and scientific uncertainties. Understanding and addressing these factors can help researchers improve the design, conduct, and interpretation of early phase trials, increasing the likelihood of successful outcomes. Through continuous learning and adaptation, the scientific community can refine early phase clinical trial strategies and contribute to the development of safe and effective therapies that benefit patients and advance medical knowledge.

While early phase clinical trials play a crucial role in drug development, it is important to acknowledge that not all trials achieve their intended objectives. This chapter explores the factors that can contribute to the failure of early phase clinical studies, highlighting the challenges and complexities researchers may encounter during this critical phase of investigation.

Inadequate Safety Profile

Insufficient safety data can pose a significant challenge in early phase trials. If unexpected adverse events or dose-limiting toxicities emerge, it can lead to trial termination or modification. Poor safety profiles may result from limited preclinical data, inadequate participant selection criteria, or an incomplete understanding of the compound's mechanism of action.

Lack of Efficacy Signals

Early phase trials also aim to identify preliminary efficacy signals, but sometimes fail to demonstrate the desired therapeutic effect. Reasons for the lack of efficacy signals may include inappropriate dose selection, suboptimal patient population, variability in drug response, or a flawed study design. Insufficient evidence of efficacy can hamper the progression of the investigational compound to later stages of clinical development.

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EARLY PHASE CLINICAL TRIALS REASONS FOR FAILURE

Inadequate Study Design and Endpoints

Flawed study design and inappropriate choice of endpoints can contribute to trial failures. Early phase trials require careful consideration of appropriate study designs, such as dose-escalation strategies or controlled comparator arms, to address specific research questions. Additionally, selecting relevant and sensitive endpoints to measure the desired outcomes is crucial for evaluating both safety and efficacy.

Technical and Operational Challenges

Early phase trials often face technical and operational challenges that can impact their success. These challenges may include difficulties in recruiting an adequate number of participants, delays in study initiation and enrollment, challenges in collecting and analyzing pharmacokinetic data, or issues related to trial execution and monitoring. Inadequate resources, insufficient infrastructure, or poor trial management can hinder the smooth conduct of early phase studies.

Regulatory and Ethical Considerations

Non-compliance with regulatory requirements and ethical standards can lead to trial failures. Inadequate adherence to Good Clinical Practice (GCP) guidelines, failure to obtain proper regulatory approvals, or ethical concerns related to participant welfare and informed consent can compromise the integrity and validity of early phase trials.

Scientific Uncertainty and Compound Characteristics

The inherent scientific uncertainties and unique characteristics of the investigational compound can also contribute to trial failures. Factors such as complex pharmacokinetics, unpredictable biological interactions, limited understanding of the target pathway, or emerging safety concerns during early clinical development stages can pose challenges that may lead to trial setbacks.

Pharmacovigilance challenges in early phase clinical trials

EARLY PHASE CLINICAL TRIALS REASONS FOR FAILURE

40%

Lack of Efficacy

Failure to demonstrate the desired therapeutic effect

35%

Safety

- Dose limiting toxicities
- SUSARs
- AESIs

10%

PK/PD

Poor pharmacokinetic/pharmacodynamic properties

15%

Business Reasons

Lack of commercial needs and poor strategic planning

Pharmacovigilance challenges in early phase clinical trials

IDENTIFICATION & MITIGATION OF RISKS

Identifying and mitigating risks in early phase clinical trials are essential for successful drug development. By conducting thorough risk assessments, implementing participant safety measures, addressing protocol design challenges, and ensuring data integrity, organizations can enhance the likelihood of achieving trial objectives while minimizing risks. Proactive risk management strategies contribute to the ethical conduct of trials, the generation of reliable data, and the advancement of novel therapies.

Risk Assessment and Planning

Thorough risk assessment is vital in early phase clinical trials. This involves identifying potential risks associated with the investigational product, study design, participant population, and trial procedures. A comprehensive risk management plan should be developed, outlining strategies to mitigate identified risks and contingency plans to address unforeseen challenges.

Participant Safety and Ethical Considerations

Participant safety is of paramount importance in early phase trials. Rigorous safety monitoring measures, including dose escalation strategies, frequent assessments, and close medical supervision, should be implemented. Ethical considerations, such as informed consent procedures, monitoring vulnerable populations, and risk-benefit assessments, must be carefully addressed to ensure participant welfare.

Pharmacokinetic and Pharmacodynamic Risks

Early phase trials often involve evaluating the pharmacokinetic and pharmacodynamic properties of investigational products. Risks associated with drug metabolism, bioavailability, drug-drug interactions, and potential adverse effects need to be carefully assessed and mitigated. Strategies such as pharmacokinetic modeling, dose optimization, and adaptive trial designs can help manage these risks effectively.

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IDENTIFICATION & MITIGATION OF RISKS

Protocol Design and Execution Challenges

Early phase trials require robust protocol design to achieve study objectives while minimizing risks. Challenges in protocol design may include determining appropriate endpoints, defining inclusion/exclusion criteria, selecting the right control group, and choosing relevant biomarkers. Effective execution of the protocol, adherence to Good Clinical Practice (GCP) guidelines, and ongoing monitoring are critical to mitigate risks and ensure data integrity.

Operational and Logistical Risks

Operational and logistical challenges can impact the success of early phase trials. These may include difficulties in participant recruitment, site selection, trial site capabilities, and ensuring reliable drug supply. Risk mitigation strategies may involve engaging experienced investigators and research sites, implementing efficient trial management systems, and fostering effective communication and collaboration among stakeholders.

Data Integrity and Quality Assurance

Maintaining data integrity is crucial in early phase trials to draw accurate conclusions. Robust data management systems, including secure data capture tools, standardized data collection processes, and rigorous quality assurance procedures, should be implemented. Independent monitoring, source data verification, and data validation checks help ensure data accuracy and reliability.

Risk-Based Monitoring and Adaptive Trial Designs

Risk-based monitoring approaches tailored to early phase trials can optimize resource allocation and enhance risk detection. Utilizing adaptive trial designs allows for modifications based on emerging data and reduces unnecessary exposure to risks. These approaches facilitate efficient decision-making, enhance participant safety, and contribute to overall trial success.

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IDENTIFICATION & MITIGATION OF RISKS

Specific & Detailed plan for safety monitoring activities

1. DLTs & AESIs based on pre-clinical research and data from molecules having a similar mode of action
2. DMC Working Procedure – Set stopping rules based on pre-defined safety criteria
3. Timing of subject safety assessments should be pre-specified in line with the known pharmacological and non-clinical safety profile – Extended FU is required
4. Safety training to Clinical Staff/Site Investigator team by the safety team is crucial for them to identify AEs that need to be reported
5. Exemptions from reporting & clear unblinding process for regulatory reporting purposes
6. Well-structured process for serious safety breaches/ protocol deviations

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THE CHALLENGE OF CAUSALITY

The Challenge of Causality is the assessment of whether there is a reasonable possibility of a causal relationship between the adverse event (AE) and the investigational medicinal product (IMP)

Causality should be assessed by the Investigator and the Sponsor

Assessing the reasonable possibility of a causal relationship between an adverse event and the investigational medicinal product requires a thorough evaluation of various factors, including temporal relationship, known safety profile, biological plausibility, dose-response relationship, exclusion of alternative explanations, and expert opinion. It is crucial to consider the totality of evidence and exercise caution when drawing conclusions regarding causality. Clear and transparent documentation of the assessment process and the supporting evidence is essential for regulatory submissions, risk-benefit assessments, and decision-making regarding the investigational medicinal product.

Regulatory Considerations and Guidelines

Regulatory agencies provide guidelines for assessing causality in clinical research. These guidelines often recommend specific statistical approaches and criteria for establishing causality. Compliance with these guidelines ensures that the statistical methods employed are rigorous, transparent, and aligned with regulatory expectations.

However, no universal method and causality scaling exist at EU level.

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THE CHALLENGE OF CAUSALITY

The thorough examination of the Challenge of Causality in clinical research is crucial to ensure patient safety by accurately identifying and understanding the causal relationships between interventions and outcomes.

- Many methods and scales are used to assess the degree of causality between a medicinal product and an event – medical judgment , algorithm methods (WHO, Naranjo) – inconsistency among studies
- Defined method of causality by EMA for cosmetics and medical devices but not for medicinal products
- No matter which causality method and scaling is used, for reporting purposes the causality of AEs is classified either as “not related” or as “related” – binary scale
- Causality can be assessed by the Medical Monitor only or safety team can also reduce the bias by an additional assessment

Harmonization is necessary – One reliable causality method is needed to be imposed by EMA as it is a critical component for reportability of events and success of the clinical trial

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CONCLUSION

Early phase clinical trials play a pivotal role in assessing the safety and efficacy of potential new treatments, making it imperative to identify and address the unique challenges faced during this crucial period.

Awareness of the factors that can result in the failure of a study is an empowering baseline to attempt to avoid them coming into fruition. Mitigating risks and taking reasonable steps to avoid any negative outcomes such as poor strategic planning and dose limiting toxicities can be best avoided by involving subject experts in your study from day one.

Lack of efficacy accounts for the majority of study failures at a reported 40% of all studies failing due to this reason. While a drug or medical device's failure to demonstrate a desired therapeutic effect can seem like a devastating outcome, it can instead be seen as an opportunity to extract crucial insight into potential reformulation requirements or dosing adjustments. Adaptive designs allow for real-time conclusions to be drawn and for the next steps to be pre-emptively determined and actioned, saving time and resources.

The ultimate goal of early phase trials is to determine drug effectiveness in a safe and controlled way so as to not cause risk to patients. In this context, proactive and comprehensive pharmacovigilance strategies are a necessity, since they enable the rapid identification, evaluation, and reporting of adverse events. Early phase clinical trials demand close collaboration between sponsors, investigators, ethics committees, and regulatory authorities to ensure patient safety while fostering medical advancements.

A knowledgeable, specialised team will ensure effective and streamlined navigation throughout this process. By adhering to best practices, embracing innovation, and fostering collaboration, sponsors can ensure that the quest for medical advancements remains steadfast while safeguarding the well-being of patients participating in these crucial trials. Ultimately, a robust pharmacovigilance framework will foster public trust and drive the development of safer and more effective therapies for the betterment of global healthcare.

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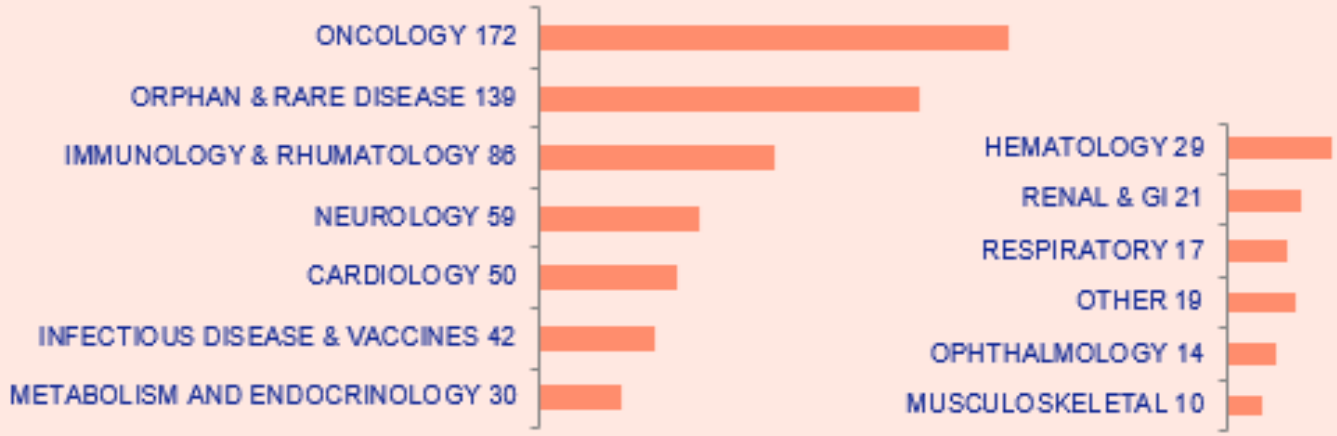
A LEADING GLOBAL MID-SIZED CRO, HEADQUARTERED IN EUROPE

900 PEOPLE

28 COUNTRIES

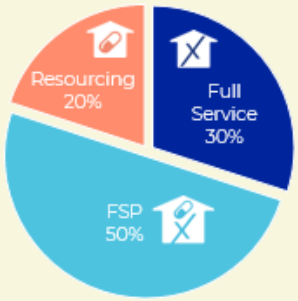
US, EUROPE & ASIA COVERAGE

540+ CLINICAL TRIALS CONDUCTED



STRENGTH IN KEY CRO FUNCTIONS

ONE STOP PROVIDER: 3 OPERATING MODES



SPLIT OF STUDIES BY PHASE TYPE

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6 Therapeutic & Speciality Areas

Oncology & Hematology	Rare Disease & Pediatrics	Inflammation & Immunology
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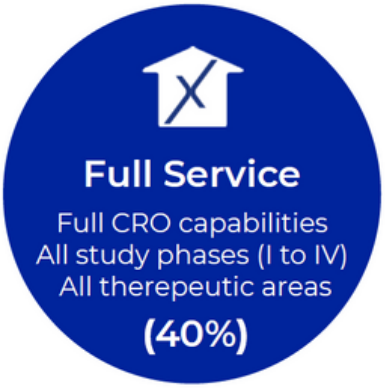
One-stop Provider: 3 Operating Modes



6 Core Centres of Excellence

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