International Council for Harmonisation E6(R2) addendum: Challenges of implementation

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INTRODUCTION

In 2016, the International Council for Harmonisation (ICH) E6 – good clinical practice (GCP) (R2) addendum – was amended to foster implementation of improved approaches for the management of clinical trials. The changes in different sections include new approaches – quality management system, risk-based monitoring with emphasis on human subject protection, and data integrity. The article discusses challenges in adoption and implementation of the changes in ICH GCP guideline for clinical trial stakeholders.

ADDENDUM CONTENT

In the addendum, the amendments in several sections – glossary, principles, investigator responsibilities, sponsor responsibilities, and essential documents – reflect new approaches and systems with emphasis on human subject protection, and data integrity. The article discusses challenges in adoption and implementation of the changes in ICH GCP guideline for clinical trial stakeholders.

Keywords: Addendum, International Council for Harmonisation, investigator, regulatory, sponsor

Abstract

The International Council for Harmonisation (ICH) E6 – good clinical practice (GCP) (R2) addendum – was released in 2016 to encourage implementation of improved approaches for the management of clinical trials. The changes in different sections include new approaches – quality management system, risk-based monitoring with emphasis on human subject protection, and data integrity. The article discusses challenges in adoption and implementation of the changes in ICH GCP guideline for clinical trial stakeholders.

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Validation of computerized systems is a process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system.\[1\]

Monitoring plan requires description of the strategy, methods, responsibilities, and requirements for monitoring the trial.

The GCP principle 2.10 on clinical trial information will apply to all records, irrespective of the type of media used, and 2.13 demands that quality systems and procedures should be focused on aspects of the clinical trial that are essential to ensure human subject protection and data integrity.\[1\]

INVESTIGATOR RESPONSIBILITIES

The investigator’s responsibilities now include (a) supervision of individuals or parties to whom trial-related duties and functions are delegated and (b) ensuring individuals and parties are qualified and implement procedures to ensure integrity of study tasks and data. The term individuals or parties, as described in the Food and Drug Administration (FDA) guidance on investigator responsibilities,\[3\] would include study staff not in the direct employment of the investigator, for example, site management organization.

The investigator should ensure (1) maintenance of adequate and accurate source documents and trial records that include all pertinent observations on each of the site’s trial subjects, (2) that source data are attributable, legible, contemporaneous, original, accurate, and complete, and (3) that changes to source data are traceable, do not obscure the original entry, and can be explained.\[1\]

The investigator also has new responsibilities for electronic trial data and essential documents.

SPONSOR RESPONSIBILITIES

In the addendum, there are significant additions in the sponsor responsibilities.

Quality management system

The sponsor should implement quality management system (QMS) which focuses on trial activities essential to ensuring human subject protection and reliability of trial results. The QMS includes the design of well-organized protocols, tools and processes for data collection and management, and collection of all information that is crucial to decision-making.\[1\]

The QMS approach is an adaptation of ICH quality risk management (QRM) approach for pharmaceutical quality systems to clinical trial quality systems.\[4\] QRM is a systematic process for the assessment, control, communication, and review of risks associated with the planning and conduct of clinical trials and clinical development programs.\[4\] QRM is based on the identification of clinical trial priorities and mitigation of the critical and serious risks on a continuing basis and defining tolerance limits for operational and areas and processes, for example, trial management procedures, clinical trial data, protocol procedures, and GCP compliance.\[4\]

This stepwise risk-based approach includes\[1,4\]

1. Identification of critical process and data during protocol development
2. Risk identification requires information of potential risks at different levels
   • System level – organization, quality systems, standard operating procedures (SOPs), computerized systems, personnel, regulatory, and ethical framework
   • Clinical trial project level – trial design, investigational product (IP), trial population, informed consent process data collection, study management team, clinical trial site, and study budget.

The next steps are (3) risk evaluation, (4) risk control, (5) risk communication, and (6) risk review (7) risk reporting. All these QMS processes are dynamic and require adaptation based on ongoing review of accumulating information.\[4\]

Contract research organization oversight

The sponsor is expected to ensure oversight of any trial-related duties and functions carried out on its behalf, document approval of any subcontracting of trial-related duties and functions by a contract research organization (CRO).\[1\] In recent past, there have been questions about CRO qualifications, ethics, regulatory accountability, and quality issues in outsourced clinical trials.\[5\] These additional requirements would help the sponsor in fulfilling the prime responsibility for the quality and integrity of the trial data.

Computerized systems

The computerized system includes computer hardware, software, and associated documents (e.g., user manual) that create, modify, maintain, archive, retrieve, or transmit in digital form information related to the conduct of a clinical trial.\[6\]
The sponsors should base their approach to validation of electronic trial data handling and/or remote electronic trial data systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and data integrity.[1] The monitoring plan should describe the strategy, the responsibilities of all the parties involved, the different monitoring approaches to be used, and the justification for their use.[1]

FDA recommends that the sponsors who plan to use centralized monitoring processes should ensure that the processes and expectations for site record keeping, data entry, and reporting are well defined and ensure timely access to clinical trial data and supporting documentation.[7]

The monitoring report should document results of monitoring activities, in a timely manner for review and follow-up. The report should contain sufficient details to check that the monitoring plan was adhered.[1]

Noncompliance actions
When the sponsor team – auditor or monitor – discovers noncompliance that significantly affects or has the potential to significantly affect human subject protection or data integrity, the sponsor should conduct a root cause analysis and implement appropriate corrective and preventive actions.[1] If required by applicable law or regulation, the sponsor should inform the regulatory authorities when the noncompliance is a serious breach of the trial protocol or GCP.

A serious breach is a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.[8] In the UK[9] and in Europe, there is a regulatory requirement for the sponsor to notify the regulatory agencies about a serious breach within 7 days.

Essential documents
This section specifies responsibilities of the sponsor and the investigator for control and maintenance of essential documents.

The sponsor and the investigator should maintain a record of the location of their respective essential documents. Storage system should provide for document identification, version history, search, and retrieval.[1]

The sponsor should ensure that the investigator has control of and continuous access to the case report form data.

Essential documents for a specific trial should be supplemented or may be reduced as appropriate.

When a copy is used to replace an original document, it 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.

**IMPLICATIONS OF IMPLEMENTATION**

Adoption and implementation of the changes in ICH GCP guideline will pose significant challenges for all clinical research stakeholders.

**Regulatory and ethical issues**

In India, clinical trial approval from the Central Drugs Standard Control Organization (CDSCO) requires that the trial should be conducted in compliance with requirements of Schedule Y and Indian GCP guidelines.

Internationally, RBM approach has been promoted by FDA and ICH. However, whether CDSCO will accept such an approach is uncertain. Hence, Indian companies developing new medicinal entities for international market and foreign multinational companies conducting global clinical trials will wonder whether they can implement centralized monitoring in Indian trials. As Indian GCP does not support RBM, a company adopting such an approach and reducing frequency of on-site monitoring runs the risk of regulatory noncompliance.

Ethics committee (EC) has a responsibility for continuing review based on progress reports from investigator, review of consent, safety, protocol deviation/violation, and monitoring based on visits. Some of the information, for example, protocol deviation is detected during monitoring visit by clinical trial monitor. As RBM is likely to reduce on-site visits, the EC would be concerned about missing important issues in conduct of clinical trial-protocol compliance.

The sponsors have to create awareness among regulators and ECs about the challenges, opportunities, and benefits of new quality management and RBM approaches.

**Investigator site concerns**

For the investigator site, change from on-site to centralized monitoring will bring major adjustments. During on-site monitoring, the clinical trial monitor spends time on reviewing informed consent form (ICF), IP accountability, adverse events (AEs) and serious AEs, source document verification, and site file review. As the frequency of on-site visits would be reduced, the site will have to provide some of these documents by e-mailing or faxing the records. Site staff will also have to gather data on items that were previously reviewed by an on-site visit, for example, IP accountability, ICF, and send it to the clinical trial monitor for central remote review or upload on an internet portal. There is also likely to be additional site burden of frequent telephone calls, photocopying, encrypting e-mail correspondence, document scanning, and/or e-mailing documents to the monitor. Of course, these processes will raise issues of maintaining privacy and confidentiality. There are also concerns that RBM will have negative impact on relationship between site and sponsor and quality of trial data and will have significant increase site costs.

The investigator site will also require an archival area which meets the addendum requirements for essential documents.

The sponsors should proactively educate investigator sites about RBM and provide necessary resources – technology, personnel, budget, and support in training of site teams to manage the change.

**Sponsor challenges**

ICH addendum brings new challenges for pharma company sponsors. Adoption and implementation of ICH E6(R2) guideline will require major changes in all areas – quality systems, SOPs, technology, team, training – and at all levels – organization, investigator, sites, CROs, and vendors.

Centralized monitoring is a new approach that has been implemented for a maximum of 2 years. Effective centralized monitoring requires competent team with appropriate skills, well-defined SOPs, and electronic technologies that facilitate the translation of data into information. Implementation of RBM will require investments in validated electronic systems, for example, electronic data capture, electronic solutions for remote data access, for example, cloud-based storage, secure websites, fax machines, web portals, direct access to site files, and electronic health records. QMS and RBM approach require participation of all functions, with special cross-functional responsibilities for data management, statistics, clinical trial monitor, and medical and safety monitor. The sponsor teams will require training in novel concepts, for example, risk assessment and management, setting quality tolerance limits, validation of electronic systems, and analytical approach to monitoring.

Adoption and implementation of ICH E6(R2) will require an attitudinal shift for the pharma company sponsors.

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**Conflicts of interest**

There are no conflicts of interest.
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