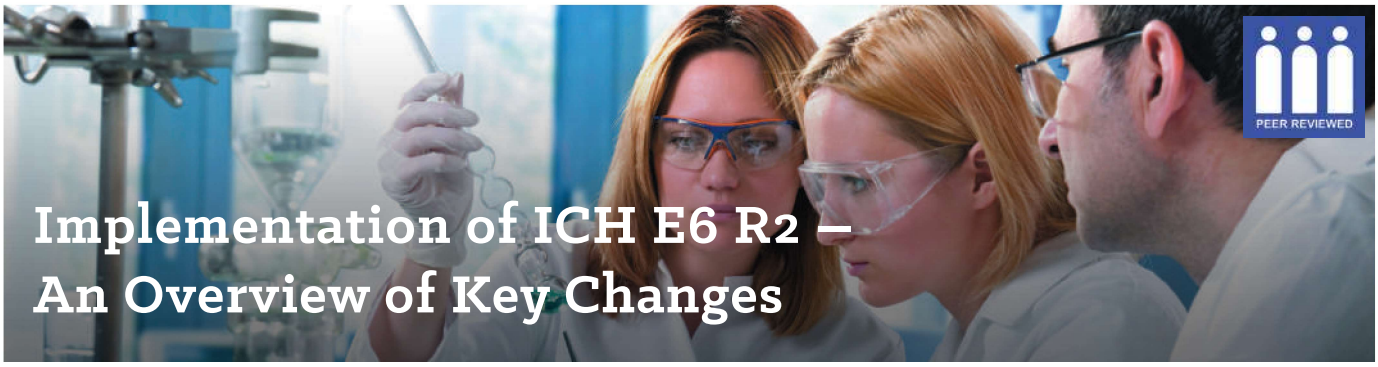

Implementation of ICH E6 R2 – An Overview of Key Changes

After release of the final draft of ICH E6 R2 in November 2016, the regulatory bodies have been announcing the implementation of E6 R2, one after the other. This makes sponsors and CROs look actively into implementing the new guidelines in their clinical studies. The changes in the guidelines are clear to understand but the challenging part is to change the mindset, culture and practice of the traditional way of designing, planning and executing clinical trials and take a more proactive, risk-based quality management approach. The guidelines also recommend new monitoring processes with combination of on-site and centralised monitoring to improve data quality and monitoring of patient safety, taking proactive risk control measures.

Key Changes of ICH E6 R2

Let's look at what the key changes are in ICH E6 R2 and how one can look into operationalising them. The addendum related to the key topics such as quality management, risk management, monitoring, oversight, non-compliance and validation of computerised systems are listed below.

Quality Management

The guidelines emphasise design of efficient, quality clinical study protocols, study-related and other operational processes and documents. While designing and planning the study, the sponsor should ensure that all aspects of the study are operationally feasible, and complexities can be manageable. For example, designing of inclusion/exclusion criteria or patient procedures or any other protocol-specific procedure, one needs to maintain a proper balance in terms of feasibility of execution of the protocol at site level and, at the same time, scientific validity is needed to fulfill the objectives of the study. The sponsors also need to place the utmost importance on high quality while setting up various processes involved in the study which include, but are not limited to, site selection or other start-up activities, data collection, monitoring , analysis, reporting and also relevant technology needed for those processes. The sponsor should implement a system to manage quality through all stages of the clinical trial processes. It is important to proactively identify important risks that could adversely affect the ability to protect patients during the trial or to obtain meaningful information and reliable results from the trial.

The guidelines recommend a risk-based approach to quality management throughout the clinical trial by identifying risks to

Topics	Key Changes of E6 R2	Practical Aspects to be Considered

Quality Management	• Risk-based Quality Management System
	  • Risk Identification
	  • Risk Evaluation
	  • Risk Control
	  • Risk Communication
	  • Risk Review
	  • Risk Reporting
		• Need changes in the processes to include risk-based quality management and also quality by design approach
		• Change in mindset and practice to consider risk management approach in design, planning, managing and conducting of clinical trials
		• Defining roles and responsibilities in risk management processes such as risk identification, assessment, tracking, controlling etc.
		• Appropriate technology adoption to support risk-based approach
		• Relevant documentations

Monitoring	• Risk-based approach to monitoring • Risk-based monitoring plan	• New monitoring process with combination of on-site and centralised monitoring to improve effectiveness and efficiency of monitoring • Risk-based monitoring plan with on-site, centralised and off-site monitoring strategies and rationale • New emerging role like central monitor • Communication plan related to risks triggered and issues identified • Relevant technology to facilitate central monitoring • Documentation related to RBM plan and centralised monitoring activities
Oversight	Oversight of trial-related duties, functions, CRO/vendor oversight	• Define oversight plan and KPIs • Documentation – oversight reports • Use of appropriate technology for almost real-time or on-time update
Non-compliance	Root cause analysis and CAPA	• Process for root cause analysis and CAPA for the non-compliance related to patient safety, critical data, processes and quality affecting reliability of study results • Relevant documentation
Computerised System	Emphasis on system validation	• Validation of the systems based on the intended use and their potential to affect reliability of trial results and patient safety • Documentation related to validation

critical data and processes involved in the trial which are essential for data quality, patient safety and overall validity of the study results. The methods or controls used to ensure quality should be proportionate to the intensity of the risks and criticality of the information collected. This risk-based approach should focus on key steps of risk management cycles, such as –

Risk identification: All potential risks related to critical data and processes should be identified. These risks would be: 1. System level – the risks associated with the systems or organisation levels, such as SOPs, personnel etc. 2. Project level/clinical trial level – information directly linked with the trial or project should be analysed to identify the risks that are trial-specific, such as study protocol design, any protocol procedure, patient selection or data collection process, etc. The relevant study management team members across the functions should be involved for robust risk identification and assessment process.

Risk Evaluation: Risk evaluation can be done on a three-dimensional scale – likelihood, impact and detectability. Considering these three dimensions, the total risk score can fall into high, medium or low category. The risks falling into the medium to high category need up-front risk control strategies and action planning and, at the same time, continuous monitoring during the conduct to ensure timely risk control or mitigation.

Risk Control: The risk control should be planned appropriately based on the risk score and risk significance. Risk control strategies should be incorporated in study implementation plans such as monitoring plan, safety reporting plan or communication plan, or by clearing defined roles and responsibilities of the stakeholders involved in the study. For example, if there is a protocol-specific critical procedure to be performed with the patients at a specific time interval during the study which can affect patient safety and/or the reliability of study results, then there should be a proper strategy in the monitoring plan to ensure adequate and timely monitoring of that procedure and the relevant data collected from that procedure.

The guidelines also recommend establishing a predefined quality tolerance limit (QTL) for a study by taking into consideration the medical and statistical characteristics of the variables and study design. A QTL is a value or limit associated with a variable or a parameter that should trigger attention and further evaluation if that value is reached. QTL helps to investigate if there is any possible systematic issue which can affect subject safety or validity of the study results. Some of the examples of QTLs are: % of subjects randomised not fulfilling inclusion/exclusion criteria, % of subjects discontinued due to AE/SAEs, number of protocol deviations in randomisation procedures, etc. Some of the variables have QTLs defined at a study level which can be used as the same variables or parameters as KRIs at site level. It may be possible that KRIs might reach thresholds at a site level but may not have significant impact on the study level QTLs. However, defining the threshold at an appropriate level for such KRIs at site level helps in proactive control of quality risks (QTLs) at study level.

Risk Communication: Communication with the right stakeholders or risk owners about risks triggered or issues identified during study conduct is very important to the risk management process. The guidelines recommend proper documentation of risk communication to facilitate risk review and proper control of risks or resolution of issues. The documentation of quality management activities or action planning will help to create clarity in the processes and will also provide scope for continual improvement.

Risk Review: As risks are dynamic, the periodic assessment of risks and planned control measures during study conduct will help in fine-tuning quality management activities. There are chances that one risk may give rise to another, or multiple risks, or there may be a change in risk or its root cause. Also, at the same time new knowledge and information emerging during study conduct helps in effective management of risks.

Risk Reporting: The guidelines recommend reporting QTL in the clinical study report, summarising the important deviation from limits defined for the variables selected, control/mitigation actions taken, and the impact on data quality and integrity.

As risk management is a dynamic process, the use of appropriate risk management technology helps in implementing a risk-based quality management approach efficiently. There are tools available in the market which are designed based on risk management principles and can be effectively used for risk assessment, real-time risk tracking, planning trigger/thresholds, risk communication etc. The technology can be useful to track KRIs at site level and also QTLs of quality parameters at study level. As the technology enables the risk management process, it is essential to have the right technology in place that can track various aspects and changing scenarios of the risks to get a right picture of the risk status, and to implement risk control effectively.

Risk-based Monitoring Approach

One of the key changes in E6 R2 is implementing a risk-based approach to monitoring by adding centralised monitoring techniques to analyse site performance metrics, examine data trends, and evaluate systematic errors or data integrity issues etc. to take proactive risk control measures to ensure quality and patient safety. Centralised monitoring offers many of the capabilities of on-site monitoring, as well as additional capabilities. With the advent of various eClinical technologies, analytical and visualisation tools, it is easy to check the data, risk reports and KRIs centrally or remotely. One needs to choose a combination of on-site, centralised and off-site monitoring which should be tailor-made for every study, based on critical data and processes identified for that study. Developing a risk-based monitoring plan with documenting strategy and rationale for a combined monitoring approach is a critical part of RBM. The RBM plan should emphasise monitoring methods used for critical data and processes, risks identified, communication plan, roles / responsibilities and additional training needs, etc.

Also, there is an emerging role of central monitor with these new monitoring processes. An appropriately qualified and trained person should be involved to support the centralised monitoring process. The central monitor is responsible for early identification of risks triggered or issues during study conduct and is responsible for timely escalation to relevant stakeholders, and tracking of risks/issues until control or resolution. Critical thinking and analytical skills are some of the important attributes that the central monitor should possess to understand and analyse complex data and provide insights into risk reports, trends and outliers in data. The new monitoring approach also leads to additional documentation requirements related to risk-based monitoring activities, centralised monitoring activities, documentation related to communication of risks triggered or issues seen during centralised monitoring till resolution, to ensure compliance related to the monitoring plan.

Technology plays a critical role in implementation of risk-based monitoring. The technology used to facilitate risk-based monitoring should have analytical and visualisation features to support centralised monitoring. The technology should be capable

of integrating clinical and operational data from disparate sources – for example, EDC, CTMS, IRT and ePRO or e-diary, etc. The right analytical tool is important to identify operational and site performance risks related to patient recruitment, patient screening failure, CRF completion, or drop-out rate, as well as to identify non-performing sites. The technology should be robust enough to apply a statistical approach to data in order to figure out data quality issues, data trending, data outliers, or the number of protocol deviations, violations, and AE/SAE rates, etc.

Oversight

As per changes in the guidelines, the sponsor needs to assume responsibility for the oversight of the clinical trial, and relevant trial-related activities and functions carried out by the CRO or vendor on the sponsor's behalf. Adequate oversight is essential not only to achieve the expected quality and reliability of trial results and to ensure patient safety, but is also helpful to sponsors to achieve the planned objectives, minimise risks and maximise the returns on investment. Oversight is a high-level but intellectual task which needs a proper oversight plan and right technology support to bring real insights from the vast amounts of data being generated and activities happening on a study. One of the essential aspects of an oversight plan is to decide key performance areas or critical success factors to track through the oversight process. These key areas are quality, safety, timelines or any other specific area related to vendors' site performance, which is vital for a study success. Identification of the right KPIs (key performance indicators) or KQIs (key quality indicators) which will facilitate an adequate amount of oversight of those critical areas is very important. The KPIs or KQIs should allow easy assessment of performance and identification of risks and issues related to those key areas. At the same time, KPIs or KQIs should be "insightful" to plan risk, issue controlling measures or take corrective and preventive actions to ensure the achievement of critical success factors.

Non-compliance

The compliance related to critical data, processes and patient safety should be monitored diligently. Non-compliance with the protocol, SOPs and applicable regulatory requirements should be addressed effectively. If there is any non-compliance, sponsors need to do complete root cause analysis to understand the actual reason for non-compliance. The effective root cause analysis helps in implementation of appropriate preventive and corrective actions to avoid such non-compliance incidences in future.

Validation of Computerised Systems

After the release of first ICH E6 (R1) guidelines around two decades back, there has been increased use of different technology systems in clinical trial management. The addendum recommends proper validation of computerised systems. Also, the approach to validation should be based on the intended use of such systems and potential of the systems to affect subject safety and reliability of the trial results. These systems could be EDC, randomisation systems (IRT), safety reporting system, e-diaries or ePRO, or technology used for central monitoring or overall risk management. There should be proper standard operating procedures (SOPs) explaining setup, installation, use, validation, security measures, data backup, recovery and contingency planning, etc. The roles and responsibilities of all stakeholders involved in the study from sponsor, vendor and site level should be clearly defined and appropriate training should be provided to the users.

Thus, effective implementation of ICH E6 R2 definitely needs changes in some processes, people roles and technology requirements. At the same time, the internal cultural change and flexibility to adopt a new risk-based approach in designing, planning and executing clinical trials is also important for successful implementation of the ICH addendum. Moving to a risk-based approach in quality management and in study-monitoring activities by identifying risks to critical data and processes at the beginning and tracking them during study conduct, and applying proactive risk control measures in response to any risk triggered which might affect subject safety, data quality or validity of study results, are the essence of ICH E6 R2 implementation. There should be proper leadership to steer change management which brings relevant changes in processes, SOPs, policies, training needs, knowledge management. Additionally, there is a need for integrating the right tools and technology into new processes which will support successful implementation of ICH E 6 R2.

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