

Review Article

Quality management in risk based monitoring

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ABSTRACT

The essential thought of risk based quality administration is the recognizable proof of risks on a ceaseless premise for risk bearing exercises all through the configuration, behaviour, assessment and reporting of clinical trials. The procedure ought to begin at the season of convention outline so moderation can be incorporated with the convention and other trial related archives. Clinical Research is about creating information to bolster choices for creating and changing medicinal items and rehearses while ensuring the security, rights, prosperity of taking part subjects are ensured and coming about information are dependable. Choice making must be in the same class as the procedures used to deal with the clinical trials. Scholastic and industry driven clinical exploration is gradually adjusting quality danger administration forms for ahead of schedule recognizable proof of components with potential to influence subject wellbeing and convention consistence; preparing for those leading, directing and observing the study; ceaseless re-evaluation of needs; and corrective and preventive action (CAPA). Flawless control of exercises is once in a while conceivable to accomplish, yet a quality controlled and organized danger based methodology can be next best to flawlessness.

Keywords: Risk based monitoring, Quality management, Clinical trials, Triggers, Key risk indicators, Risk analysis, Quality, Static risk, Dynamic risk, Fixed risk, Risk review, Risk acceptance, Risk communication, Risk control

INTRODUCTION

Clinical trial is one among the important part of drug development program that not only help in proving the drug safe to patients but also help to gain trust of regulatory agency in quality of data that was generated. Clinical trials even though its importance have been major driver of biggest drug development cost as they have become far larger and more complex compared to the past due to increase in trial duration, routine procedures, trial staff work burden and stringent enrollment criteria. Thus, pharmaceutical industry has been in search of solution to improve trial performance through cost reduction and improving patient safety and efficiency.

The present way in which a few components of a quality framework are actualized by sponsors and their service providers (CROs and so forth) is by and large recognized to be tedious and constitutes a noteworthy extent of the expense of improvement of prescriptions. What's more, International conference on harmonization (ICH), good clinical practice (GCP) rule was finished in 1996 when clinical examination was generally paper based, yet the accessible innovation and the way to deal with the behavior of clinical trials has advanced impressively meanwhile.

Whilst regularly accomplishing a decent quality clinical trial, the present practice can however be costly and there are an excess of trials in which avoidable quality issues emerge.¹ This is shown by the nature and degree of discoveries, distinguished by European GCP

investigators, amid examinations. The mix of these discoveries and the high cost of the oversight of clinical trials categorically recommends that present way to deal with clinical quality administration need survey and reorientation.²

Risk-based monitoring (RBM) approach that was introduced by food and drug administration (FDA) in September 2011 through its “Draft guidance for industry: Oversight of clinical investigations - a risk-based approach to monitoring” presented the pharmaceutical industry with a holistic approach to analyze and continuously improve trial data integrity and patient safety with reduction in monitoring cost.^{3,4}

Even as pharmaceutical companies embrace the opportunity of using risk-based monitoring approach, challenges persist with respect to establish the process and implement it in desired way.⁵ This can be addressed by referring to recommendations stated in ICH Q9 quality risk management standards.^{6,7,8} Thus, this article concentrates on implementing the recommendations of ICH Q9 in setup of risk-based monitoring process.

Principles of quality risk management

ICH Q9 defines risk as combination of probability of occurrence harm and severity of that harm. ICH Q9 emphasizes on protection of patient by managing the risk to quality by proactively identifying and controlling potential quality issues during drug development stage.⁶

It supports use of quality risk management to improve decision making when a quality problem arises. Quality risk management standards are as “the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk.”⁶

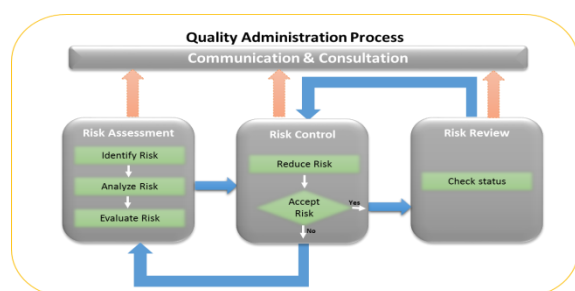


Figure 1: Diagram of standard quality administration process with emphasis on risk assessment, risk control and risk review.

The ICH Q9 Quality Risk Management Standards recommends evaluation of risk on basis of two primary principles⁶

- Scientific knowledge that should eventually link to protection of trial participants.

- Level of risk should match with efforts, formality, and documentation applied during quality risk management process.

Quality management in RBM

Quality management in risk based monitoring can be segregated to following steps^{2,9,10-15}

- Risk Assessment
- Risk Identification

In RBM known or anticipated risks should be identified using a systematic approach based on risk/benefit profile of investigational product under study, study procedures and potential site related risks. These risks can be classified as fixed and dynamic risk as stated below

Fixed/static risks

Fixed risks are generally constant throughout the duration of study and can be further classified as follows⁴

Protocol risks

- Therapeutic area
- Drug Safety profile
- Target product profile
- Invasiveness of drug delivery
- Patient population
- Study design
- Study duration and schedule of events
- Study objective

Study site risks

- Investigator and staff experience
- Location of site
- Number of competitive study
- Expected rate of patient enrollment
- Past history of site

Dynamic risks

Dynamic Risks are those that are variable throughout the study and contribute to real-time risk evaluation.⁴

- Real-time enrollment
- Number of adverse events
- Number of protocol deviations
- Time to first-patient-first-visit
- Primary/secondary efficacy range
- Site performance matrix

On the basis of evaluation, at the beginning a tailored risk-based monitoring strategy should be developed for each site by referring to fixed risks. Then later as the study progresses, considering the dynamic risks the

monitoring strategy should be intelligently updated on a near real time basis.

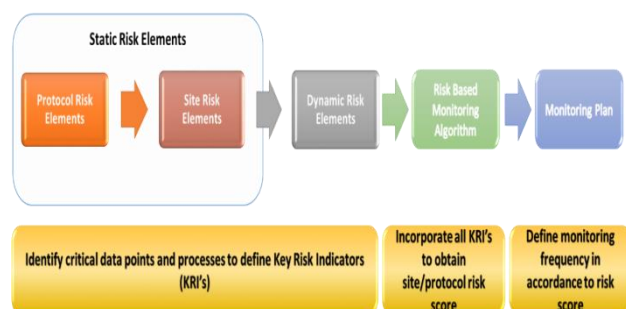


Figure 2: Three elements of risk analysis.

Risk analysis

After the risks are assessed these can then be classified either qualitatively as high, medium or low risk on the basis of their impact on patient safety and data integrity or quantitatively on the basis of

- Impact on patient safety and integrity of data.
- Probability of occurrence.
- Ease of their detectability.

Risk evaluation

During the risk evaluation stage, using the information obtained during the risk identification and analysis stage should be evaluated to validate if the risks are identified as per the criteria that have been setup. The initial step is to plainly comprehend the procedures and results which truly matter with a specific end goal to accomplish the destinations of the study convention and great clinical practice. After the efficient distinguishing proof of dangers and before the meaning of relief activities, it is first important to recognize the dangers that truly matter and to build up needs. Prioritization ought to be arranged to meet the destinations of good clinical practice (affirmation that the rights, security and prosperity of trial subjects are ensured, and that the after effects of the clinical trials are believable) and the investigative targets of the clinical trial.

The needs require first to be built up at the season of arranging and planning (outline) of the clinical trial, including the relating reports, trial particular arrangement, information accumulation devices and all procedures that will be utilized at the diverse phases of the trial. They ought to be deliberately set out so that hazard investigation is completed and control measures are planned in a way that is constantly adjusted to them.

Risk control

It includes decision making to reduce and/or accept risks. At this stage in reference to study protocol, past

therapeutic experience and literature review the acceptable level of risk should be defined which can be used as a threshold to raise a trigger. During this stage the decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

- Risk control might focus on the following questions
- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. At this stage we should define the intensity and mode of monitoring that should be performed against a trigger.² The actions should be decided in consideration of study protocol relevant literature and risk analysis.

Risk acceptance

Risk acceptance is a decision to accept risk. Risk acceptance can be formal decision to accept the residual risk or it can be a passive decisions in which residual risk are not specified.

Risks may be worthy when they have constrained effect on subject's wellbeing and rights and in addition information honesty and dependability.

Risks is not adequate, it should be diminished by proper danger moderation activities. Those should be indicated in a danger administration arrangement. The last should be explored and adjusted likewise.

Moderation activities ought to be executed to address distinguished dangers regarding the framework and could include:

- Recorded methodology to formally connect quality frameworks of association.
- Point by point contracts between gatherings plainly characterizing parts, obligations and assignments to be embraced.
- Measures of oversight of designated/contracted assignments;
- Determination of correspondence arrangements, incorporating correspondence accomplices, destinations, objectives, timetables and apparatuses for all interchanges.
- Customized preparing in procedures/systems that may be new and/or new.

- Use existing information in diverse databases for danger appraisal and hazard moderation, e.g. create IT-devices and programmed information interfaces.
- Quality execution estimation for inward and outer administration suppliers, connected to adaptability in arrangements for oversight and checking.

Risk communication

Risk communication is sharing of information about risk and risk management between the decision makers and others. This should be appropriately documented and included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risk to quality.

Risk review

Risk administration ought to be a continuous piece of value administration process. A system of audit or screen occasions ought to be executed. The yield/consequences of the danger administration procedure ought to be looked into to consider new learning and encounter. Once a quality risk administration process has been started, the procedure ought to keep on being used to occasions that may affect the first quality risk administration choice.

The idea of risk based quality administration in clinical examination spins around the accompanying cycle:

- Risk evaluation with data assembling, the foundation of needs and the ID of dangers connected with the study.
- Risk control which includes setting resilience limits moderation and acknowledgment of dangers.
- Risk audit which requires information of the past strides with the incorporation of the danger administration instruments and the correspondence on the survey of the outcomes and information related to the danger recognized and the documentation of the activities required.

CONCLUSION

In outline, two administrative offices have issued reciprocal reports giving direction on the most proficient method to better guarantee quality, trustworthiness and unwavering quality of data produced from clinical examination. Employers and manufacturers association (EMA) concentrates on offering you some assistance with understanding the ideas and regulated way to deal with danger administration, while FDA concentrates on risk based making arrangements for clinical study checking. Both pass on that hazard based observing is about focused, productive, and astute checking to dispense with mistakes that matter. It is clear that FDA perceives that checking is one and only part of the procedures expected to guarantee clinical trial quality and trustworthiness and subject wellbeing and tells us that it is considering the requirement for extra direction

depicting a more over-coming to hazard administration approach. Receiving the EU reflection paper could be the continuation for FDA, as the EMA's direction on more extensive utilization of danger administration forms for clinical trials may be what is expected to fill the crevice. Application of risk based quality management approaches to clinical trials can facilitate better and more informed decision making better utilization of the available resources.

Towards the end of a trial it ought to be conceivable, in a reasonable subjective and/or quantitative path, to write about the degree to which a trial has worked inside of as far as possible built up and kept up amid the trial and whether it has been led to adequate level of value as evaluated by a foreordained procedure. Such a report could be incorporated into the clinical study report and could depict activities, where conceivable, that were actualized to amend and keep deviations from resilience limits amid the trial conduct. Review results will add to and serve to accept the quality report of a trial.

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