ICH
harmonisation for better health

Module 5.1 Transcript

Interpretation and Application of ICH E6(R3):

GOOD CLINICAL PRACTICE (GCP)

Welcome to the Interpretation and Application of ICH E6(R3): Good Clinical Practice.

For instructions on how to navigate the system, please select the type of device you are using to view this module.

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Module 5 of this training discusses essential records in clinical trials.

Module 5 contains 2 submodules, which should be taken sequentially. We'll begin with Module 5.1, Essentiality of trial records.

Key questions you will be able to answer after completing this module include:

- What is an essential record?
- How do you determine if a record is essential?
- And, how should essential records be managed and retained?

Module 5.1 will focus on the first two questions.

An overarching statement about essential records is included in Principle 9 of the guideline, and the definition of an essential record is provided in the glossary.

Detailed information on essential records for the conduct of a clinical trial can be found in Appendix C of the ICH E6(R3) guideline. Appendix C should be read together with Section 2.12, Investigator Records, and Section 3.16, Sponsor Data and Records, which define the investigator and sponsor responsibilities for maintaining and retaining records.

Together, these sections provide a clear and comprehensive framework for understanding what records are considered essential, who is responsible for them, and how they should be managed across the clinical trial lifecycle.

As we reviewed in Module 1.2, Principle 9 states that clinical trials should generate reliable results. In this module, we'll continue the discussion of Principle 9, including the subparts that highlight the following.

The quality and amount of the information generated in a clinical trial should be fit for purpose. Trials should incorporate efficient and robust processes for managing records to help ensure record integrity and traceability. And essential records should be retained securely by sponsors and investigators for the required period in accordance with applicable regulatory requirements. Records should be available upon request to enable appropriate evaluation of the trial conduct.

“Records” refers to data, information and documents associated with a trial. They may exist in different media, for example, paper or electronic records.

The E6(R3) guideline defines essential records as documents, data, and relevant metadata, in any format, associated with a clinical trial that facilitate the ongoing

management of the trial and collectively allow the evaluation of the methods used, the factors affecting the trial, and the actions taken during trial conduct to determine the reliability of the trial results produced and the verification that the trial was conducted in accordance with GCP and applicable regulatory requirements.

The E6(R3) guideline uses the term “essential record” rather than “essential document” because it better reflects system-generated and dynamic forms of evidence, such as data and relevant metadata, that do not function as discrete authored documents.

Essential records can be generated at different points throughout the clinical trial life cycle.

Before the trial begins, examples of records generated include the trial protocol, informed consent materials, record of IRB approval of the trial, and system and validation records for an electronic case report form.

During the trial, examples of records generated include trial data collected and source data such as laboratory results and the investigator's assessment of a trial participant's adverse event and records of quality assurance and quality control such as monitoring reports.

And finally, at the end of the trial, records typically include the analysis output generated from the trial's statistical software programmes and the Clinical Trial Report.

The responsible party, the investigator or sponsor, should ensure the retention of the records that are essential and associated with their scope of responsibilities. Retaining a record means to keep and store the record as part of the trial's required documentation.

The retained records serve as proof that the trial was conducted according to the protocol and GCP, and had adequate oversight.

The E6(R3) revision encourages a more thoughtful, risk-proportionate approach to the handling of essential records. Rather than keeping every record generated regardless of its importance, or relying on a rigid checklist, E6(R3) encourages the sponsor and the investigator to carefully determine which records are important to enable evaluation of the conduct of the trial and actively support the assessment of data integrity and decision making.

Why is it important to determine which trial records are essential and should be retained? Why not retain every record?

A modern clinical trial could generate a large volume of individual records.

Trying to retain them all could quickly become overwhelming!

Retaining every single record associated with a clinical trial does not reflect a risk-based approach and, in some cases, results in effort disproportionate to the importance of the records.

Simply put, not all records are essential to demonstrate the integrity of a trial.

Similarly, not all records are essential to allow an evaluation of the conduct of a trial.

Given how many records can be generated in a clinical trial, determining what is essential allows the sponsor and investigator to focus on those records that demonstrate appropriate conduct of the trial, participant protection, and reliability of trial results.

A proportionate approach should be applied to the management of essential records.

This approach may assist investigators and sponsors in avoiding unnecessary burden while maintaining focus on the essential records.

Sponsors and investigators should assess which records are essential based on the guidance provided in Section C.3, Essentiality of Trial Records. Doing so ensures that unnecessary records aren't kept.

When the trial is designed using a proportionate risk-based approach, it naturally results in a proportionate set of essential records.

The nature and extent of essential records generated and maintained are dependent on, for example, the trial design, assessments performed, systems used, service providers engaged, types of safety reports generated, and decisions taken.

Section C.3 of the Appendix C provides criteria to assist in the assessment of whether a record is essential.

Considering whether certain records are relevant to demonstrate the appropriate conduct of the trial will help to determine whether those records are essential.

Trials designed and conducted using a Quality by Design approach, which focuses on what matters most to ensure the protection of participants and the reliability of the data, and avoiding unnecessary complexity and data collection, will generate a proportionate set of trial records.

This approach supports efficient trial management and ensures that the documentation accurately reflects the methods used, factors affecting the trial, and actions taken during its conduct.

Simply put, proportionate trial design and conduct lead to the generation of a proportionate set of essential records.

To assist in determining whether a record is essential, Appendix C of E6(R3) includes a table of records which, if produced, would be considered essential when the guidance in section C.3.1 is applied.

While this table is useful, it should not be used as a rigid checklist because records generated depends on the trial design, its conduct, application of risk proportionate approaches, and the importance and relevance of that record to the trial. The table does not necessarily represent an exhaustive list of essential records.

The table also uses an asterisk to identify some documents which should generally be in place prior to the trial's start.

A clinical trial may generate records not listed in the table that are nonetheless essential to the evaluation of trial conduct.

For example, if a trial includes a help desk to support participants with IT issues, documentation of the issues raised and how they were resolved would be an essential record as it could help identify systemic issues that may affect data reliability.

Alternatively, some records listed in the table may not be generated for a given trial, depending on its design and conduct.

For example, if a sponsor or investigator does not engage service providers, records related to the selection and oversight of service providers would not exist and would not be expected.

It is important to note that the assessment of whether a record is essential and has to be retained should take into account the criteria outlined in section C.3, Essentiality of Trial Records.

Such assessment, while important, is not required to be documented.

Sponsors and investigators may use a structured content list, such as a Trial Master File reference model to structure and manage their trial records. In some cases, these models are used to prospectively identify which records are essential.

Essential records may be generated by the investigator and the sponsor and by persons or parties to whom activities have been delegated by the investigator or transferred by the sponsor.

The investigator and delegated investigator site staff may generate essential records in a clinical trial.

For example, these records may include documentation confirming a participant's eligibility to enrol in the trial, records of any adverse events experienced by participants and clinical assessments performed, and investigator delegation of specific trial tasks to investigator site staff.

The investigator may record this information in appropriate sponsor systems such as electronic case report forms.

The sponsor may generate a variety of essential records before the trial begins that describe the design, conduct, and management of the trial, including, but not limited to, the protocol and the investigator's brochure.

During the trial, sponsors continue to produce essential records, for example, monitoring reports and safety reports that represent oversight of the trial conduct.

Sponsors should also maintain and retain records received from regulatory authorities as these documents are considered essential and provide evidence of regulatory decisions.

The Institutional Review Board or Independent Ethics Committee, IRB or IEC, generates records of their review of the clinical trial that are provided to the sponsor or investigator.

These essential records may include correspondence with the sponsor or investigator that reflects the review, required modifications, and approvals associated with the clinical trial.

IRB or IEC correspondence also includes materials submitted to the IRB or IEC as well as any responses from the investigator or sponsor. These records demonstrate the IRB or IEC's oversight of the trial.

Service providers, a person or an organisation providing a service used by either the sponsor or the investigator to fulfil trial-related activities, will also generate essential records. For example, a service provider may provide central laboratory services and perform the processing, testing and analysis of biological samples drawn from trial participants.

The records documenting their processes for sample handling and analysis and results reporting are essential.

Other common service providers include organisations providing electronic case report forms, or systems that manage participant randomisation and drug supply, commonly known as interactive response technology.

These service providers will generate essential records, for example, computer system validation records and help desk records.

Essential records may be generated and used by anyone conducting, overseeing or evaluating a clinical trial. This includes investigators, sponsors, monitors, auditors, and service providers, as well as regulatory authorities during inspections. Certain essential records may also be reviewed by the IRB or IEC.

Let's practise determining whether a record is essential. In this exercise, we will compare records from 2 trials.

Trial A is a randomised, double-blind, placebo-controlled trial on the efficacy and safety of an intravenous immunoglobulin product (IVIG) versus placebo in patients with dermatomyositis. Participants will have an infusion every 4 weeks for 16 weeks. The primary efficacy endpoint is the total improvement score of at least 20 at week 16.

Let's consider an example of some records generated in the trial that the sponsor should consider essential.

In the case of Trial A, the trial is double-blind, meaning that neither the investigator nor the participant knows which treatment is being administered. Maintaining the blinding is critical to trial integrity, but there must also be a mechanism to protect participant safety in emergencies.

Therefore, procedures for emergency unblinding should be clearly defined, documented and available to the investigator. These procedures ensure that treatment allocation can be revealed quickly when medically necessary, while avoiding unnecessary unblinding.

Because they are essential for both participants safety and the reliability of the trial results, records related to such unblinding procedures are essential records in trial A.

Now compare that to Trial B, a single-arm open-label trial evaluating the efficacy and safety of a subcutaneous immunoglobulin (scIG) for maintenance treatment in chronic inflammatory demyelinating polyneuropathy. Participants receive subcutaneous immunoglobulin weekly for 24 weeks. The primary efficacy endpoint is the percentage of participants who relapse during the subcutaneous treatment period.

In Trial B, the trial is open-label, meaning parties, including the investigator and participant, know which treatment is being administered.

As a result, there is no need to develop or maintain emergency unblinding procedures since treatment allocation is already known at all times. Because these records are not generated in the trial, they are therefore not an essential record in this trial.

Instead, because participants are self-administering treatment at home, records documenting participant training on self-administration become critical. These records demonstrate that participants have been properly trained to safely and correctly administer the treatment.

As this directly impacts participant safety and data reliability, training records for self-administration would be considered essential records in Trial B.

In this interactive activity, you will sort 4 records based on the trials for which they would be considered essential.

You may hover over each trial to review the details. Then drag the record to the trial or trials for which it is considered essential.

Click next to begin the activity.

Thank you for completing Module 5.1.

Module 5.2 will describe how essential records should be managed and retained.