



Module 3.3a Transcript

Interpretation and Application of ICH E6(R3):
GOOD CLINICAL PRACTICE (GCP)

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

Module 3 of this training discusses Data Governance in clinical trials.

Module 3 contains 4 sub-modules, which should be taken sequentially. This is Module 3.3: Risk-Proportionate Approach to Management of Computerised Systems. This module is split into two parts: Module 3.3a and 3.3b.

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

- How should a risk-proportionate approach be applied to managing computerised systems in a clinical trial? And,
- What are the responsibilities of sponsors and investigators for managing computerised systems?

Both the sponsor and the investigator have responsibilities for managing computerised systems (including data acquisition tools or DATs) used in a clinical trial. These responsibilities will vary depending on who deploys the system for use in the trial and whether the system was designed specifically for clinical trial purposes or designed for other purposes and used in a clinical trial.

Requirements and responsibilities are described in dedicated sub-sections of the guideline within the investigator (2.12.10) and sponsor (3.16.1(x)) responsibilities sections that specifically address the management of computerised systems. General requirements for the management of computerised systems can also be found in section 4.3.

Responsibilities related to management of the data lifecycle are further elaborated in Module 3.4.

This sub-module focuses on the requirements that apply specifically to computerised systems. It also illustrates how these requirements can be applied in practice using the Crohn's Disease case example.

All computerised systems used in a clinical trial should be fit for purpose. This means that the system should be designed, implemented, operated and managed in a way that ensures the protection of participants and the quality and integrity of clinical trial data and records.

The fit for purpose assessment is a risk assessment that begins with understanding:

- The functionality of the system and how the system will be used in the trial
- How it links with other systems
- The criticality of the data and processes it supports, and
- The potential impact of system failures or misuse on participant protection, data integrity, and reliability of trial results.

The fit for purpose assessment should guide how proportionality is applied by defining the level and extent of procedures, safeguards, oversight, and attention given to key processes, such as validation, and key functionalities, such as audit trails and access controls.

Systems supporting data or processes of higher criticality may require proportionally more comprehensive procedures, stronger safeguards, and greater focus on key functionality, while lower criticality systems can be managed with appropriately simplified measures.

The fit for purpose assessment is not a single assessment made before system deployment; it is the conclusion reached by evaluating evidence generated across the entire computerised system lifecycle.

Proportionate processes should be in place throughout the computerised system lifecycle to manage systems and ensure they remain fit for purpose and are used appropriately.

The system lifecycle begins with system specification...

... followed by design.

Representatives of intended participant populations and healthcare professionals should be involved in the design of the system, where relevant, to ensure that computerised systems are suitable for use by the intended user population.

Next, the system is developed according to the specification.

System validation should then demonstrate that the system conforms to the established requirements for completeness, accuracy and reliability and that its performance is consistent with its intended purpose.

Systems should be appropriately validated prior to use. Deployment and implementation should be controlled and verified.

And the system operation and maintenance period starts and continues until...

... eventually the system is decommissioned.

After system deployment, fitness for purpose is ensured through risk-proportionate controlled operation, training, oversight, and change management throughout the system lifecycle. This is particularly important in trials where systems may be used over long periods and across multiple protocol amendments.

Let's now look at some examples of computerised systems used in clinical trials and the respective roles and responsibilities of the sponsor and the investigator - as well as the involvement of service providers - in managing computerised systems.

This matrix shows examples of computerised systems categorised by whether they are deployed by the sponsor or by the investigator and/or institution and whether they were originally designed for clinical trial or other purposes.

Please note that each quadrant of the matrix may include both custom-built and commercially available off-the shelf systems.

Some systems are designed to support configuration while others are not. In some cases, systems may also be altered through custom coding. In this module, we will explore the risk-proportionate management of these different types of systems, including the management of risks related to individual systems in greater detail.

Click each quadrant to see some examples of different computerised systems in each category, starting with the top left.

Systems deployed by the sponsor and designed for clinical trial purposes may include bespoke (custom-built) as well as configurable systems, such as electronic case report forms (eCRFs), electronic clinical outcome assessments (eCOAs), and interactive response technology (IRT) systems.

Click on the green quadrant to advance.

Systems deployed by the sponsor that are used for clinical trials but were designed for other purposes may include systems such as standard wearables, sensors, electronic questionnaires, and safety databases originally developed for post-marketing pharmacovigilance.

Click on the green quadrant to advance.

Next, let's look at some examples of systems designed for clinical trial purposes that are deployed by the investigator and/or institution. This category may include the electronic investigator site file and an artificial intelligence algorithm used to pre-screen patients or to determine selected imaging eligibility criteria.

Click on the green quadrant to advance.

The final category is systems deployed by the investigator and/or institution that are used for clinical trials but were designed for other purposes. This may include electronic medical records and imaging systems.

Now, let's apply the E6(R3) guideline thinking using examples from the Crohn's Disease case. In this context, we can clearly see how different systems come into play.

Click on the eCOA system to continue.

We'll start with the eCOA system, an example of a system designed for clinical trial purposes and deployed by the sponsor. This system is also considered a data acquisition tool.

In the Crohn's Disease case, participants use the eCOA system, specifically the eDiary component, to report their symptoms. Investigator site staff also use the eCOA system to extract patient-reported outcome data to transcribe into the eCRFs.

In Module 3.2, this system was identified as a system that is critical to quality in the Crohn's Disease trial because it is the source of the co-primary efficacy endpoint data.

Because errors in the design, implementation, validation, management, or use of the eCOA system could directly affect the quality of co-primary efficacy endpoint data, the sponsor should apply more intensive management and oversight of the system and quality control to the relevant stages of data handling.

This enhanced approach supports the early identification of potential issues related to the collection, handling and management of these data. For example, it can help in the early identification of system problems, such as programming errors or technical problems, highlight systemic issues that might call for additional training of participants or investigator site staff, and detect data trends such as missing information or unusual patterns that could affect the reliability of the trial results.

Inbuilt functionality can help reduce missing data and help define problems in data entry early, e.g. by having alarms reminding participants to fill in data or by alerting investigator site staff if data has not been entered for a while.

In this example, the sponsor is responsible for ensuring that this data acquisition tool is built in accordance with the trial protocol and available prior to its required use in the trial.

The sponsor should also:

- Have a record of this important computerised system that includes a description of its use, functionality, interfaces, validation status, implemented access controls, internal and external security measures, and who is responsible for its management.
- Ensure that the requirements for computerised systems in section 4 of the guideline are proportionately addressed and implemented and that documented procedures and adequate training are in place to ensure the correct development, maintenance and use of computerised systems in clinical trials.

In Module 3.3b, we will discuss specific requirements, such as audit trails, validation, security controls, user management, backup, and disaster recovery.

The sponsor should maintain a record of the individual users who are authorised to access the system, their roles and their access permissions and ensure that access permissions granted to investigator site staff are in accordance with delegations by the investigator and visible to the investigator.

Finally, the sponsor should ensure processes are in place for service providers and investigators to inform the sponsor of system defects.

The investigator also has responsibilities related to the eCOA system deployed by the sponsor. Because the data maintained in the eCOA system are critical to the trial's quality, the investigator should place more intensive oversight on the data entered and stored in the system as well as how the participants and investigator site staff use the system.

The investigator should ensure that both participants and investigator site staff use the eCOA system as specified in the protocol or trial-related instructions.

In this trial, this includes ensuring adequate training so participants can access, use, and accurately complete eDiaries, particularly for correct recording of daily stool frequency, abdominal pain, and well-being ratings.

It also includes ensuring that investigator site staff receive the necessary training needed to be able to access, use, and navigate the eCOA system and devices and assist participants with access, data entry, or technical issues.

The investigator should ensure that traceability of the eDiary devices to the correct participants is maintained.

In addition, the investigator should notify the sponsor when access permissions need to be changed or revoked from an individual.

Next, we'll look at the sponsor safety database, an example of a system deployed by the sponsor that was originally designed for other purposes but is also used in clinical trials.

These are pharmacovigilance systems designed to manage adverse event data across a sponsor's entire product portfolio for post-market surveillance activities. Their use in clinical trials, where they are also used to capture and manage trial-related safety data, is an extension of their primary purpose.

Click on the safety database to continue.

This system is used by the sponsor to manage safety-related information about a product, including all serious adverse events.

The system is considered critical to quality because it supports the sponsor's assessment of a product's safety profile and supports regulatory reporting of suspected unexpected serious adverse reactions, or SUSARs.

The investigator does not have responsibility for tasks in this system.

The sponsor has the same responsibilities for this system as for the eCOA but without the added complexity of supporting participants, investigators or investigator site staff as the end users are sponsor staff or service provider staff.

As the safety database is used across products and clinical research programmes, the sponsor's approach to system-level controls, such as validation, security, and user management can be on a system level rather than on a trial level.

The electronic Investigator Site File is a common example of a system deployed by the investigator and/or institution, designed for clinical trial purposes.

Click on the electronic Investigator Site File to continue.

In the Crohn's Disease case, the electronic Investigator Site File, which is maintained by the investigator, stores the essential records for the trial and serves as a centralised resource to support day-to-day trial management, including investigator oversight and regulatory compliance.

Because the investigator and/or institution is deploying this system, the investigator should ensure the Investigator Site File system is fit for its intended use in the trial and that the requirements for computerised systems in section 4 are proportionately met.

This risk-proportionate approach should consider factors such as whether the system being used is a commercial, off-the-shelf electronic Investigator Site File or whether the investigator or institution develops a custom system themselves.

In addition, the investigator should ensure that appropriate individuals have secure and attributable access to the Investigator Site File and that data are protected from unauthorised access, disclosure, dissemination, alteration, destruction or loss.

In this case, the sponsor should also assess whether the Investigator Site File is fit for purpose for use in the specific trial and whether any risks can be appropriately mitigated.

Finally, examples of systems deployed by the investigator and/or institution, used for the trial but developed for other purposes include the endoscopy imaging system or the institution's electronic medical record. These systems are primarily used in usual clinical practice.

Click on the final box to continue.

In this case example, both systems contain important source records for the trial. The endoscopy imaging system is used to support the co-primary efficacy endpoint, and the electronic medical record is used to document that visits occurred and allows for information about the participant's treatment to be shared with other healthcare professionals.

For these systems, the investigator should ensure that appropriate individuals have secure and attributable access.

As both systems contain source records for the trial, the sponsor should assess whether the electronic medical record and the endoscopy imaging system are fit for purpose in the context of the trial or whether the risks from a known issue can be appropriately mitigated.

This assessment should occur during the process of selecting clinical trial sites and should be documented.

The assessment should be proportionate to the importance of the data managed in the system, covering factors such as data security, back up, user management and audit trails.

In the Crohn's Disease trial, the two systems have different risks and therefore require different considerations.

The electronic medical record is being used for its intended purpose within usual clinical practice and contains important source records for the trial. The sponsor's assessment should focus on audit trail, IT security and user management.

The endoscopy imaging system, however, plays a different role. In this trial, it supports the co-primary efficacy endpoint by producing images that are subsequently transmitted to central readers for independent assessment. The sponsor should therefore assess whether the equipment and system meet any minimum standards that the sponsor may have to ensure the reliability of their co-primary endpoint data. A fitness for purpose assessment may also include pre-qualification of the system by the sponsor or their service provider.

For example, this may include defining approved imaging equipment and reviewing test images from the site.

For all systems used in a trial, the sponsor should ensure that processes are in place for service providers and investigators to inform the sponsor of incidents that could potentially constitute serious noncompliance with the clinical trial protocol, trial procedures, applicable regulatory requirements, or GCP.

Related to this, the investigator is responsible for ensuring that incidents in the use and operation of computerised systems which may have significant and or persistent impact on the trial data or system security are reported to the sponsor and, where applicable, to the IRB or IEC.

This is especially important for computerised systems handling data supporting the primary endpoint, for example the eCOA system. This means following up promptly on system issues that are reported by participants and investigator site staff, documenting them clearly, and reporting them to the sponsor in a timely manner.

Thank you for completing Module 3.3a. Next, in Module 3.3b, we'll use the Crohn's Disease case example to explore the requirements for computerised systems outlined in section 4.3.