November 2017: The One Year Mark for ICH E6 R2 Addendum

A State of the Industry Report

Since the 1996 adoption of ICH E6 GCP, clinical trials have evolved substantially due to increases in globalization, study complexity, and technological capabilities. Approach to Good Clinical Practice (GCP) requires modernization to keep pace with the scale and complexity of clinical trials, and to ensure appropriate use of technology.

In November 2016, the second revision to ICH Good Clinical Practices E6 R2 was the biggest revision to GCP in 20 years. It was crafted partly in response to the concerns raised from hundreds of international GCP regulatory inspections that revealed the following findings:

- Inadequate records and/or record keeping
- Deviations from clinical trial protocols
- Improper storage, maintenance, and/or archiving of records and essential documents
- Inadequate or non-existent quality management systems
- Inadequate or poorly documented training, education, and qualification of clinical research personnel
- Inadequate or improper delegation of authority
- Inadequate access to source documentation
- Inadequate or non-compliant informed consent process or documentation

The addendum was introduced to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight recording and reporting, while continuing to ensure human subject protection and reliability of clinical trial results.

Denise Redkar Brown, principal at Sunburst Clinical Solutions, consulting in training, data management and Auditing, shared that "the ICH E6 (R2) guideline brings us a new paradigm for clinical research. The concepts of risk management, quality by design, and data quality are not new, but the combination recommended to realize new efficiencies is important for the industry to embrace."

One Year Later

Different stakeholders in the industry, especially sponsors and clinical research organizations (CROs), are coming to terms with these new requirements. Organizations utilizing traditional models of clinical research are in different stages of process gap identification and solution planning to become ICH E6 (R2) compliant. Understandably, there are challenges to building or modifying processes and methodologies on the existing clinical execution model.

The changes in ICH E6 (R2) in many ways encompass best practices adopted from other industries, such as manufacturing and aeronautics. Large pharma and CROs that have evolved with changing times by adopting data-driven and risk-based approaches to monitoring are in a better place today because these approaches form the backbone of the new requirements. However, there are a significant number of organizations in the industry that have not previously had the requirement to explore such processes, and are now faced with a need to quickly become compliant with the new guideline that regulatory agencies will soon adopt. This paper discusses important aspects to consider while implementing ICH E6 (R2) in these organizations as it relates to:

- **Process**
- **People**
- **Technology**

Process: Current State Risk Planning

The planning and execution of a clinical trial currently applies a sequential and siloed or function-focused approach, where risk planning and downstream risk evaluation are applied in a limited manner. Here are some key process gaps against ICH E6 (R2):

- The processes adopted do not formally and consistently reflect changes proposed in sections 5.0.1 to 5.0.4 of the ICH E6 (R2) amendment that relate to identification of risks, critical processes and data, risk evaluation, and risk control.
- There is limited collaboration and input from functional stakeholders, such as medical monitoring and data management, to ensure functional alignment and holistic risk monitoring.
- The key risks are not linked to data-driven key risk indicators (KRI). Even if there are risk indicators, they have not been consistently and optimally monitored through ongoing review of data collected.
- Mitigation of risk is often not considered and where it exists, the process is often incomplete, not considering the need to forecast different scenarios and actions to be taken.
- Functional risk plans are created in isolation by different functional groups and they do not undergo continual review during the study.
- Regulatory compliant documentation to prove process execution is not created.

Site Monitoring

Conventional site monitoring utilizes a standard approach to monitor sites at periodic intervals without factoring in prioritization of site monitoring based on risk or quality issues in a proactive manner. We have found that current on-site monitoring relies primarily on “monitor driven” subjective decision making that is not consistent across sites in the study. Also, there is a high focus on source data verification process. This contributes to limited visibility and review of data trends and patterns at sites, and data managers are unable to piece all the risk elements of a site to understand the overall risk at the site.

New Process Framework Considerations | Risk Planning

(Section 5.0.1 to 5.0.5 of revised ICH E6)

Risk planning procedures need to be tailored to your organization type, structure, function and scope. Some good practices include the following action list:

- Appoint a lead for risk planning and defining which functional stakeholders will be represented during the risk planning process, and involve teams from medical/scientific, clinical monitoring, data management, and biostatistics functions.
- Establish a timeframe for the Lead to identify and record base risks and finalize risk plan.
- Collect and document inputs from different stakeholders to add or modify the risk list.
- Harmonize inputs from different stakeholders to inter-link, align, and develop a holistic risk plan to also include inputs that forecast scenarios and risk mitigation strategies.
- Determine risk thresholds based on scientific-, historic- or organization-driven rationale.
- Define the right framework to monitor (by including simple or complex statistical calculations), and recommend to differentially act when a threshold is breached.
- Establish review meetings to evaluate structure, frequency, and governance of risk for continual improvement.

Risk Review

(Section 5.0.6)

The review process should consider defining specific aspects of risk:

- Personnel and their role in performing risk monitoring.
- Frequency of risk review.
- Channels for feedback on risk review to enable functional stakeholders to take downstream actions as defined in risk planning, and to track ineffective risks and/or risk thresholds to identify threshold levels.
- Decision documentation on trending of risks and actions taken.

Risk Reporting

(Section 5.0.7)

The risk reporting process needs to define upfront any and all of the following:

- Deviations that impact outcomes from a scientific as well as quality perspective.
- Internal interim reporting to decision makers.
- Governance of risks and effectiveness of decisions being taken on risk mitigation on an ongoing basis.
- Publishing reports and circulating to important stakeholders.

Monitoring Related

(Sections 5.18.3 & 5.18.6)

Risks and data need to be monitored centrally with standard processes and guidelines to ensure data review consistency and scalability. On-site monitoring activities need to adapt to different focus areas during on-site monitoring, and some of them will be to perform site process related reviews, documentation compliance, and review of source data to verify process and data congruence.

Monitoring Process Considerations

- Standard processes and guidelines for central monitoring.
- Document modified approaches in the clinical monitoring plan.
- Modify focus on on-site activities.
- Site process related reviews.
- Documentation compliance.
- Process and data congruence check in SDR.
- The central data monitoring plan should define critical data points. that will be reviewed, KRI/ KPI, data review frequency, and data insights and outcomes.
- Monitoring reports will comprise of both on-site and central monitoring reports.
- The central monitoring report documents subject or site-specific review and actions taken.
- Need to formally document the approaches to be utilized in the clinical monitoring plan and clinical data monitoring plan.
- The clinical data monitoring plan also needs to call out important aspects such as which data points will be reviewed, key performance indicators, frequency of data review, data insights to be reviewed, and types of data review outcomes. This should be linked to the clinical monitoring plan so that holistic efforts of risk, data, and performance linked to sites are fully realized.
- Site monitoring reports will comprise of both on-site monitoring reports and central monitoring reports. The central monitoring reports should also be able to document details of whether it was subject or site-specific review and actions taken based on data review.

People Considerations

The changes specified in the addendum by and large impact clinical and data operations personnel the most in the clinical research continuum. One of the biggest industry challenges that needs to be addressed is how people, especially in clinical and data operations, will be able to adapt to these changes. The last significant revision to ICH E6 was made in 1996 which means human resources have worked a significant part of their professional lives in the traditional model. Compliance to ICH E6 (R2) requires different types of skill sets.

Emerging New Roles

New roles are required to handle and own risk planning and central monitoring (sections 5.0.1 to 5.0.6, 5.18.3 and 5.18.6). With regard to risk planning, experienced study leads who understand and have managed studies across functions to distill out technical or operational risks in the study or program. With regard to central monitoring, this lead professional requires a combination of scientific and operational monitoring acumen, as well as savviness in data analysis. Functionally, they will be responsible for performing a combination of subject centric reviews, as well as surveillance of site performance. A lead role with responsibility for crafting a central data monitoring plan will need to be included.

Modified Existing Roles

Site monitors in the new paradigm will be required to be more focused on observing study and site operation processes and linking them with performing source data. They will also play an important role in recommending actions based on the insights generated from the central monitoring team and the sites. Functional leads will have to integrate and form the core team of risk planning where they need to understand, correlate, and link risks to their functional plans and assess its impact on overall risk mitigation.

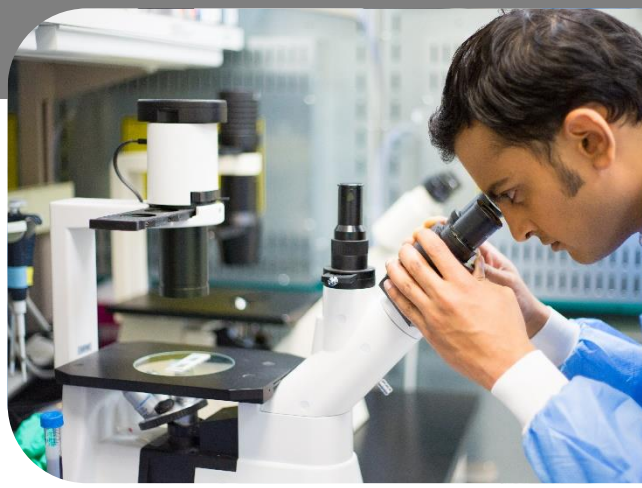
Change Management

Organizations need to make a structured and committed investment in getting different stakeholders aligned and trained appropriately. Process framework needs to be developed by having cross-functional views. This can be achieved by having cross-functional nominated representatives in the core team. In parallel, there should be continuous communication and messaging of the changes expected in operations to be compliant to the new regulation.

A structured approach, along with a team who will champion the change and a leader of change management needs to be appointed, who will be part of the core process development team. The key aspects to be continually communicated to the team are:

- Explaining changes in regulatory landscape and operational impact of non-compliance and what it means for operations and process. (At a minimum, a high-level view of the new or additional processes needs to be provided so that they can be better prepared for the forthcoming changes and the expected timelines to implement the new processes).
- Indicate how roles and responsibilities of existing operational and functional team members are expected to change. Explain finer skill set requirements for these new roles.
- As appropriate, lay out a skill upgrade training program, especially for aspiring central monitors.
- Once process framework and SOPs are drafted, it is important to share the new process and procedures to the different functional teams.

Kathleen Yeager and Donna Gugger of UBC, a global clinical research organization, emphasized the need for getting buy-in from all stakeholders and understanding the critical role that a champion can play in taking the lead and in engaging others. They shared, "We've seen some delay, particularly for reasons of higher cost around implementation, but the overall receptivity is good. It comes down to as the guidance is finalized … how does this affect me? What does this mean for me?"



Organization-wide training needs to be focused into different areas like orientation to the new regulation, articulation of the new SOPs and processes, explanation of new roles, and responsibility in the new process and procedures.

A less discussed, but important component, is the impact on sites. Some of the areas where site personnel and process will be impacted are quicker data entry, less frequent visits of study monitors, more phone or web conference time, and data-driven responses. Monitoring teams need to be sensitive to these factors so that sites are informed about the new changes. This should also be one of the topics that need to be proactively discussed during site selection and initiation meetings.

Regular and frequent feedback from operations during the initial six months is critical to understand course corrections and pain points in implementation.

Technology Considerations

In the past, technology tools have complemented processes being followed. In the new paradigm, leaders in organization need to use technology tools to enable their teams to be effective and comply with regulatory requirements by embedding them in processes. This improves efficiency, scalability, and reduces potential information leaks. A major misconception in the industry today is that existing e-clinical tools can be extended and utilized to deliver ICH E6 (R2) risk planning and monitoring. Electronic data capture (EDC) solutions have capabilities to allow targeted source data verification based on various data principles, which only partially enables risk-based approaches to monitoring. Current industry challenges to implementing ICH E6 (R2) requirements utilizing existing tools are mentioned below:

Things to Consider while Choosing a Technology Platform

Risk Planning

Utilizing industry recommended tools like the Risk Assessment and Categorization Tool (RACT) and related documents to be compliant to ICH E6 (R2) in sections 5.01 to 5.05 is possible, but there are limitations. Some of these limitations include the inability to iterate the risk plan as the risk planning process matures.

Additionally, lack of version control can lead to multiple versions being used by different functional stakeholders. For instance, can there be assurance that the systems/tools used are compliant with Section 1.65 (Validation of Computerized Systems) of ICH E6 (R2)?

Furthermore, the stakes of not using a validated technology tool needs to be understood. For instance, can the risks be linked to different functional plans so that the functional lead can be assigned risks that are relevant to their function? Does it allow functional teams to collaborate by providing transparency to the same risk that are linked to different functions, and whether such risk mitigation strategies can be holistic and aligned? Is there a possibility to create a knowledge repository of risks? Will it be able to reuse risks created in a library? Is there an audit trail of the changes being made by the different users in the system?

- End to end risk management & monitoring system
- Provide intelligence across different data sources (CTMS, EDC, IXRS, eTMF etc)
- Enables Risk planning, records functional mitigation plans & link to KRIs
- Allows reuse of risks, KRIs, and data visualizations
- Enables decision making by applying statistical or data driven methodologies
- Enables central monitoring – Capturing actions on risks

Risk Review and Data Monitoring

EDC and CTMS are currently two data sources that the industry is primarily relying upon for KPI and KRI reviews. However, with more eClinical solutions widely available such as electronic trial master file (eTMF), (electronic informed consent form) eICF, interactive application response systems (IxRS), and electronic clinical outcome assessments (eCOA), these data sources will also need to be reviewed and holistically mapped to risk and performance measurement of sites.

The complexity increases when best of breed technologies are used as data from different source systems need to converge, and risks reside in different systems that require monitoring. Currently, we see data being exported into spreadsheets and reviewed by clinical and data operation team members. There are inherent challenges with such a manual approach:

- Manual review of data is cumbersome and inefficient, especially if bi-variate or multivariate review of data needs to be performed.
- Data signals need to be mined and this effort is not automated.
- Programming algorithms to generate alerts is not scalable.
- Data aggregation needs to be performed every time.
- Correlating parameters and calculating across different data sources is cumbersome.

Risk Reporting & Actions Taken

The logical next step after data review is taking actions or assigning actions to the relevant stakeholders. Currently, this is being recorded in disparate source systems such as clinical trial management system (CTMS), trackers, emails, and monitoring reports, which do not give the historical sequence of events and delays encountered. Bigger challenges are in store when an action item is not resolved because it is lost in transition. This places a significant risk especially on clinical operation team members who eventually interface with the site, and hence is an important consideration for clinical monitoring teams.

"The emphasis on system validation is an underrated but much-needed upgrade to the guidelines," noted Gary Avedovech, manager, quality and compliance at Medrio. He added "System reliability and data integrity and security have been the Achilles heel of many clinical platforms. We hope that Rev 2 will prompt vendors to devote more resources to these very important areas. This will benefit the entire industry as clinical software platforms become more robust and easy to use, as well as more secure."

Process Driven Technology Solution

An ideal technology solution will use a process driven end-to-end validated system that:

- Allows for easy convergence of key data elements from disparate sources and all relevant clinical trial informatics tools and moreover allows for easy adaptation of integration as maturity model evolves.
- Enables risk planning, records functional mitigation plans, and links them to KRIs.
- Integrates and converts data into insights from data sources such as CTMS, EDC, eTMF, IxRS etc.) to enable holistic risk-based approaches to monitoring
- Simplifies data review through data visualizations and embedded algorithms and alerts, which will significantly help in simplifying and consistently performing data review.
- Enables operations to utilize pick and choose validated standardized data visualizations as well as utilize created custom data visualizations that will be relevant to what the study requires.
- Enables data-led decision making aided by the utilization of statistical and or data-driven methodologies.
- Enables central monitor generated action items as well as the assignment of the same site monitor, tracking it centrally and closing them rapidly.
- Creates a knowledge repository of risks, KRIs, data visualizations, and actions so that it can be reused effectively in the future.

Conclusion

Though ICH E6 (R2) is the biggest revision to GCP since its release in 1996, and is likely to cause disruption in industry functioning, it needs to be viewed positively. Correct and timely modifications at a process, people and technology level can surmount the challenges posed by the new regulatory landscape.

The question, until a few months ago, was never whether risk-based approaches to monitoring will need to be implemented, it was when will this become “business as usual”? That time has arrived. Now is the time for the clinical trials industry to become compliant with the new requirements or perish. The industry needs to seize this opportunity to transform.

As action is taken and various technology solutions and approaches are weighed, careful consideration should be given to the fact that no single technological solution will work for all and that the final solution space may include a heterogeneous collaborative of best in breed technologies that seamlessly work with each other.

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References: ICH harmonized guideline integrated addendum to ICH E6 (R1): guideline for good clinical practice E6 (R2) 2. European Medicines Agency: Guidelines for good clinical practice E6 (R2) Advantage Clinical. Special thank you Abby Abraham, Vice President, Clinical Solutions at Algorics. With 17 years’ experience within the pharmaceutical and clinical research industry, he is responsible for Intellectual Property development, customer scientific engagement and enhancing enduser experience of Acuity, the best in breed clinical analytics solution. Abby also works with stakeholders in the clinical industry to provide tailored processes and solutions for implementing risk based management/monitoring (RBM) based on organizational and study needs. He advocates the need to transform the existing model of clinical research by adopting smarter technologies, data-driven models to improve quality and efficiency in clinical research.