

Patient Centric Monitoring Methodology

An ICON White Paper



The ICON approach to risk based monitoring in clinical trials

25%
potential saving in monitoring costs

Introduction

The pharmaceutical and CRO industries are undergoing a radical shift in their approach to ensuring quality in the conduct of clinical trials that involves a more targeted, risk based approach to site monitoring and data handling. The primary goal of this shift is to improve the efficiency, effectiveness and quality of clinical trial research and the data generated together with improving patient safety. A significant impetus has been the recognition by regulatory agencies that traditional approaches to clinical trial monitoring are no longer sustainable in an era of global multinational studies. For example, data indicate that the 100% verification of source data has not delivered the anticipated increase in the effectiveness of clinical trial research. Recent technological advancements in electronic data handling have also enabled this revolution in clinical trial monitoring.

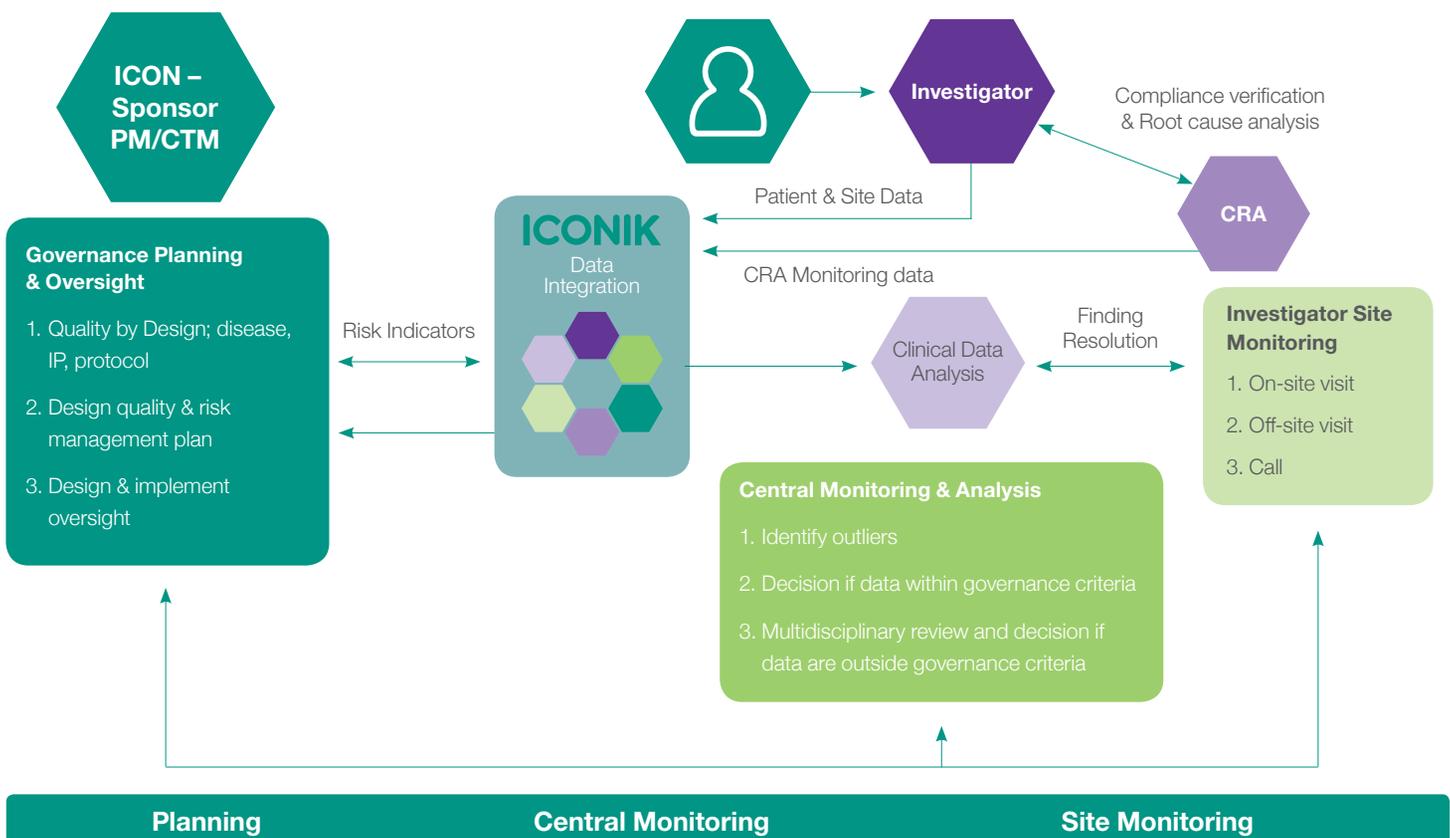
The US Food and Drug Administration (FDA) [1] and the European Medicines Agency (EMA) [2] both issued guidance on risk based monitoring in 2013 and the principles of quality

risk management are outlined in International Conference On Harmonization (ICH) guideline Q9 [3]. The aims of the FDA and EMA guidance are to improve patients' safety and data quality in clinical trials by focusing oversight on the most important aspects of study conduct and reporting.

Patient Centric Monitoring is ICON's methodology for the design and execution of an adaptive risk based monitoring strategy using ICONIK™ analysis. In the design and execution of the monitoring strategy, ICON puts the patient at the centre of decision making.

Risk based monitoring in clinical trials is a monitoring approach where activities, resources and technologies are adapted to the risks in the study. Patient Centric Monitoring further focuses on the probability of errors that matter in decision making for patients. This adaptive approach focusses monitoring activities on the areas which have the greatest potential to improve patient safety and data quality. The key benefits of Patient Centric Monitoring are proactive early detection and mitigation of risk and error together with cost effective resource deployment.

Figure 1.
Patient Centric, Risk Indicator Driven Monitoring
The Central Monitoring Schematic Process Flow

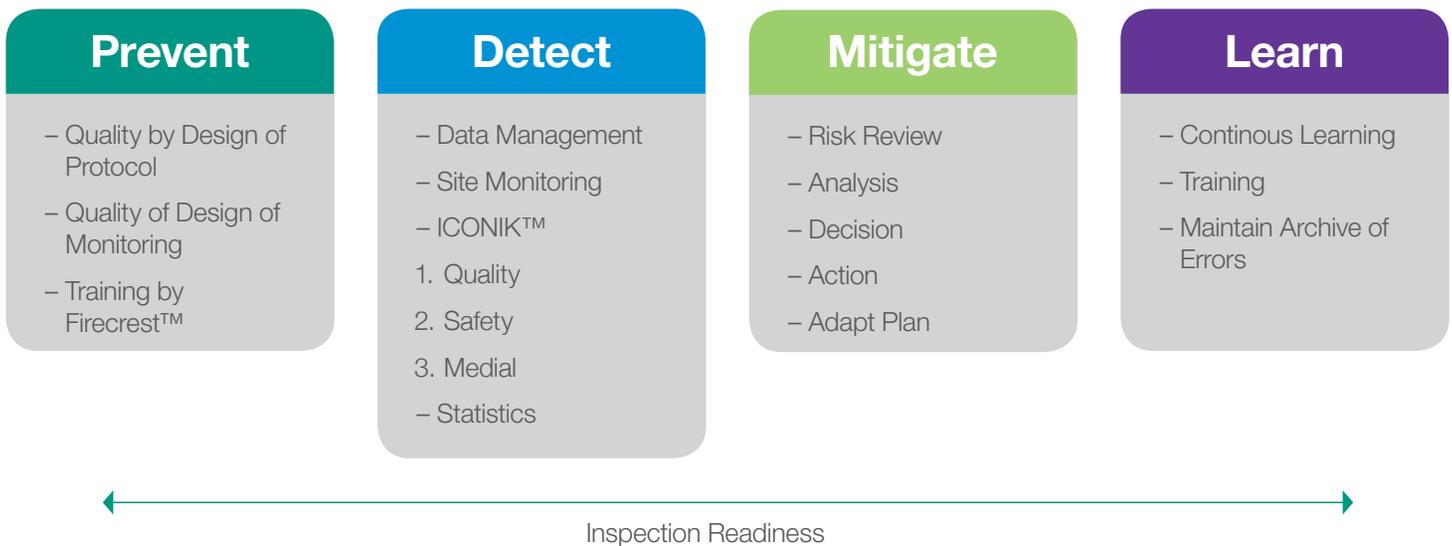


The ICON Approach

Patient Centric Monitoring is designed to prevent, detect, mitigate and learn from risks and errors in the conduct of clinical trials, whilst maintaining inspection readiness in line with regulatory guidance (Figure 1). Within the Patient Centric Monitoring framework, initial risk assessment categorisation recommends an optimal monitoring strategy and the pre-empted clinical trials risks determine whether or not ICONIK™ central monitoring and analysis are deployed. ICONIK™ is a powerful integrated information platform that consolidates, standardises and visualises operational and clinical data from multiple sources to provide a single holistic view of all study information, enabling data review from a scientific, safety and quality standpoint at the compound level. The aim of Patient Centric Monitoring is to conduct clinical trials focused on achieving quality, defined as an absence of errors that

matter in decision making for patients. Overall, the outcome of Patient Centric Monitoring is the early detection of risks, which enables effective deployment of resources which may also result in an overall reduction in costs.

As part of Patient Centric Monitoring, the study team are trained to understand the patient's perspective. This enables them to appreciate why and how the tasks they perform contribute to the rights and wellbeing of the research subject and also for future patients who will use the clinical research data in order to make decisions for their health. The study team can then make decisions based on this understanding, as well as the data at hand, to deploy prioritisation, discretionary effort and escalation procedures accordingly, while maintaining robust and disciplined compliance with standard operating procedures.



Patient Centric Monitoring

Prevent

Prevention involves these main components:

- A Quality by Design approach to the study protocol and monitoring strategy
- A tailored, practical, on-line training tool for investigators: Firecrest™

Prevention is first achieved through the study protocol, using a Quality by Design. This involves a cross functional team

conducting an in-depth scientific as well as compliance risk review. Where possible, investigator and patient perspectives are considered in order to improve the protocol and maximise the support to investigational sites in achieving compliance with study processes. The next step in effective prevention and achievement of high quality data is effective staff training. Within the Patient Centric Monitoring framework, the Firecrest™ training solution, offers customised, study specific, web-based training modules to deliver training to site staff and the study team. Investigator led development teams generate dynamic and engaging training solutions to facilitate training to both site staff and study team.

Training is self-paced and customised for each participant type. Firecrest™ enables efficient prevention of risks and errors, through its effective up-to-date training and guidance to site staff. It also fosters timely mitigation of risks and errors at sites through time sensitive delivery of updated information and communications to site staff.

The third component of effective prevention is a tailored monitoring strategy, focused on the risk to safety, the overall risk of error and the risk of possible lack of compliance with ethical principles and regulations. The design of Patient Centric Monitoring starts with a thorough risk assessment within a Quality by Design framework, which drives the development of an integrated quality and risk management plan (IQRMP). As part of the IQRMP, a study specific monitoring strategy is deployed that is supported by systems and processes for error checking and tracking. Risk assessment is the basis for a holistic monitoring strategy and oversight plan, encompassing risk indicators with thresholds and triggers as well as a predefined baseline monitoring schedule, which are designed to enable the discovery of risks and/or consistent errors. The pro-active anticipation of risks and errors is incorporated in an Error Management Plan (EMP) that lists possible errors for each study activity with instructions for their prevention, detection and mitigation.

A study risk assessment includes a number of steps. A protocol event risk assessment, consisting of a definition of critical data and a thorough analysis of possible errors in processes and protocol procedures at the investigator site; with the identification of study specific risks and the choice of the most effective monitoring strategy for each of these risks. The creation of a monitoring manual, including a tailored schedule of on-site and off-site monitoring, central monitoring, safety monitoring and the flexible use of additional targeted monitoring activities.

Detect

Patient Centric Monitoring enables the design of an effective detection methodology for quality, integrity, safety and performance risks and errors by bringing central and site monitoring together in an optimal technology, people and process paradigm. Central monitoring focuses on centrally available data, in aggregated visualisations or individual sets. Site monitoring focuses on direct or virtual interactions with the investigator sites.

Central monitoring follows the instructions of the Error Management Plan (EMP) and associated Central Monitoring Plan. ICONIK™ provides efficient visualisations that are deployed for the detection of quality, integrity, safety and performance risks and errors with aggregated data that enable ongoing analysis of study progress. ICONIK™

interrogates data in real time to detect site-to-site variations and to help direct the use of resources.

For errors, quality, integrity and performance verification, Clinical Data Analysts (CDAs) perform a non-medical review and analysis of ICONIK™ centralised, aggregated data in order to identify triggers in risk indicators at an early stage. The CDAs identify indications that a site is an outlier as compared to their peers in terms of quality, safety or performance. CDAs may also oversee the central monitoring of study data quality edit check trends, specific logistics, training trends and essential document filing compliance. When a CDA detects an outlier site, or an indication of risk or systematic error, they issue a finding to the CRA. For safety and medical trends, Medical Monitors perform trend analysis to identify safety risks to the research subjects. For data quality, Data Management promptly verifies data edit checks and trends in data edit checks.

Site monitoring also follows the instructions of the Monitoring Manual and associated EMP. CRAs liaise with site staff to follow-up on site requests and support regulatory, logistical and documentation processes. Through regular contacts via email and telephone, the CRA can promptly support the site to ensure compliance with protocol processes and procedures and timely entry of subject data. Regular contact with the site also helps to build trust, enabling early sharing of detected errors or risks. CRAs detect errors through Source Data Verification, Source Data Review and/or interviews. A baseline schedule of structured, planned on-site or off-site visits enables the minimum established verification of errors as per the instructions in the Monitoring Manual. An Error Capture and Analysis/Action Tool (ECAT) enables CRAs to systematically check records and categorise any errors that occur at a site.

Should significant errors or risks be detected by the CRA or a finding be issued by the CDA, the Monitoring Manual then directs the CRA to verify additional study events and deploy triggered on-site or off-site visits or calls in order to mitigate the detected risk.

Mitigate

Effective root cause analysis facilitates the identification of the causes of errors and risks which, if corrected, will prevent an error or risk from happening again. This can then guide mitigation and allow tracking in a quality register. The categorisation of errors enables consistency and focus for corrective and preventive actions at a site, project and corporate level. Errors are categorised into seven human factor categories: process, training, supervision, engineering, communication, resource allocation and culture. When a CRA or SMA detects a risk or error or a CDA issues a finding for the CRA to follow-up, action is undertaken as guided by the monitoring manual. Actions include simple correction, verification of a repeat error and root cause analysis with human factor categorisation for effective mitigation and escalation.

Detected errors, their root cause analysis, human factor classification and mitigation are documented in ECAT or the Clinical Trial Management System (CTMS). At an agreed frequency, holistic Quality and Risk Review Meetings (QRRMs) are held to verify the effectiveness and efficiency of the chosen monitoring strategy. The purpose of the QRRM is to review and maintain oversight of the risks and errors that are detected and mitigated during the study. Project oversight meetings are held regularly with the cross-functional project team in order to adapt the monitoring strategy, the EMP and/or the resources allocated to the sites, countries or overall study.

Learn

Based on the outcome of a QRRM, the project team can issue a 'lessons learned' item to the study team or across the organisation if necessary. A QRRM may also lead to the development or update of study or corporate training content. The EMP template is updated with any new risks identified on an ongoing basis. ICON maintains an archive of risks and errors so that future studies can avoid making similar mistakes by implementing effective preventive action. Any new risks or errors detected via the QRRM are added to the error and risk archive.

Conclusion

ICON's Patient Centric Monitoring is fully aligned with the guidance on risk based monitoring issued by the FDA and EMA, as well as TransCelerate. By applying technological innovations and recent behavioral sciences, Patient Centric Monitoring enables faster data access and quality checks, enabling early detection of errors and risks and ensuring improved patient safety plus data quality and integrity. Patient Centric Monitoring can also improve cost effectiveness compared with traditional monitoring, with potential savings of 25% in monitoring costs.

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