Risk Assessment in Clinical Trials

PEER REVIEWED

Risks are an integral part of clinical trials. We routinely come across various risks while managing clinical trials which are related to quality, safety, timeline, or budget and they may easily affect the objectives and outcomes of the trials. Risk management, which involves risk identification, assessment, planning, tracking and controlling, is an important aspect that one has to look into to ensure successful completion of a clinical trial. With increased clinical R & D budgetary constraints and complexities of clinical trials, risk management has become an essential piece of clinical trial management to ensure good return on investment. The core of risk management is the identification and assessment of the risks on a continuous basis for risk-bearing activities throughout the planning, conduct and close-out phase of clinical trials.

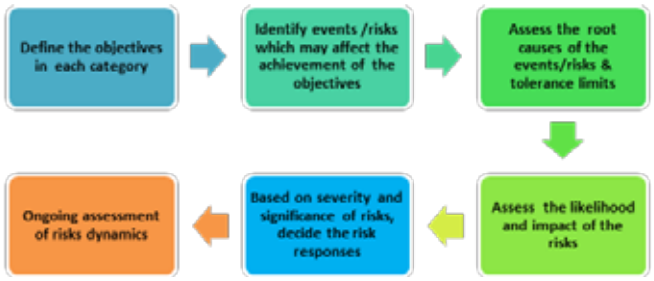
Risk Assessment in Clinical Trials

A robust risk assessment process in clinical trials forms the foundation for an effective risk management programme. Risk assessment is a systematic process for identifying and evaluating events that could affect the achievement of clinical study objectives related to quality, safety, timelines and budget, positively or negatively. After issuance of the guidance on risk-based monitoring by the FDA, sponsors/CROs have demonstrated a keen interest in adopting a systematic approach to risk assessment in clinical trials. It is all about taking a study-specific holistic approach to identify all potential risks and evaluate those risks, to assess the probability of occurrence and impacts. Effective risk action planning involves effective risk identification and proactive root cause analysis. Therefore, it is necessary to thoroughly identify the sources of all potential risks and root causes to improve action planning for better outcomes. A right implementation of a robust risk assessment process during planning, conduct and close-out of a clinical trial empowers the study management team to better identify and evaluate the right risks for a clinical trial, all while maintaining the appropriate controls to ensure effective and efficient quality conduct, patient safety and regulatory compliance.

Risk Assessment Process

Define the objectives of each category:

Identifying objectives of each category or aspect is key in order to achieve the overall goals of the study. The categories may be timelines, safety, quality and budget, etc. For example, in the timelines category, one of the objectives would be meeting expected patient recruitment timelines or achieving regulatory approval as per the planned duration. In safety, one of the objectives would be keeping the average SAE rate per subject below the expected value. The other objective could be keeping the



dropout rate below the expected number in the protocol in quality category. Once the category and objectives are set, it provides a platform to identify risks or events which may affect the achievements of these objectives.

Identify events/risks which may affect the achievement of the objectives :

For complete risk assessment, one needs to take a holistic approach of risk identification and assessment. This requires through assessment of various internal and external processes, systems, people and technology involved in a clinical trial, which may pose risks to achievements of the objectives. Clear identification of risk/s which will affect the objective/s is essential for risk planning and controlling action. The table below illustrates some categories with key types of risks which may affect the achievements of the objectives in those categories.

Categories	Example of Types of Risks/Events
Timelines	Patient recruitment rate Regulatory approval timelines CRFs incompletion rate
Safety	Number of AEs/SAEs per patient Number dropped out due to AE Number of AEs/SAEs with definite causal relationship
Quality	Number of protocol deviations/violations per site Number of DCFs generated per site Number of incidences with incomplete/missing subject diary
Compliance	Number of deviations in SAE reporting Number of incidences with improper ICF process/ documentation Inadequate monitoring of clinical investigations
Budget	Increase in monitoring visits per site Increase in clinical trial duration Increase of sites' budgets

Assess the root causes of the events/risks and tolerance limits:

Root cause analysis (RCA) is an important process of risk assessment and it involves scientific principles. Even formulating a proper risk statement helps to identify the actual risk and root cause. For example, a risk statement could be 'Because it is a rare disease study, there is a risk

Risks	Example of Tolerance limit / Threshold*
Patient recruitment rate	>20% sites below expected recruitment rate
CRF completion rate	>20% pending CRFs for more than 30 days
Pending DCFs for any site	>10% pending DCFs for 30 days or more
Number of times a subject misses subject diary	>2
Number of subjects randomised that do not meet eligibility criteria	>1
Major protocol deviation	>1

*Tolerance limit/threshold will vary study to study

that the sites may not recruit patients as per the expected rate, resulting in delays in patient recruitment'. Another example could be 'Because the site does not have enough experience in GCP, there is a risk that the site may not follow the protocol correctly, resulting in issues related to data quality'. Such a complete risk statement helps to identify the actual risk, root cause and consequences. Identification of right root cause facilitates effective action planning and thereby controlling or mitigation of risks. RCA also supports improving processes/systems to minimise risk or eliminate it completely. As per an FDA guidance document on "Oversight of Clinical Investigations – A Risk Based Approach to Monitoring", following the identification of critical data and processes, a thorough risk assessment should be performed to identify and understand the nature, sources, and potential causes of risks that could affect the collection of critical data or the performance of critical processes. The risks to critical data and processes carry the highest consideration during risk assessment, to ensure that monitoring efforts are focused on preventing or mitigating important and likely sources of error in their conduct, collection and reporting. Risks are acceptable up to certain limits and therefore defining tolerance or threshold will help in deciding trigger points to initiate controlling/mitigation measures during conduct phase. Examples of these tolerance limits or thresholds are given in the table below, which will vary study to study.

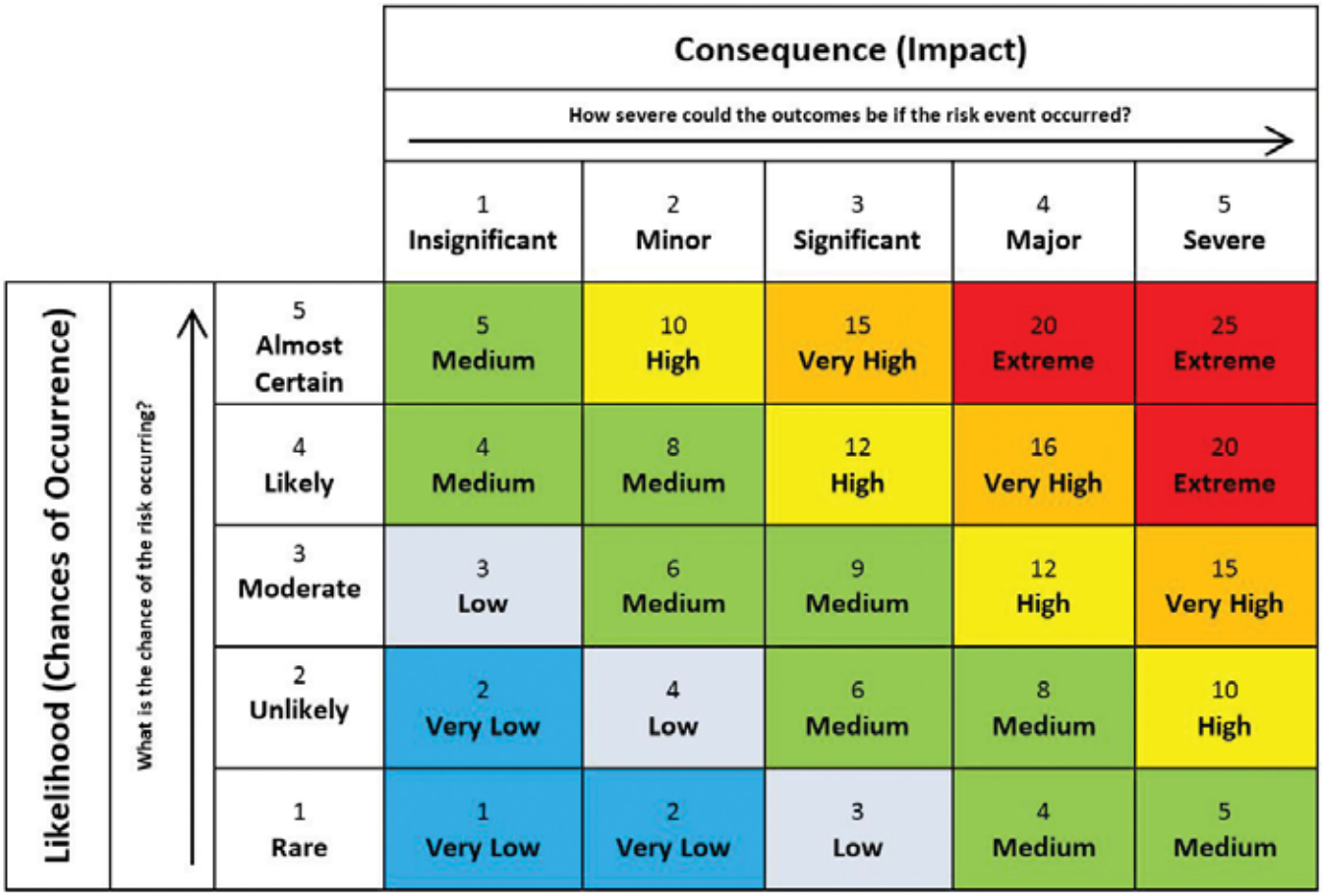
Assess the likelihood and impact of the risks:
The root cause analysis helps in assessing the risk source further for its chances of occurrence (likelihood) and the impact (consequence) it may have on the study. There are different scales to assess the likelihood and impact of the risks. These are based on a 1 to 3 scale or a 1 to 5 scale. The risk matrix given below can facilitate the risk assessment and action planning process based on the risk score as low, medium, high or extreme. The risks falling into high, very high or extreme categories need right action planning and close monitoring to ensure effective risk control. Risk detectability is another dimension which can be considered in the risk assessment process.

Based on severity and significance of risks, decide the risk responses:
The risk responses should be planned appropriately based on the risk score and risk significance. The risk responses and action planning should be done appropriately for high and extreme (critical) risks. The responses could be one of four types – Avoid, Transfer, Accept or Mitigate.

An 'Avoid' response could occur if there is any real show-stopper risk, like no approval of clinical trial by an EC or IRB because of the placebo design of a trial. In such a case, the clinical trial plan should be reviewed and changed to avoid such a risk. It means probably eliminating such investigational sites from the clinical study plan. Regarding 'Transfer' of a risk, if any potential risk response is outside of the sphere of influence of the team involved, it may be necessary to identify an alternative group to whom the risk could be transferred for action or decision-making.

An example of an 'Accept' response could be selecting a country for a clinical trial, even if there is a high chance of a delay in regulatory approval. Even if it is a significant risk, it is accepted as that country would be very important, maybe because of the pool of patients or future marketing plans. A 'Mitigate' response is very commonly used. Mitigation actions may have one of several objectives, like eliminating the risk completely, minimising the impact of the risk, reducing the likelihood of the risk occurring, or increasing the chances of the risk being detected if it should occur. An example of a Mitigation response could be having an investigational site on a study with less or no GCP experience. This risk can be mitigated by close monitoring of the site or additional training to the site.

Ongoing assessment of risks dynamics:
Risks are dynamic and therefore, risk assessment should not be limited to only before and during the planning stage, but should also be ongoing during the conduct and closing phases of a trial. There are chances that one risk may give rise to another or multiple risks, or there may be changes or increases in the root causes of a risk. Ongoing assessment of risk helps to fine-tune risk response and action planning to improve overall risk management.



The appropriate technology is helpful in making the risk assessment and management process more efficient and effective. As these are dynamic processes, they require the right technology that can catch various aspects and changing scenarios of the risks, to get the right picture of the risks involved. As the industry is moving towards a quality risk management (QRM) or risk-based monitoring (RBM) approach, the market is witnessing the customised tools for risk management catering to the needs of clinical trials project/programmes.

Conclusion:

Risk assessment is a systematic process for identifying and evaluating events that could affect the achievement of clinical study objectives. A robust risk assessment in clinical trials forms the foundation of an effective risk management programme and helps the achievement of regulatory, strategic, operational and budgetary targets. With a right risk assessment process which involves a systematic way of root cause analysis, deciding risk scores and significance of risks, and planning risk responses with actions, are important in successful completion of a clinical trial. A combination of effective process and right tools/technology will be helpful in comprehensive risk assessment and, in turn, effective risk management.

References

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