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Research Article

Risk-Based Thinking as a Systematic Approach to the Processes of Phase 1 Clinical Trials

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Abstract:

The aim of this project was to mitigate risk in Phase 1 peditaric clinical trials by applying a risk-based approach. A customized web application was used to map and analyze five key trial processes: quality management, clinical trial study management, pediatric clinical management, investigational medicinal product management, and operations management. A comprehensive risk assessment methodology was then applied, evaluating factors such as severity, probability, and risk priority. Overall 228 processes were identified and assessed. Out of the 228 processes, 78 (34%) exceeded the predefined risk threshold and required corrective actions. These actions were monitored and demonstrated a 92.4% effectiveness in risk reduction. Regular risk re-evaluations, driven by updates to investigator's brochures, new safety data, and internal audits, ensured continuous monitoring. As a result, the implemented risk mitigation measures led to fewer adverse events, maintained high data integrity, and successful regulatory audits. We therefore demonstrated that integrating continuous, proactive risk management into routine clinical trial practice improves patient safety, ensures regulatory compliance, and enhances the overall reliability of Phase 1 pediatric studies.

Keywords: phase 1 clinical trials; risk assessment; risk-based thinking; risk-based quality management; pediatric clinical trials

Introduction

Phase 1 clinical trials represent the foundation of the drug development process, providing essential data on the safety and pharmacokinetics of investigational medicinal products. A critical component of Phase 1 trials is the risk assessment process, aimed at identifying, evaluating, and mitigating potential risks to patient safety, trial integrity, and regulatory compliance. Given the high level of complexity and sensitivity of these trials, adopting a risk-based thinking approach is essential to systematically manage and mitigate risks across all trial processes. By applying structured risk assessments, the methodology seeks to identify, assess, and prioritize risks in clinical trial processes, focusing on those with the greatest potential impact on patient safety and data quality, while mitigating high-risk issues through targeted improvements and continuous monitoring to ensure long-term safety and success in clinical trials.

Methods

The risk assessment methodology was implemented using a customized web application specifically designed for process mapping, employing FMEA/FMECA methodologies.

All the activities of the Phase 1 Clinical Trial Unit were divided into five macro processes: quality management, clinical trial study management, pediatric clinical management, investigational medicinal products management, and operations management. The five macro processes were mapped in accordance with the Quality Management System's Standard Operating Procedures (SOPs).

Each macro process was then divided into 65 primary processes that were identified as essential to the trial's success. Risk assessments were conducted for each primary process, focusing on those with potential impact on critical trial phases. Each assessment involved evaluating the severity and likelihood of identified risks, calculating partial risk levels, and assigning risk priority numbers for each process. Process risks were assessed for 36 predefined macro risk areas, concerning operators and patients, using a 5x5 risk matrix to categorize risks into five levels: negligible, low, moderate, high and very high. In particular, for each primary process in Phase I clinical trials, a risk analysis regarding the following areas was performed:

1. Risk of malpractice (patient identification, protocol deviation, inadequate informed consent procedures, improper administration of investigational products, errors in trial procedures, etc.);
2. Risk related to the safety of patient/ caregivers/visitors health and well-being;
3. Risk related to the safety and quality of biological samples/blood derivates/cellular product/tissues (collection, handling, storage);
4. Risk related to quality of competences (continuous training

and performance evaluations for the all staff involved in patient care and in support activities);

5. Risk related to the preparation, prescription, administration of drugs (adherence to the Good Manufacturing Practices);
6. Risk related to the medical devices;
7. Risk related to the operational continuity;
8. Risk related to the data breach;
9. Risk related to appropriate budget management.

MATRICE DEI RISCHI

PROBABILITY (FREQUENCY)
RARE = IT IS LIKELY THAT IT WILL NOT HAPPEN AGAIN
UNLIKELY = IF IT HAPPENS, IT WILL BE RARE POSSIBLE = IT COULD HAPPEN
PROBABLE = IT IS LIKELY TO HAPPEN OFTEN
ALMOST CERTAIN = IT IS CERTAIN THAT IT WILL HAPPEN

SEVERITY
CATASTROPHIC = DRAMATIC IMPACT
MAJOR = SIGNIFICANT IMPACT MODERATE = MODERATE IMPACT
MINOR = MINOR IMPACT
NEGLIGIBLE = NEGLIGIBLE IMPACT OR NO IMPACT

RISK
R = P X S

RESULT:

☐15-25 very
☐8-12 high
☐4-6 moderate
☐0-3 low

PROBABILITY (FREQUENCY) / SEVERITY	☐ 1 RARE	☐ 2 UNLIKELY	☐ 3 POSSIBLE	☐ 4 PROBABLE	☐ 5 ALMOST CERTAIN
☐5 catastrophic	5	10	15	20	25
☐4 major	4	8	12	16	20
☐3 moderate	3	6	9	12	15
☐2 minor	2	4	6	8	10
☐1 negligible	1	2	3	4	5

Figure 1: 5x5 Risk Matrix

The results were expressed as Detectability: This refers to the likelihood that the risk event or its effects can be detected before they cause harm. It assesses how easily the hazard or failure can be identified. A higher detectability score indicates that the risk is more easily noticed and can be addressed before causing significant damage.

The concept of detectability is applied to each identified risk situation. Detectability refers to the likelihood that a defect or failure will be discovered before it can cause significant harm or adverse effects. The detectability value is used to calculate the IPR (Risk Priority Index) indicator, which allows us to prioritize the interventions to be implemented to mitigate the potential effects of detected risk situations.

The final results were used to prioritize risk mitigation actions and and monitor the effectiveness of corrective interventions over time.

Results

The risk assessment revealed that 34% (78 out of 228) of the processes exceeded the predefined risk threshold (RK > 8). These processes were classified as moderate to very high risk and triggered the implementation of improvement actions. For each identified risk, improvement actions were developed, which included clear descriptions of the issues, assigned responsibilities, performance monitoring indicators, deadlines, and the projected risk reduction following the implementation of mitigation strategies.

The effectiveness of these risk mitigation actions was evaluated annually, showing a 92.4% reduction in risk levels. The annual reviews included re-assessments caused by changes in the investigator's brochures, new safety data, and regulatory amendments. In addition, the risk management strategy included continuous monitoring tools, such as internal audits and an anomaly register, to ensure the ongoing effectiveness of mitigation strategies.

Discussion

The implementation of a systematic risk management approach in Phase 1 pediatric clinical trials processes has proven to be an effective method for identifying critical risks and implementing necessary improvement actions. The assessment of risks related to the investigational medicinal products, clinical management, and quality management processes ensured early identification of potential issues and timely implementation of mitigation measures.

Regular assessments, re-evaluations of risks, and the implementation of improvement actions based on risk prioritization contributed to reducing the likelihood of adverse events, and ensuring the quality of the data obtained.

Conclusion

The results from this study highlight the importance of adopting a proactive, continuous approach to risk management in clinical trials to ensure long-term safety and reliability. Through continuous monitoring, regular re-assessments, and data-driven improvements, clinical trial sponsors and investigators can better manage the complexities of Phase 1 trials while safeguarding the health of participants and ensuring regulatory compliance.

This study demonstrates that the integration of continuous, proactive risk-based management across all key processes of Phase 1 pediatric trials significantly reduces operational and patient-related risks. Its adoption as a routine standard in early-phase trials could represent a best practice model to ensure long-term safety, regulatory compliance, and clinical data integrity.

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