

What's New in GCP? EMA Opens Public Consultation on ICH Good Clinical Practice Addendum

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The European Medicines Agency (EMA) released an addendum to the International Conference on Harmonisation guideline on good clinical practice Aug. 21. The addendum, which is open for public comment until Feb. 3, adds a new section on sponsor quality management.

"Developments in technology and risk management processes offer new opportunities to increase [clinical trial] efficiency by allowing sponsors to focus on relevant activities," the EMA said in announcing the addendum.

The EMA said the guideline was amended to: encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure the protection of clinical trial participants, and data integrity; and update standards regarding electronic records and essential documents intended to increase the quality and efficacy of clinical trials.

Quality Management Emphasized

The addendum on quality management states that sponsors should implement systems to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials. "Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results," the addendum said.

It said the methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. "The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, case report forms, and other operational documents should be clear, concise and consistent."

The EMA advised that the quality management system should use a risk-based approach, which includes:

- Critical process and data identification – "During protocol development, the sponsor should identify those processes and data that are critical to assure human subject protection and the reliability of study results."
- Risk identification – "Risks to critical study processes and data should be identified. Risks should be considered at both the system level (e.g., facilities, standard operating procedures (SOPs), computerized systems, personnel, vendors) and clinical trial level (e.g., investigational product, trial design, data collection and recording)."
- Risk evaluation – The identified risks should be evaluated by considering: the likelihood of errors occurring, given existing risk controls; the impact of such errors on human subject protection and data integrity; and the extent to which such errors would be detectable.
- Risk control – The sponsor should identify the 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 SOPs, and training in processes and procedures," the addendum said. "Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or data integrity. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed," the document said.

- Risk communication – Quality management activities should be documented and communicated to stakeholders to aid risk review and continual improvement during the clinical trial.
- Risk review – "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."
- Risk reporting – The sponsor should describe the quality management approach used in the trial and summarize important deviations from the predefined quality tolerance limits in the clinical study report.

The addendum added that when using a contract research organization (CRO), the sponsor "should ensure oversight of any trial-related duties and functions carried out on its behalf. The sponsor should document approval of any subcontracting of trial-related duties and functions by a CRO."

In addition, when using electronic trial data handling and/or remote electronic trial data systems, the sponsor's "SOPs should cover system setup, installation and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning and decommissioning. The responsibilities of the sponsor, investigator and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in the use of the systems."

Sponsors also need to "ensure the integrity of the data, including any data that describe the context, content and structure of the data. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data," the addendum said.

Centralized Monitoring Covered

Regarding the extent and nature of monitoring, the addendum said the sponsor "should develop a systematic, prioritized, risk-based approach to monitoring clinical trials," which could include "varied approaches that improve the effectiveness and efficiency of monitoring," the document said. "A combination of on-site and centralized monitoring activities may be appropriate. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan)."

The document noted centralized monitoring provides "additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring" by using methods such as:

- Routine review of submitted data;
- Identification of missing data, inconsistent data, data outliers, or unexpected lack of variability and protocol deviations that may be indicative of systematic or significant errors in data collection and reporting at a site or across sites, or may be indicative of potential data manipulation or data integrity problems;

- Statistical analyses to identify data trends such as the range and consistency of data within and across sites; and
- Site characteristics analysis and performance metrics to select sites and/or processes for targeted onsite monitoring.

The document added that “monitoring results should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up.” In addition, the results of monitoring activities “should be documented in sufficient detail to allow verification of compliance with the monitoring plan,” which should be “tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use.” The plan also should emphasize the monitoring of critical data and processes with particular attention given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan also should reference the applicable policies and procedures.

“When significant noncompliance is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions. If required by applicable law or regulation, the sponsor should inform the regulatory authority(ies) when the noncompliance is a serious breach of the trial protocol or GCP,” the addendum said.

Other Additions Detailed

The addendum notes that a certified copy of the case report form (CRF) is a “paper or electronic copy of the original record that has been verified (e.g., by a dated signature) or has been generated through a validated process to produce an exact copy having all of the same attributes and information as the original.”

The addendum also noted that the ICH GCP principle that “all clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification” applies to all records (paper or electronic) referenced in the guideline.

In regard to adequate resources for investigators, the addendum states that “the investigator is responsible for supervising any individual or party to whom the investigator delegates study tasks conducted at the trial site. If the investigator/institution retains the services of any party to perform study tasks, they should ensure this party is qualified to perform those study tasks and should implement procedures to ensure the integrity of the study tasks performed and any data generated.”

The addendum adds under records and reports that the investigator “should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site’s trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).”

The addendum added that the sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents. “The storage system (irrespective of the media used) should provide for document identification, search and retrieval. Depending on the activities being carried out, individual trials may require additional documents not specifically mentioned in the essential document list. The sponsor and/or investigator/institution should include these as part of the trial master file. The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data. When

a copy is used to replace an original document, the copy should fulfill the requirements for certified copies. The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during and after the trial.”

To Find Out More

The guideline with the addendum items is available at
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/08/WC500191488.pdf.

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