

Less is the New More: Risk-based Approaches in Clinical Trials



Abstract

The continuously evolving clinical research industry requires new solutions and a renewed approach. Rising costs, studies getting more and more complex and, what is more important, constant focus on quality and safety of patients, demand devising new methods to conduct clinical trials. At the same time as electronic systems are used more widely, statistical methods and capabilities get more sophisticated and work moves to virtual offices. All these are prerequisites for implementing risk-based monitoring – an approach which is built around focus on preventing or mitigating important and likely risks identified for the study. This method helps us to keep our attention and resources exactly where they are needed.

Risk-based Monitoring is Not a Fad Any More

“5.18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators’ training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.”¹

Thus far, these GCP’s obligations have been mostly fulfilled by scheduling frequent on-site visits and performing 100 per cent source data verification (SDV). These methods were implemented to ensure the safety of study participants and the integrity of the study data following the logic that the more often and thoroughly the data will be checked, the better the quality depicted. In actuality, the 100 per cent SDV approach became a “comfort blanket” for sponsors and does not do much to maintain quality assurance. Research on this approach revealed that clinical site monitoring can consume up to 30 per cent of overall costs of the trial.⁸ As per results published by The Tufts Centre for the Study of Drug Development at Tufts University, clinical research associates (CRAs) worldwide spent approximately 20 per cent of their time travelling and only 41 per cent on-site. Also, taking into consideration the limitations of on-site monitoring visits such as the human error factor (manual process is only 85 per cent accurate)⁸, narrow perspective, or tendency to capture only certain types of errors (e.g. protocol violations, transcription errors), we come to the conclusion that 100 per cent SDV approach is not only

very costly and resource-consuming, but also inefficient in terms of maintaining quality.

All the above reasons led to the change in the quality focus process across the whole industry. “Quality by QC” has been replaced by “Quality by design”, a concept which briefly can be explained as the rule of spending little more time up-front to save hours later on.

As a response to the shift in industry mind-set, regulatory authorities released industry guidance and regulations on risk-based, quality driven management of trials.^{1,2,3,4} Risk-based monitoring is no longer a fad, it is now a stipulation.

The Concept of Risk-based Monitoring: Five Steps

Assessment of risks was always present in clinical trials but currently it has become the central axis for building up the monitoring strategy of clinical trials. The concept of risk-based monitoring is to allocate resources exactly where they are needed by identifying risks, preparing the action plan at the beginning of the trial and reviewing it during the life of the study.

ICH Q9 Quality Risk Management lists two main principles of quality risk management:

- “The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.”²

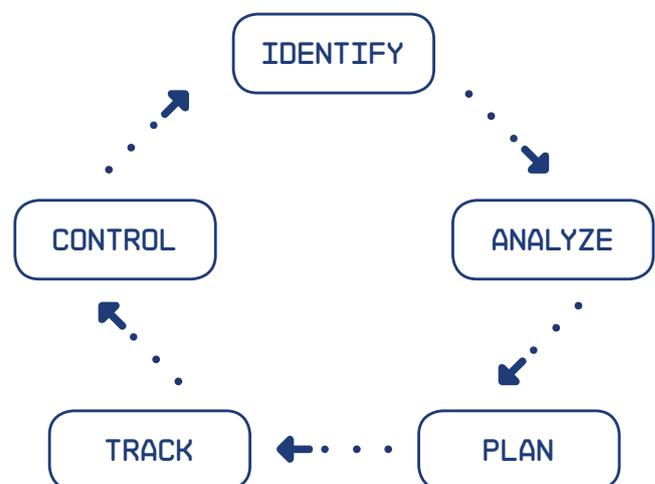


Figure 1: Schema of typical quality risk management process.

Generally, the concept of risk management consists of five steps (Figure 1): identifying the risks, prioritising them – taking into consideration their impact on the study as well as their likelihood, planning how to manage the most significant ones, tracking and lastly controlling the risks.

This is not a one-time process. Risks and their status should be assessed on an ongoing basis. It is important to underline that all parties involved in the study should actively participate in this process. Multidisciplinary teams (consisting of project managers, data managers, biostatisticians, medical monitors etc.) must be involved in the process of risk assessment as e.g. a data manager might identify a risk that the clinical operations team should be aware of, and vice versa.

Risk assessment is not only the first step, but is also a critical component in implementing a risk-based approach. Based on identified, well defined and prioritised risks, an adequate and tailored monitoring strategy can be defined.

TransCelerate BioPharma Inc., a non-profit organisation which associates with the leading pharmaceutical companies, and which focuses on advancing innovations in research and development (R&D) came up with the TransCelerate Methodology for Risk-Based Monitoring (Figure 2).

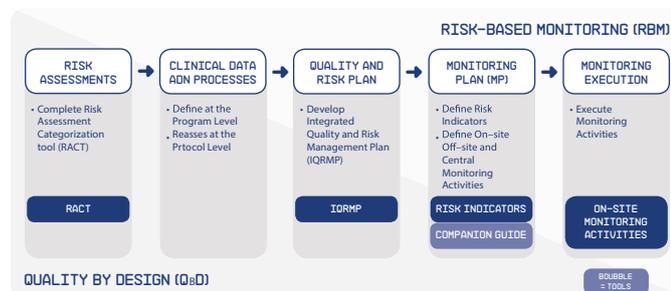


Figure 2: TransCelerate Methodology for Risk-Based Monitoring – High Level Process and Associated Tools [5]

This methodology describes the steps to be taken to assess risk, to determine critical data and processes, and to mitigate those risks through the utilisation of the Integrated Quality Risk Management Plan (IQRMP).

Risk-based monitoring generally means targeting monitoring activities where they will bring the greatest benefits. Sometimes it might even mean performing 100 per cent SDV, but not always. There are several approaches to reducing SDV. Figure 3 presents a high-level overview of three of them: 100/20 rule-based monitoring, targeted monitoring and triggered monitoring.

Currently formulating a paradigm of monitoring of clinical trials is a combination of central, off-site and on-site monitoring activities triggered based on risks associated to the study. In today’s time there are multiple tools that are not only in use, but are also recommended by regulators e.g. centralised monitoring, statistically

MONITORING APPROACH	DEFINITION	TECHNOLOGY COMPLEXITY
100/20 rule based monitoring	SDV of 100% of data in 20% of CRFs and 20% of key data in 100 of CRFs.	1 bubble
Targeted monitoring	Prioritizes critical data and uses random sampling methods to select data for SDV.	2 bubbles
Triggered monitoring	Uses data to initiate an on-site visits based on predefined triggers eg. protocol based, volume-based ones or time threshold.	3 bubbles

Source: KCR

Figure 3: High level overview of reduced SDV approaches.

controlled sampling of selecting data to be verified, etc. In “Guidance for Industry Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring” released by the FDA on August 2013, centralised monitoring is defined as “a remote evaluation carried out by sponsor personnel or representatives (...) at a location other than the sites at which the clinical investigation is being conducted”³ and should be used to “supplement or reduce the frequency and extent of on-site monitoring activities that can be done as well or better remotely (...)”³.

This strategy uses data analytics and visualisation of data coming from different sources to identify outliers, data trends, potential site performance issues to predict, prevent and proactively manage issues in real-time. TransCelerate’s latest update to their position paper “Defining a Central Monitoring Capability: Sharing the Experience of TransCelerate BioPharma’s Approach, Part I” indicates three key areas which should be considered while building an effective central monitoring approach: **people, processes** and **technology**.

People: implementing central monitoring will, most probably, result in the creation of a central monitor / remote monitor role. Such roles will require merging capabilities of several currently existing roles e.g. data manager, project manager and CRA. Utilising broad competencies is critical to the success of centralised monitoring as well as the risk-based approach in general.

Processes: the whole process should be built around

using data to provide a holistic review which will allow companies to identify issues and mitigate risks. The usage of statistical methods seems to be essential for identifying outliers, alerting trends, and other data anomalies.

Technology: this is a critical area of focus, not only in terms of implementing centralised monitoring, but also in building up a thorough, efficient and quality-driven framework for risk-based monitoring as a whole. This also appears to be the most challenging aspect of executing risk-based monitoring as it would require integration of clinical and operational data from disparate sources with no standardisation in place, e.g. electronic data capture, IXRS or clinical trial management systems. Incorporating all of those components is foundational to building a predictive analytics environment which will allow holistic review of data. According to TransCelerate BioPharma Inc., there are quite a few complexities to be managed while creating this working environment:

- “Data reside in several clinical systems
- Data reside at and with multiple vendors, organizations and stakeholders.
- Different Technology solutions exist that drive the same process (e.g. multiple electronic data capture [EDC] solutions).
- Different operating models across the industry may have the source systems reside within the company’s firewall, hosted by the application service provider or supported by contract research organization.
- The systems can be a blend of off-the-shelf and custom-developed applications.
- There is an absence of systems for certain data (e.g. Excel trackers).”⁷

It seems very difficult to create such tools, especially for clinical research organisations where dispersion of clients’ needs and systems usage is much bigger. But if those challenges are overcome, full implementation of risk-based monitoring might bring not only higher quality by dealing with critical risks and better utilisation of resources; it may also bring savings. Of course the initial costs will be higher because of the additional investment of time and resources to develop the strategy, but as per PwC, a potential trial cost savings may reach 15-20 per cent. (Figures 4 and 5)

Risk-based Monitoring: The Path Ahead

Sponsors and CROs should very closely cooperate from the very early stages of the project, as effective implementing of a risk-based monitoring approach is a collaborative effort. Sponsors should carefully select research partners, taking into consideration their therapeutic, operational and regulatory expertise, flexibility, technology and analytical capabilities. As a starting point, all parties involved should clearly define expectations and responsibilities to make sure that everyone is working from common assumptions. The FDA indicates that sponsors should share information with

Traditional vs Triggered Monitoring

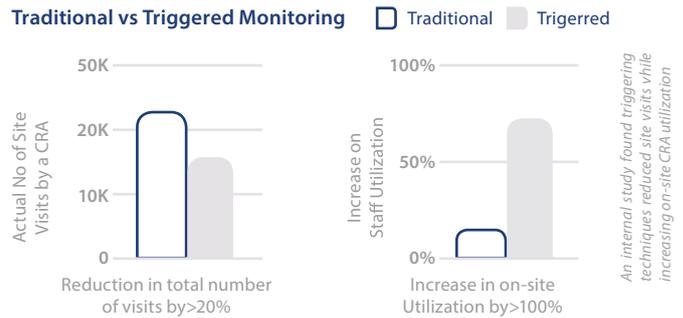


Figure 4: Impact of triggering techniques on on-site visits number and on-site CRA utilization. [12]

Cost: Initial estimates show potential of risk-based monitoring to save 15–20% in study portfolio costs

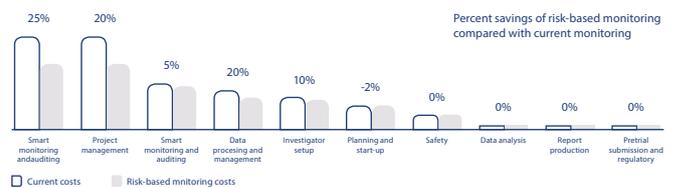


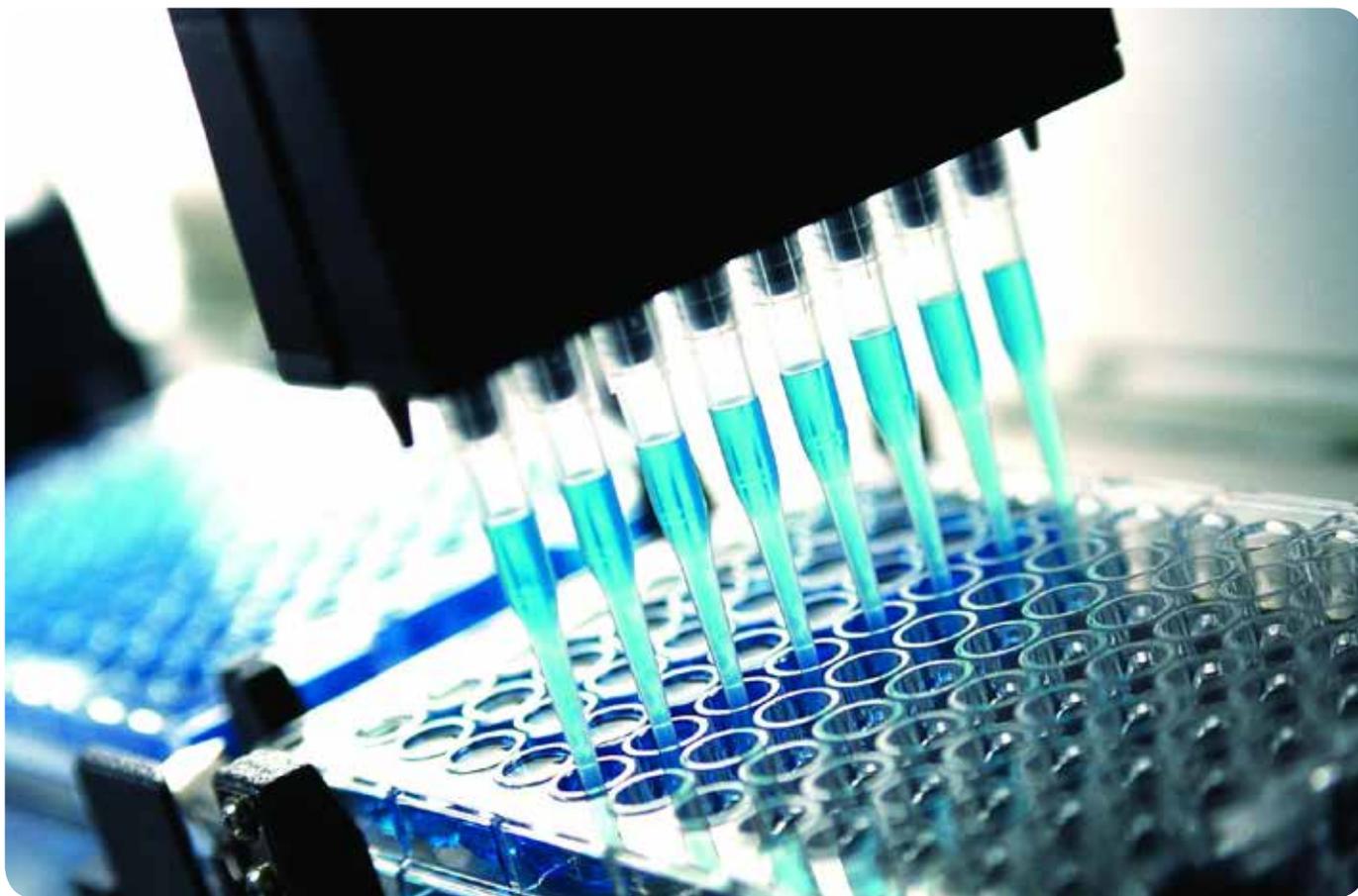
Figure 5: per cent savings of risk-based monitoring compared with current monitoring. [9]

a CRO, even on past experiences, as this may change the CRO’s approach to monitoring practices (e.g. risks identified during previous studies may be managed from the very beginning of the study). The dialogue between all parties should be opened at the very beginning. This will give the CRO a chance to prospectively plan and develop the most optimal and quality-driven monitoring strategy.

Clinical trials have already gone through several paradigm shifts during their history. Starting from being unregulated to strictly regulated, from being paper-oriented to technology-based, from assuring quality by QC to assuring quality by design. Now this is the time to fully understand risk-based monitoring, embrace the opportunities it presents, and develop a strategy and tools that are efficient. It definitely requires a lot of work and restructuring of processes, used technologies and budget work-up. But it will be the game worth the candle.

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