The CenterWatch Monthly

May 2017 A CenterWatch Feature Article Reprint Volume 24, Issue 05

Preparing for the ICH E6 Revisions

Quality management and risk-based approaches take center stage

By Barbara Bolten

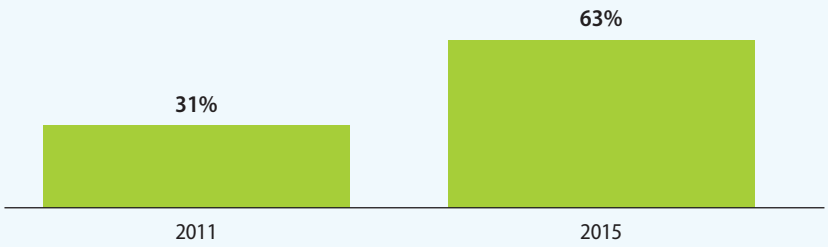
In November 2016, the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) issued Step 4 of the new Good Clinical Practice (GCP) E6 (R2) guideline. A core principle of E6 (R2) is the integration of quality management (QM) and risk-based approaches to span the entire clinical trial process. The addendum embodies the concept of proactive planning for quality, oversight, preventive action and documentation.

"This requires prospectively putting a QM system in place," said Michael Hamrell, president of Moriah Consultants. "The approach used to be: run the study, monitor it and we'll know we have quality if we find good results. Now, sponsors will have to plan for quality."

Because the industry has not typically focused on QM and risk management in clinical research, many organizations may not yet fully understand what these systems mean for the clinical side of their businesses. Learning about the expectations of E6 (R2) and integrating them into diverse activities such as planning, monitoring and data management will take time and training. While some companies are further ahead—for example, some already have risk-based monitoring systems in place—others will take longer to comply with the guidelines. The EMA is the first regulatory authority to set an effective date for E6 (R2)—June 14th, 2017—so global companies with business in the EU are under the most immediate pressure to achieve compliance.

Growth in company implementation of risk-based monitoring

Percent of companies that report implementing 'Aspects' of RBM



Source: QuintilesIMS, 2016

ICH developed the addendum in response to dramatic increases in the complexity of clinical trials since the first E6 (R1) guideline was issued in 1996. New technologies, including powerful electronic data collection, reporting and management systems, have created both opportunities and challenges for clinical research teams.

"Trials are more complex, with multiple levels of technology," said Erika Stevens, vice president, Research Programs, Integrity and Operations, Northwell Health. More personnel and vendors are needed to manage the greater volume of data collected and protocol procedures, which thus increases the difficulty of risk mitigation by sponsors. "As trials become more complex, the likelihood of non-compliance increases," said Stevens. "The changes to E6 may have been driven by issues of non-compliance that have emerged."

Areas of focus in E6 (R2) highlighted by experts interviewed by CenterWatch include QM and risk-based approaches, risk-based centralized monitoring and related privacy concerns, electronic data and investigator responsibilities.

Focus on the essentials

The E6 (R2) addendum update draws on previous guidelines from other regulatory bodies (FDA, EMA, MHRA), and the principles of the original E6 guideline remain intact. "I see the guideline as a logical extension of what was there before," said Hamrell. "The core document hasn't changed." The addendum asks sponsors to focus on the most important aspects of clinical trials to protect human subjects and ensure the reliability of results, and specifically "to avoid unnecessary complexity, procedures and data collection." Sponsors are advised to identify critical processes, elements and data; identify, evaluate and control risks; and develop processes to identify mistakes and prevent them from happening in the future.

"The updates in ICH GCP encourage the industry to focus on what matters," said SAM

Sather, vice president of Clinical Pathways Research. "When choosing a system to support clinical trials, be sure to focus on what is essential." This risk-based approach for clinical studies is not new to the industry. "The ICH guideline update related to quality risk management is consistent with the EMA's reflection paper for quality risk management in clinical trials, and it also has reflections of ICH Q9 Quality Risk Management and of the FDA's 2013 guidance promoting a risk-based approach to monitoring," noted Sather.

"Most of the addendum is not new, but it is looking at processes from a risk-management framework," said Stevens. "The changes in the guideline are fine-tuned to require a certain level of risk mitigation and accountability. Define the problem, measure and map out the current process, analyze it, improve it and control it going forward."

Climbing the learning curve: A cross-functional effort

A cross-functional approach to introducing and executing risk management is essential. "To implement quality risk management within a clinical program, an organization first needs to do an impact analysis," said Sather. "Ask how this approach will impact current procedures, quality control and quality assurance, training programs, computerized systems and documentation systems. A lot of cross-functional work is needed to integrate quality risk management."

Reaching across functions is important to align an organization with quality risk management principles. "The first challenge is getting people in the industry comfortable with quality risk management," said Madeleine Kennedy, senior vice president at INC Research. "Companies need to identify the critical elements of a protocol and the critical processes associated with a study. Doing so will require a cultural shift, mainly because of the fear that something critical will be missed. Risk management is also a challenge because it requires input from multiple parties. The clinical research team will have to spend more time planning and be willing to change course along the way—at a time in the industry when cycle time has never been so critical."

Kennedy suggested developing and sharing practical training and other tools across the industry. "We are putting together case scenarios in which our staff can practice quality risk management, and we plan to share lessons learned from those sessions across the company," said Kennedy. "The more tools we have and can share, the better off we're going to be as an industry."

Glenda Guest, vice president of Norwich Clinical Research, also cited the importance of industry-wide sharing and interdisciplinary training. "I'd like to stress the importance of networking and sharing best practices as an industry to prepare for implementation of the addendum," said Guest. "The first step is ensuring adequate training on risk-management strategies and documentation. Monitors, project managers and clinical study managers will all need this training."

QM lessons from manufacturing

Sponsors can also draw on their extensive experience with existing QM manufacturing processes to implement new QM systems for clinical research, although this shift in thinking may not be easy. "Our manufacturing colleagues may be a resource for learning how to apply the concepts of quality management systems to clinical operations," said Guest.

The addendum asks sponsors to perform a root cause analysis and implement a corrective and preventive actions system (CAPA) if it identifies investigator non-compliance. CAPA involves finding the root cause of a problem, fixing it, taking steps to prevent it from happening again and monitoring to ensure the preventive action is effective. "Sponsors will need to address whether they are going to have a separate CAPA system for their clinical issues, or whether to incorporate it into an existing manufacturing CAPA system," said Guest. She recommends that "sponsors track their clinical CAPAs separately from manufacturing unless they have a really robust CAPA system that works for them."

Electronic data and centralized monitoring

Electronic data handling, ensuring data integrity and SOPs for computer systems are all addressed in the new guideline. For example, the addendum emphasizes the data characteristics, also known as ALCOA-C, required to ensure the reliable reconstruction and evaluation of what occurred during a trial. The addendum also clarifies the use of validated processes for making copies of original records.

"In the definition for certified copy, the addendum says that if the document has all the same attributes as the original, it doesn't matter if it's a copy of a paper or an electronic

ICH E6 addendum background

- Expert Working Group (EWG) formed June 2014 to evaluate current ICH E6 guideline in light of:
  - Increasing global nature of clinical trial activity
  - Rising involvement of intermediaries
  - Increasing clinical trial complexity
  - Growing adoption of Information Technologies
- Addendum finalized by the EWG in June 2016
- Approved by the ICH Steering Committee in November 2016
- Timelines for Addendum to go into effect beginning Q3 2017 but varying across ICH regions

record," said Sather. "If you have a system that is validated to make an exact copy, you would not need to certify the copy. Also, if you have a quality-controlled, formal process in place that maintains all the same attributes as the original, you wouldn't have to certify each page." This approach will be helpful at sites when providing source documentation for sponsor monitoring and independent auditing. Additionally, this helps a site determine how to manage source documentation when they are not able to provide monitors or auditors with direct access to electronic health records (EHRs).

The widespread expansion of electronic data technology in clinical studies is enabling centralized monitoring approaches. E6 (R2) allows sponsors the flexibility to combine on-site and centralized monitoring strategies, and requires a monitoring plan as well as documentation of results. However, centralized monitoring raises concerns around data protection, security and privacy. "An unintended consequence of centralized monitoring will likely be more tension with privacy regulations," noted INC Research's Kennedy. "Some companies will want to do things, such as reviewing informed consent documents and other source data remotely, without having the proper controls in place." Industry experts are looking for more guidance in these sensitive areas. "Cloud-based systems, mobile apps, electronic informed consent and signatures—all of those will need to be addressed," said Kennedy.

E6 (R2) also asks sponsors to develop a risk-based monitoring approach. "In risk-based monitoring, you don't have to monitor and verify 100% of the data to have quality," said Moriah Consultants' Hamrell. "You can focus on key parameters and critical variables, such as inclusion/exclusion criteria, key evaluations and endpoints. But a lot of companies are still not comfortable with risk-based monitoring, because they feel they're going to miss something."

ICH E6 addendum focus

- Addendum builds on, but does not alter, existing ICH E6 requirements
- Facilitate innovative approaches to clinical trial conduct, including risk-based quality management and quality-by-design
- Promote standard practices and procedures for the use of Information Technology tools
- Promote standard practices regarding electronic records and essential documents

Oversight of investigative sites and vendors

While investigators are already responsible for clinical trial conduct and oversight, the addendum focuses specifically on the supervisory role they play for individuals and third-party contractors to whom responsibilities are delegated. "There needs to be a change in the framework around accountability for all of the sub-components related to research," said Northwell Health's Stevens.

The guideline requires that investigators ensure that individuals and external parties are qualified to perform required tasks. "The addendum says that investigators should implement procedures to ensure the integrity of those tasks and the data generated," said Kennedy. "Clinical trial agreements with sites or institutions that don't address this expectation will need to be updated to make sure this is covered."

Some experts feel that the guideline could have gone further in applying QM systems to investigative sites. "The addition of quality risk management in the addendum is focused on the sponsor's function," said Sather. "Performing trials with a risk-based mindset would be very beneficial for sites and IRBs to do also."

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—Madeleine Kennedy, senior vice president, INC Research

Progress so far

In December 2016, the EMA proposed an effective date for E6 (R2) of June 14, 2017. As of this writing, neither the FDA nor Japan has set an effective date. Companies are taking different approaches toward compliance. "We see various states of preparation and implementation now," said Guest. "Some companies prepare in advance so they hit the ground running. Most wait for the release of the final guideline, and then do their gap analyses and training plans prior to the effective date."

Prompt implementation of compliance can provide CROs, in particular, with a competitive advantage. "Our goal is to be compliant by June 14th, but it is a journey, and we will continue to enhance our processes to ensure that we are not only compliant, but remain competitive," said Kennedy.

Developing QM and risk-based approaches for diverse functions such as data management, centralized monitoring and clinical study management is a major undertaking, and some companies are better positioned on the learning curve than others. Professional organizations can help companies learn what the new guidelines require and train employees in the new processes and skill sets needed to implement risk-based management in the clinical environment. Executing these changes will require cultural shifts and new ways of thinking for many in the industry.

"Everybody is looking at updating their systems to comply with E6 (R2)," said Hamrell. "But companies that have a global-compliant program already have a lot of the requirements in place. I don't think this is a radical change, but it takes some planning and thinking to change a mind-set that reflects 30 years of industry practices."

Trends in protocol data

Means	2005	2015
Total data points collected per phase III protocol	494,236	929,203
Percentage of data collected from 'subjective' endpoints	6%	24%
Proportion of protocol procedures performed that are targeting supplementary secondary, tertiary and exploratory endpoints	18%	31%

Source: Tufts CSDD; <csdd.tufts.edu>

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