ICH
harmonisation for better health

Module 5.2 Transcript

Interpretation and Application of ICH E6(R3):

GOOD CLINICAL PRACTICE (GCP)

Welcome back to Module 5, Essential Records.

In Module 5.1, we answered:

- What is an essential record?
- And how do you determine if a record is essential?

Now, in Module 5.2, we will answer:

- How should essential records be managed and retained?

As noted in Module 5.1, essential records may be produced prior to, during, or at the end of a trial.

These records may be used by sponsors, investigators, IRB or IECs, and regulatory authorities for oversight, monitoring, and evaluation of compliance with GCP and applicable regulatory requirements. They support a range of activities throughout the trial life cycle, including site selection, monitoring visits, statistical analysis, audits, and inspections.

Where an investigator is referenced in this module, we are describing expectations that may be applicable to the investigator and/or the institution in some regions. Because expectations may differ across regions, applicable regulatory requirements should also be consulted.

The sponsor and investigator should ensure that essential records are collected and filed in a timely manner.

Investigators should be able to access, maintain, and retain control of their essential records in accordance with applicable regulatory requirements.

In particular, investigators and institutions specifically should maintain control of essential records they generate.

Maintaining appropriate control is critical not only for protecting personal information that may identify a trial participant, but also for maintaining the integrity of trial data. This includes ensuring that records are protected against unauthorised manipulation, alteration, or undetected changes.

Particular attention should be given to source records to ensure they remain attributable, legible, contemporaneous, original, accurate, and complete throughout the trial life cycle.

According to Appendix C, both the sponsor and investigator should retain the essential records in a way that ensures that they remain complete, readable, readily available, and directly accessible upon request by regulatory authorities, monitors, and auditors.

Essential records should be clearly identifiable and when appropriate, version controlled. This includes documenting relevant metadata, such as authors, reviewers, approvers, dates, and any required signatures.

Since essential records can take many forms, the following examples illustrate how version control and traceability are applied in practise.

For example, let's consider the informed consent materials.

The site informed consent materials for a trial should identify the version number and the version date. In addition, documentation of IRB or IEC approval, including the approval date, should be retained to demonstrate that the correct version of the informed consent materials were used.

In another example, let's use a protocol.

The protocol should have clear and well-defined version control. Each version should be uniquely identified by a version number and date, and changes should be documented through numbered amendments as applicable. This allows verification of which protocol version was in effect at any point during the trial.

Finally, in our third example, we'll use an Electronic Case Report Form (eCRF).

When trials use an eCRF, records should identify the eCRF version number and approval or release date. For details on relevant metadata, see Module 3: Data Governance.

During a trial, records often need to be made available to multiple parties. For example, when investigators identify a serious adverse event, they report it to the sponsor. If the sponsor determines it is a Suspected Unexpected Serious Adverse Reaction (SUSAR), the SUSAR report should be shared with investigators, the IRB or IEC, and regulatory authorities, so that participants' safety can be continuously monitored.

Investigators rely on this information to assess risk to their participants, while sponsors use it for ongoing safety evaluation and reporting obligations.

To support shared access, the sponsor may provide essential records to other parties, for example, by providing copies or access to them through a sponsor's portal.

Providing access does not change retention responsibilities.

Original records should generally be retained by the responsible party who generated them. However, copies should be retained by the parties that use them as well.

When a sponsor's portal is used to provide copies of sponsor generated records to investigators for their use, the records would need to be downloaded and retained at

the end of the trial to allow evaluation at the investigator site, unless investigator access to the portal is maintained throughout the record retention period.

When a copy is used to permanently replace the original essential record, it should be a certified copy.

The E6(R3) guideline defines “certified copy” as a copy, irrespective of the type of media used, of the original record that has been verified by a dated signature or by generation through a validated process to have the same information as the original, including relevant metadata where applicable.

Some essential records may be relevant to more than one trial. Such records may be stored in repositories that are not trial-specific.

For example, this could include:

- The investigator’s brochure, where numerous trials are taking place with the same investigational product.
- Investigator site staff GCP training records or other training records where staff are working on more than one trial but have training that covers these trials.
- Standard Operating Procedures (SOPs) where the SOPs apply to more than one trial.
- Records of the validation of the software used for an electronic case report form, independent of any trial-specific builds.
- Or master service agreements with service providers that span a drug development programme.

Essential records should be maintained in repositories, either electronic or paper-based, that are held by the sponsor and investigator.

These repositories may be referred to as a trial master file. The repository held by the investigator may also be referred to as the investigator site file.

Although a Principal Repository typically contains authored and versioned documents, other essential records may be retained in separate repositories and still be part of the Trial Master File. During trial design, prior to trial start, the responsible parties should identify these repositories and describe how they communicate with or cross-reference each other.

Examples of essential records that might be stored in repositories other than the principal repository include:

- Datasets and statistical analysis programs stored in a statistics system, while the corresponding statistical analysis plan is in the principal repository.
- Safety database records documenting adverse events, workflows, including records of case handling and serious adverse event assessments.

- Computerised systems managing investigational products, treatment assignment, or participant randomisation.
- And systems containing evidence of computer system validation.

All repositories should be managed appropriately for the entire length of the required retention period for all essential records contained in the repository.

The sponsor and investigator should maintain a record of where essential records, including source records, are located. This should also include the locations of all the different repositories.

This is of particular importance where service providers are involved in a trial. Service providers may generate both trial-specific and non-trial-specific essential records.

Not all records are routinely provided to the sponsor or investigator, as some are maintained solely within the service provider's record maintenance and retention system.

There should be arrangements in place to show what records the service provider holds during and after the trial for the required retention period.

For example, for computerised systems service providers, the software validation records are not always trial-specific, but are essential records. Sponsors may access these through copies, on-site review, or a portal, with agreements in place to maintain access during the required retention period.

Access to essential records necessary to perform trial-related tasks should also be provided to service providers carrying out roles and activities transferred by the sponsor or delegated by the investigator as applicable.

For example, service providers developing trial-specific computerised systems may require access to the trial protocol to support system design.

Service providers who handle and support the review of serious adverse reactions may require access to reference safety information to assess the expectedness of such reactions.

Let's look at an example. A service provider may be contracted by the sponsor to develop a trial-specific eCRF. To develop appropriate specifications that accurately reflect the trial procedures, randomisation, and reporting process, the sponsor should provide the service provider access to the protocol.

Prior to a trial, careful consideration should be given to determine which essential records may contain potentially unblinding information and which records may be subject to applicable data protection legislation.

During a trial, this same consideration should be given to the sharing of records, where blinding must be maintained.

For example, a randomisation schedule is a record that contains unblinding information about the trial. Only designated sponsor staff who are unblinded should have access to this document.

Such records should be handled in a way that avoids disclosure to inappropriate individuals.

Sponsors should carefully consider how and where to store unblinded records. Appropriate access controls should be in place, and the sponsor should be able to restrict access to specific areas of a repository when required.

At the end of the trial, the sponsor and investigator should retain their essential records.

The investigator should retain essential records for the required retention period in accordance with applicable regulatory requirements or until the sponsor informs them that they are no longer needed, whichever is longest.

During the retention period, the investigator is responsible for essential record maintenance.

However, sometimes the situation may change.

For example, the sponsor should be informed if essential records are being moved to a different physical location, or if the investigator who conducted the trial leaves the investigator site and a new person is deemed responsible.

Let's put this all into practice using a multi-site trial.

This case is about essential records generated for a Suspected Unexpected Serious Adverse Reaction, also called a SUSAR, an event which the sponsor is required to report to the regulatory authorities. The SUSAR reports are considered essential records.

An investigator reports a Serious Adverse Event, SAE, to the sponsor, according to the protocol, using the electronic case report form. The investigator also provides the sponsor with information about whether the event is considered to be related to the investigational product.

The sponsor assesses the event and may request additional information about the event, sourced from the medical record.

If a causal relationship with the investigational product has been reported by the investigator or the sponsor, this event becomes an adverse drug reaction.

The sponsor then determines whether the reaction meets the criteria for a SUSAR, whether it is unexpected per the investigator's brochure. All documentation related to a SUSAR should be maintained to ensure integrity, traceability, and accessibility.

If the sponsor determines that the SAE qualifies as a SUSAR, then the sponsor reports the SUSAR to the regulatory authorities and other investigators participating in the trial in accordance with applicable regulatory requirements.

In this example, once the sponsor determines that the event is a SUSAR, the investigator also reports the SUSAR to the IRB or IEC.

All steps in this process (initial SAE report, sponsor queries, SUSAR determination, reporting to regulatory authorities, and the IRB or IEC and participating investigator review) should be documented and retained as essential records.

Some of these essential records may be retained in databases such as pharmacovigilance or safety databases as part of routine workflow activities.

The reporting investigator should retain the source records, including those related to the reported SAE at their institution, and ensure that no participant-identifying health information is inappropriately shared with unauthorised individuals.

The investigator should have access to all data and relevant metadata, including audit trails contained within the ECRFs, throughout the trial, and for the required retention period to support monitoring, verification, and regulatory inspection.

Also, the investigators' access to any communication portals, where applicable, should be maintained until the end of the trial.

At trial completion, the sponsor should ensure the investigators have been provided with the essential records from the communication portal, including the associated audit trail, documenting, for example, the investigators' review and management of essential safety information throughout the trial.

These records are also essential records and should be retained to ensure their continued availability, accessibility, and integrity for inspection or verification.

That brings us to the end of Module 5 on essential records. In this module, you learned:

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

Thank you for completing this module.

The MRCT Center of Brigham and Women's Hospital and Harvard is an ICH training associate. The MRCT Center designed and developed this training module in collaboration with ICH.