King's Health Partners Clinical Trials Office

A Partnership for Clinical Research

ICH GCP Update: Summary of Guideline for GCP E6(R2)

What is ICH?

In October 2015, 25 years after their formation, ICH reorganised as the International ***Council*** for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH is now comprised of Regulatory and Industry bodies from **Europe, America, Japan, Canada** and **Switzerland** and is now a legal entity (under Swiss law).

Many other international bodies currently cooperate and collaborate informally with the ICH. For the future they have announced that "More involvement from regulators around the world is welcomed and expected, as they will be invited to join… as ICH regulatory members."

ICH aim to become "the leading platform for global pharmaceutical regulatory harmonisation".

ICH harmonisation for better health

What is ICH GCP E6 (R2)?

ICH Guideline E6 - was finalised… in May 1996. This Good Clinical Practice document described the responsibilities and expectations of all participants in the conduct of clinical trials, including Investigators, Monitors, Sponsors and IRBs.

Since 1996, clinical trials have evolved substantially due to increases in globalisation, study complexity, and technological capabilities. As a result, the ICH Assembly has adopted an **amendment (ICH E6 - R2)** to ensure the guidelines keep pace with the scale and complexity of trials and ensure appropriate use of technology.

ICH E6(R2) has been developed 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 reliability of trial results.

Selected extracts from www.ich.org

When is E6 (R2) effective?

Implementation will be through an integrated addendum to E6(R1) showing the R2 changes alongside the original text of R1, and in the European Union, this will be adopted on **14 June 2017**.

Investigator: Delegation of Duties

The Investigator is responsible for supervising any individual or party to whom he/she delegates trial-related duties and functions conducted at the trial site.

If the Investigator/Institution delegates trial-related duties and/or functions to any individual or party, they should ensure that they are suitably qualified to perform them. The Investigator/Institution should also ensure the integrity of those trial-related duties and/or functions and any data generated.

- **Ensure that qualifications on CVs support delegated activities**
- **Ensure maintenance of detailed, accurate and up to date delegation logs listing all staff with delegated trial related activities**
- **Demonstrate effective CI/PI oversight to ensure integrity of trial-related duties and data generated**

Investigator: Source Data

The Investigator/Institution should maintain adequate, accurate and accessible source documents and trial records that include all pertinent observations on each of the site's trial subjects.

- **Ensure that source data is Attributable, Legible, Contemporaneous, Original, Accurate & Complete (ALCOAC)**
- **Changes to source data should be traceable, should not obscure original and should be explained if necessary**

Essential Documentation

The Sponsor and Investigator/Institution should maintain a record of the location(s) of their respective essential documents including source documents.

The Investigator/Institution should have control of all essential documents and records they generate before, during, and after the trial.

The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search & retrieval.

GCP standards should be applied to all records, irrespective of the type of media used.

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Essential Documentation - Continued

The Investigator should have control of and continuous access to the CRF data.

When a copy is used to replace an original document (e.g. source documents or CRF), the copy should fulfil the requirements for **certified copies**.

Certified copies must be verified (e.g. by a dated signature or by generation through a validated process) to have the same information - including data that describe the context, content & structure - as the original.

Documentation Flexibility?

R2 also promotes emphasise on the management of the critical aspects of trials. For example, the updated guidelines state: *Essential documents for the trial should be **supplemented or may be reduced** based on the importance and relevance of the specific documents to the trial.*

Any reduction or supplementation of documentation must be justified and approved.

Sponsor: Quality Management

The Sponsor should implement a system to manage quality throughout all stages of the trial process using a **risk-based approach**.

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.

Quality assurance systems should focus on those aspects of the trial that are essential to **ensure human subject protection and reliability of trial results.**

Sponsor: Computerised Systems

Validation of computer systems should be based on a **risk assessment** taking into consideration the intended use of the system and potential to affect human subject protection and reliability of trial results.

SOPs should be in place to cover set up, installation and use of all computerised systems. Responsibilities should be clear and training provided to users.

Ensure the integrity of the data including those that describe the **context, content** and **structure.** This is particularly important when performing **software upgrades** and **migrating data.**

Sponsor: Noncompliance

If **human subject protection** or the **reliability of the trial results** are or could be significantly affected by any noncompliance with the protocol, GCP or other regulatory requirements the Sponsor should perform a root cause analysis and implement a **Corrective and Preventive Action plan (CAPA)**.

Sponsor: Monitoring

Sponsors should create a **Monitoring Plan** tailored to each specific trial and based on the possible risks. The rationale for each monitoring strategy must be documented. The plan should focus on critical data & processes.

The Sponsor may choose **on-site monitoring**, performed at the sites where the trial is being conducted, or **centralised monitoring** which is a remote evaluation of accumulating data.

Monitoring, whether on-site or centralised should be performed and reported to the Sponsor in a timely manner.

Sponsor: Oversight of CROs

Any subcontracting of trial-related duties or functions by a contracted CRO (or another vendor) must be documented and a process for oversight put in place.

Further Information

More information on the ICH E6 R2 can be found at www.ich.org including the full integrated guidelines.