Five Reasons to Embrace the ICH E6 (R2) Addendum Now

Improve Study Efficiencies by Centralising Risk-based Quality Oversight and Trial Management

PEER REVIEWED

In November 2016, the ICH E6 (R2) Addendum to Good Clinical Practice was implemented, delivering a breath of fresh air for clinical trial sponsors and CROs who have been looking for guidance on best practices for achieving true, risk-based quality management during clinical development.

The Addendum is expected to increase the adoption of quality-by-design and quality risk management principles and methodologies in clinical development, while driving the use of innovative strategies and technologies for risk monitoring. It essentially mandates, harmonises and clarifies what FDA and EMA have been suggesting in their guidance about the value of embracing a centralised, technology-driven approach to risk monitoring that begins in planning and continues through the life of the research. The Addendum further defines the scope of clinical trial oversight responsibilities and describes the sponsor's responsibility to establish a risk-based quality management system, ensuring the tools and methods used are "proportionate to the risks inherent in the trial and the importance of the information collected." (792-793)

The ICH Addendum defines centralised monitoring as, "The remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner. Centralised monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring…" (1135-1138)

The Addendum suggests sponsors and CROs should *"…implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials," (786-787). It proposes that sponsors "…develop a systematic, prioritised, risk-based approach to monitoring clinical trials," and suggests that "…a combination of on-site and centralised monitoring activities may be appropriate…"* (1127-1131)

It also specifically cites "evolutions in technology and risk management processes" as the reasoning behind the change, and encourages industry stakeholders to seek out new tools and processes that will help them take advantage of these efficiencies. FDA added information to the document on conducting a centralised monitoring programme and how to manage "significant noncompliance" to further establish unified standards across the trial site network.

While the timeline of fully realising the vision of the ICH E6 (R2) Addendum may be measured in years vs. months, there are incremental yet critical gains that sponsors and CROs can realise in the near term. Here we present five reasons why sponsors and CROs should adopt a centralised approach to risk-based trial monitoring, oversight and quality management now — to not only stay ahead of guidelines and regulations, but also to reap significant benefits across many aspects of clinical development.

Improved Collaboration

By implementing a centralised approach to trial and data monitoring, greater collaboration develops between sponsors, CROs and other vendors as they all have the opportunity to contribute to risk assessment planning and agree on mitigation strategies before the trial begins. With shared data visibility, sponsors and CROs benefit from a transparent approach to risk management that fosters shared responsibility, improved operational performance and more collaborative strategic relationships.

Higher Data Quality

The Addendum states: *"The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience."* (828-830). With centralisation, sponsors and CROs have access to more targeted data oversight, giving them greater insight into data quality trends as they are identified. For example, if a site forgets to enter critical data during a patient visit, the monitor is apprised and can act/react immediately so that the data is entered in a timely fashion.

Faster Risk Mitigation

The Addendum states: *"The sponsor should identify those risks that should be reduced (through mitigating actions) and/or can be accepted. Risk mitigation activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedure."* (813-817) By implementing a centralised oversight component to their quality risk management (QRM) process, sponsors and CROs gain visibility into all trial data, which allows for real-time identification of risk trends across all trial sites. For example, standard algorithms may be used to track key risk indicators such as major protocol deviations, and send an alert when a site has exceeded acceptable thresholds, along with associated review workflows for intervention and training to improve results. The combination of a defined risk mitigation plan and insight with real-time data delivers the anticipatory oversight sponsors and CROs need to act or react to risks as they arise.

Greater Accountability
With collaborative risk planning and shared data access capabilities, sponsors can hold CROs and other vendors accountable for executing risk mitigation strategies and achieving performance targets without the level of effort currently required to manage them.

Improved Efficiencies and Reduced Trial Costs
By adopting a centralised approach to risk-based trial oversight and quality management, sponsors and CROs can select sites based on experience, performance and behavioural data to reduce oversight burden. And, they can significantly reduce onsite monitoring costs with risk-based monitoring strategies, saving as much as 15-20% per trial. All of this leads to shorter study start-up and monitoring cycle times, which improves timelines.

Choosing a Centralised Risk-based Quality Management Solution
Before choosing a centralised risk-based quality management solution, sponsors and CROs should examine their current tools and strategies and draft a plan for updating their existing systems to meet regulatory compliance. This will help them to achieve efficiencies in the way they monitor the performance, integrity, and safety of clinical trials. That vision should include strategies for risk-based oversight that define key risk indicators and analytics with targeted thresholds, automated alerts, and action plans at the study level.

These choices shouldn't be made in isolation. To build the most efficient system, sponsors and CROs should implement industry best practices as much as possible, to avoid the pitfalls of customisation on every trial.

Consideration for sponsors: When sponsors and CROs use technologies that provide different views or formats for trial information, they may have communication conflicts as well as the potential for redundant oversight, e.g., the sponsor's system alerts the CRO to a potential risk that the CRO's system has already identified but not yet acted upon.

To avoid such redundancies, sponsors should involve CROs and speciality service providers in their vendor assessment process and decision-making on which risk-based management (RBM) solutions to implement. Such collaborations also enable better alignment around data review processes, system cadence and risk analysis, and create opportunities to build latency tolerance for follow-up actions into service agreements. This will further reduce the noise and resulting bottlenecks that may otherwise accumulate.

Considerations for CROs: As CROs look to operationalise RBM, they should take into account the significant process and budgeting considerations that will result. In traditional outsourcing models, CROs can project resource allocation based on the study protocol, study plan, and variables such as complexity, number of sites, subjects, and geographic distribution. This data helps them determine the number of CRAs and data management resources that will be required to meet the needs of the trial and sponsor.

Implementing risk-based quality management and monitoring will require a more proactive and data-driven approach to risk management, using key risk indicators to drive investigator oversight. To get started, CROs can work with speciality service providers to help aggregate their vast amounts of data and make key plans for process modifications which can be fine-tuned over time by selecting the right infrastructure. It will make budgeting and resource allocation more challenging at first, but over time, sponsors and CROs will be able to adapt their processes and collect best practice information to inform future trials. In the meantime, sponsors and CROs should consider alternative budgeting strategies, with built-in flexibility to account for resource and workload fluctuations.

Conclusion
The ICH Addendum is expected to formalise trial process guidelines that will have a positive impact on data quality, so there's no reason to hold off on implementation. The Addendum should be a wake-up call for trial sponsors and CROs that it's time to change the way they think about — and address — quality risk management when planning and implementing clinical trials.

By implementing a centralised QRM system now, sponsors and CROs can significantly reduce the time and cost of clinical trials while helping to reduce risk. Sponsors and CROs who adopt the philosophies outlined in the ICH Addendum sooner rather than later will benefit from competitive advantages driven by improved trial efficiencies.

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