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Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice

E6(R2)

Introduction

Since the development of ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. This guidelines has been amended 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 data integrity. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.

This ICH GCP Guideline integrated Addendum provides a unified standard for the European Union (EU), Japan, the United States, Canada and Switzerland to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

Glossary

1.11.1 Certified Copy

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 the same attributes and information as the original.

1.38.1 Monitoring Plan

A description of the methods, responsibilities and requirements for monitoring the trial.

1.39 Monitoring Report

Outcomes of any centralized monitoring should also be reported.

1.60.1 Validation of computerized systems

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled. Validation should ensure accuracy, reliability and consistent intended performance, from design until decommissioning of the system or transition to a new system.

The Principles of ICH GCP

2.10 This principle applies to all records (paper or electronic) referenced in this guideline.

Investigator

4.2.5 The investigator is responsible for supervising any individual or party to whom the investigator delegates study tasks conducted at the trial site.

4.2.6 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.

4.9.0 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).

Sponsor

5.0 Quality Management

The sponsor should implement a system 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. Quality management includes the efficient design of clinical trial protocols, data collection tools and procedures, and the collection of information that is essential to decision making.

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 quality management system should use a risk-based approach as described below.
5.0.1 *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.

5.0.2 *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, computerized systems,

personnel, vendors) and clinical trial level (e.g., investigational product, trial design, data collection and recording).

5.0.3 *Risk Evaluation*

The identified risks should be evaluated by considering:

(a) The likelihood of errors occurring, given existing risk controls.
(b) The impact of such errors on human subject protection and data integrity.
(c) The extent to which such errors would be detectable.

5.0.4 *Risk Control*

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 procedures.

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.

5.0.5 *Risk Communication*

The quality management activities should be documented and communicated to stakeholders to facilitate risk review and continual improvement during clinical trial execution.

5.0.6 *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.

5.0.7 *Risk Reporting*

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

5.2.1 The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf.

5.2.2 The sponsor should document approval of any subcontracting of trial-related duties and functions by the CRO.

5.5.3 b) The 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.

5.5.3 h) 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.

5.18.3 The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. 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).

On-site monitoring is performed at the sites at which the clinical trial is being conducted.

Centralized monitoring is a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner. Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring by such methods as:

(a) Routine review of submitted data.
(b) 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.
(c) Using statistical analyses to identify data trends such as the range and consistency of data within and across sites.
(d) Analyzing site characteristics and performance metrics.
(e) Selection of sites and/or processes for targeted on-site monitoring.

5.18.6 e) 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 as indicated. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan.

5.18.7 *Monitoring Plan*

The sponsor should develop a monitoring plan that is 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 should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

5.20.1 When significant noncompliance is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventative 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.

Essential Documents for the Conduct of a Clinical Trial

8.1 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, individuals 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.