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ANALYSIS OF THE EMA GUIDANCE 'GUIDELINE ON COMPUTERISED SYSTEMS AND ELECTRONIC DATA IN CLINICAL TRIALS'

The Italian Group of Quality Assurance in Research (GIQAR), part of the Italian Society of Pharmaceutical Medicine (SIMeF, *https://simef.it*) has recently established a working group on GCP and computerised systems in clinical trials. We analysed the draft guideline and sent comments, requests for clarification and suggestions on various aspects of the document to EMA. The final guideline was issued in March 2023 and came into effect in September 2023. After analysing the final guideline, we came up with some topics that, unmistakably, will be posing new challenges to sponsors, CROs and, above all, to clinical sites.

We are all aware that clinical trials are increasingly turning digital. Gone are the days when, at the words 'source documents', the image of a bunch of scribbled pages popped-out in our mind. No nostalgia or regrets. Now the data life cycle involves several structured computerised systems of increasing complexity, from local devices to delocalised cloud applications. The COVID-19 pandemic has further accelerated this process and boosted the digitisation of clinical trials, introducing new challenges such as remote monitoring and remote inspections. Still, it is not all rosy. The digital environment could be difficult to understand. With paper, data source was usually easy to locate. With digital, the concept of 'source data' is much more difficult to figure out. Compliance with GCP principles like ALCOAC+ could also be challenging. In March 2023 the FDA released the 'Electronic Systems, Electronic Records and Electronic Signatures in Clinical Investigations – Questions and Answers' draft guidance aimed at providing guidance on the use of electronic systems, electronic records and electronic signatures in clinical trials. In May 2023 ICH released the draft of the much awaited, ICH E6 (R3) with modernisation of several requirements, including those related to electronic systems in clinical trials. With perfect timing, on 9th March 2023 and two years after the release of the draft, EMA released the final 'Guideline on computerised systems and electronic data in clinical trials' (EMA/INS/GCP/112288/2023), in force since 9th September 2023. The document is released by the Good Clinical Practice Inspectors Working Group and it is therefore meant to represent the current EMA inspectors' expectation. This is not out-of-the-blue.

In recent years the European inspectors published several Q&As on topics related to computerised systems, demonstrating the inspectors' high attention to this topic (probably due to common inspection findings). This document intends to replace the old 2010 EMA 'Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials'. Whilst the old reflection paper was only 13 pages long and with a narrow scope, this new guideline is an impressive, highly detailed and demanding 52-page document. As written by the inspectors 'development of and experience with such systems has progressed. A more up to date guideline is needed'. The premise has been truly fulfilled, since the updated document now covers 'currently hot' topics like eCOA (electronic Clinical Outcome Assessment), ePRO (electronic Patient Reported Outcome), eIC (electronic Informed Consent), cloud systems and AI (Artificial Intelligence). The recipients of the guideline ('responsible parties') are sponsors, CROs and investigators, as well as service providers and software vendors.
An important focus is given to migration and transfer of data across different systems and to the requirement for audit trail and audit trail review. After introduction, scope and legal and regulatory background, the guideline summarises the principles and key concepts of computerised systems in clinical trials. A very precise definition of 'electronic source data' is given as 'the first obtainable permanent data from an electronic data generation/capture'. Details on requirements for computerised systems are given.
A complete chapter is dedicated to electronic data (and audit trail) and the challenges of their management during the whole life cycle. Furthermore, six annexes provide detailed requirements on topics including agreements validation, user management, security, specific types of system (like eCOA, IRTs, eICs) and electronic medical records.

An overview of the guideline structure is provided in Figure 1.

We summarised them in the following points:

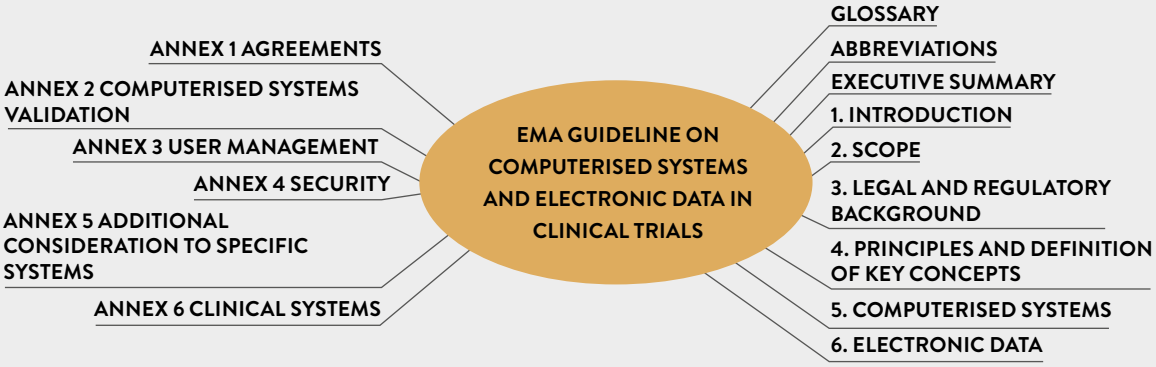
1. NEW COMPUTERISED SYSTEMS IN SCOPE

Systems in scope are those used for the creation or capture of electronical clinical data and for the control of processes potentially affecting study participants protection and reliability of data in the conduct of a clinical trial of an investigational medicinal product.

Compared to the 2010 EMA reflection paper, additional computerised systems used in clinical trials are included in the scope of the guideline, such as:

- Applications for the use by the trial participants on their own device, 'Bring Your Own Device (BYOD)'
- Tools that automatically capture data related to transit and storage temperatures for IMP or clinical samples
- eTMFs
- Electronic Informed Consents
- Interactive Response Technologies (IRT)
- Portals for supplying information from the sponsor to the sites
- Computerised systems implemented by the sponsor holding/managing and/or analysing data relevant to the clinical trial e.g. Clinical Trial Management Systems (CTMS), pharmacovigilance databases, statistical software, document management systems and central monitoring software, systems/tools used to conduct remote activities such as monitoring or auditing
- Artificial Intelligence (AI) used in clinical trials.

FIGURE 1. OUTLINE OF EMA GUIDELINE ON COMPUTERISED SYSTEMS AND ELECTRONIC DATA IN CLINICAL TRIALS



The guidance states in its introduction that the authorities do not require nor expect sponsors and investigators to use computerised systems in clinical trials, however, their implementation would greatly enhance aspects like data completeness, consistency and unambiguity, and would assist information and workflow control.

2. REINFORCING THE CONCEPT OF DATA

The guidance enhances some key concepts that are already well known from other documents. For example, the concepts of data integrity and data governance (i.e. data ownership and responsibility throughout the data life cycle). Lack of data integrity may be equivalent to data loss. It is clarified that data become information, relevant to answer a clinical question, only when viewed in context (i.e. when metadata are associated to data). Metadata could describe the characteristics, structure and relationship of data and the attributability of data to specific persons or systems performing operations on data. A clear description of 'source data' is now provided, as 'the first obtainable permanent data from an electronic data generation/capture system'. At the same time, it is clarified that 'unprocessed data records', an intermediate step prior to data recording (raw data of imaging systems, for example), is not necessarily required to be extracted and retained.

The relevance of ALCOA++ principles is underlined and the peculiar declination of these requirements for electronic data is explained.

3. EXTENT AND RESPONSIBILITIES FOR COMPUTERISED SYSTEM VALIDATION

The guideline clearly requires that the computerised systems used in clinical trials and in scope of the guideline are validated during their entire life cycle. The extent of validation required for each computerised system in scope is not totally clear and specific instructions are not provided. The guideline then clarifies that each responsible party (investigator and sponsor) should ensure validation of their computerised systems. The investigator is ultimately responsible for the validation of the computerised systems implemented by the investigator's institution; however, the sponsor should determine if such systems are fit for purpose during site selection. Whilst sponsors and CROs are generally accustomed to concepts and techniques of validations, and have specific procedures and resources in place, this requirement may be highly challenging for clinical sites.

As a matter of fact, investigators/institutions will need dedicated personnel and/or consultants to validate their systems, to plan periodic reviews and to implement change control processes. Another challenge is that site selections are performed by CRAs who are usually not specifically trained on computer system validation and could face relevant difficulties in their evaluation if not supported by technical experts.

Notably, it is specified that in case of well-established computerised systems which are used as intended in a routine setting for less critical data, the certification by a notified body may suffice as far as this evaluation is performed and justified before the use of the system in the trial.

Finally, the guideline requires that in case of regulatory inspections, the validation documentation for all the systems in scope (including those decommissioned) is made available upon request of the inspectors in a timely manner, irrespective of whether it is provided by the responsible party, a CRO or the vendors of the systems.

4. ELECTRONIC DATA TRANSMISSION AND E-SOURCE DATA IDENTIFICATION

Details of the transmission of electronic data should be described together with a dedicated diagram, including information on their transfer, format, origin and destination, the parties accessing them, timing of the transfer and any actions that might be applied to the data (e.g. validation, reconciliation, verification and review). This also applies when data is captured by an electronic device and is temporarily stored in the device local memory before being uploaded to a central server; this data transfer should be validated and, only once the data are permanently stored in the server, they are considered source data.

Certain source data might be directly recorded into the eCRF and this is true also for electronic tools directly collecting patient data: eCOAs or ePROs, such as electronic diaries, wearables, laboratory equipment, ECGs, etc. Those data should be accompanied by metadata related to the device used (e.g. device version, device identifiers, firmware version, last calibration, data originator, UTC time stamp of events). All electronically captured source data must be precisely identified in the study protocol. The guideline clearly states that any data generated/collected and the process to capture them should be clearly identified in the protocol or in a protocol-related document.

'Also, before revoking the investigator read-only access, they should be able to perform a review of the received certified copy versus the original database to assess its exact correspondence.'

5. CONTROL OF DATA AND MANAGEMENT OF DYNAMIC DATA

The sponsor should never have the exclusive control of data entered in a computerised system. For example, ePRO data must be made available to the investigator in a timely manner, since they are responsible for the oversight of safety and compliance of trial participants' data. The investigator should be able to download a certified copy of the data at any time. Moreover, after a database is decommissioned, the investigator should receive a certified copy of the data entered at the site including metadata (i.e. audit trail) and the provided file should capture all the dynamic aspects of the original file. This means that static formats of dynamic data (e.g. PDF copies containing fixed/frozen data which allow no interaction) will not be considered adequate. Also, before revoking the investigator read-only access, they should be able to perform a review of the received certified copy versus the original database to assess its exact correspondence. However, the guideline remains quite vague on the expectations of this review and on where and how this should be documented.

Finally, the integrity of data must be preserved through its life cycle together with its dynamic features; after decommissioning of the database, the possibility of restoration to a full functional status must be ensured, including dynamic features (e.g. for inspection purposes). The long-term retention of data in a fully functional status appears technically and economically challenging and hardly feasible in consideration of the retention time (up to 25 years) required by the Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use.

6. AUDIT TRAIL AND AUDIT TRAIL REVIEW

As anticipated, the guideline strongly highlights the importance of audit trails. The extension of ALCOAC principles to ALCOAC+, with the addition of the 'traceable' requirement, is simple demonstration of where the focus is, and it explicitly requires that all changes be documented in the metadata.

The guideline provides detailed requirements on the audit trail content; it should include all information on changes in local memory, changes by queries and edit check results, extractions for internal reporting and statistical analysis and access logs. Even the exceptional case, when a system administrator is forced to deactivate the audit trail, should be part of the audit trail itself.

The guideline goes on with the requirements for audit trail review and specifies that 'the entire audit trail should be available as a dynamic data file in order to allow for identification of systematic patterns or concerns in data across trial participants, sites, etc...'. This audit trail analysis should be focused on:

- Missing data
- Data manipulation
- Abnormal data
- Outliers
- Unexpected or inconsistent hours and dates
- Incorrect data processing
- Unauthorised access
- Malfunctions
- Direct data capture not performed as planned.

The arising questions, therefore, are: do we have the resources to deeply review the audit trail to the required extent? Is the end-user appropriately trained and qualified for this type of analysis? Will this be achievable, from a technical point of view, in a user-friendly way?

'Even the exceptional case, when a system administrator is forced to deactivate the audit trail, should be part of the audit trail itself. '

7. TRAINING

The guideline reinforces the staff qualification needs foreseen by ICH E6 (R2), explicitly requiring training on applicable legislations and guidelines for all those involved in developing, building and managing trial specific computerised systems, such as those employed at a contract organisation providing eCRF, IRT, ePRO, trial-specific configuration and management of the system during the clinical trial conduct.

The main concern is whether technical providers are always up-to-date and aware of all the applicable legislations and guidelines. Indeed, such vendors often provide systems for different industrial sectors and are not limited to pharma industry. Therefore, whilst they are technically skilled and should be well aware of Software Development Life Cycle requirements, more specific and documented knowledge on GCP and specific clinical requirements may be needed.

All training on computerised systems must be documented and made available to monitors, auditors and inspectors.

Training should not be limited to the use of these systems but should include security aspects, management of security incidents, social engineering and prevention of phishing.

It is clearly indicated that investigators should receive training on how to navigate the audit trail of their own data in order to be able to review changes, and that such training must be documented.

8. SECURITY

After widening the computerised systems in scope and involving new stakeholders, the guideline indirectly introduces new requirements for involved parties, such as clinical sites. For instance, availability of controlled SOPs for defining and documenting security incidents, rating their criticality and implementing CAPAs, is required. Our question here, is: are clinical sites equipped with such a well-organised quality system to support these activities?

The list of required security measures includes:

- Anti-virus software
- Task manager monitoring
- Regular penetration testing
- Intrusion attempts detection and prevention systems
- Effective system for detecting any unusual or risky user activities (e.g. shift in activity pattern).

The guideline also takes into consideration the protection of the confidentiality of the trial participants' data. The use of BYOD is particularly challenging since the device must be able to identify the trial participant in order to ensure the attributability of the captured data. That data should be collected according to the principle of 'data minimisation' and the participant should be informed about it in the patient information sheet and agree to it in the consent form.

As stated, while sponsors and CROs are quite used to work in a deeply regulated environment, clinical sites and computerised systems' vendors might need additional resources in terms of employees and/or consultants, in order to be able to fully satisfy the requirements.

9. MANAGEMENT OF COMPUTERISED SYSTEMS AT CLINICAL SITES

The entire Annex 6 is dedicated to the systems implemented at sites primarily used in clinical practice and in generating clinical trial data. All those systems must comply with all the requirements described in this guideline. Sites should ensure that the systems are fit for the purpose of collecting clinical trial data (e.g. must include audit trail), system validation and the use of a GCP compliant configuration when used for clinical trials. Robust processes for access rights should be implemented, for instance to avoid treatment unblinding in blinded trials. Direct read-only access should be granted to monitors, auditors and regulatory inspectors. This access should be limited to trial participants data in order to avoid a break of confidentiality. Particular care should be taken for the retention of all clinical trial data so as to ensure their availability for the required timelines.

CONCLUSION

The new guideline provides directions to sponsors, CROs, investigators and other parties involved in the design, conduct and reporting of clinical trials on the management of computerised systems and clinical data. It does not technically introduce new concepts but finally clarifies inspectors' expectations on several compliance areas: it provides a fresh and modern view on new and emerging technologies (e.g. wearables, AI, cloud) and establishes a solid ground to support and reinforce service providers and site compliance.

Some of the requests are demanding (e.g. retention of data preserving their dynamic state). It will take a great deal of work to achieve full compliance, especially for already ongoing trials. Additionally, some requirements could be especially complex for clinical sites as they will require a totally new approach.

Electronic systems and data are here to stay, a new challenge for compliance has started.

PROFILES

Mario has 24 years of experience in clinical research. During his career he has worked as Clinical Monitor, Project Leader, Quality Assurance and Auditor. He leads the Quality Assurance Unit of the CROss Alliance Group. For seven years Mario has been one of the coordinators of the GCP working group of the Italian Group of Quality Assurance in Research (GIQAR).

Marianna has over 22 years of experience within the pharmaceutical environment with extensive experience in GCP/ GCLP/GVP/CSV compliance and Quality Assurance (QA). She possesses a wide knowledge of ICH guidelines, European pharmacovigilance regulations, Good Clinical practices (GCP), GCLP (WHO), 21 CFR Part 11, EU Annex 11, ALCOA+ Data Integrity Principles, GAMP 5 and main FDA Guidance(s) for industry. Since 2000 Marianna has been working for PQE where she developed wide expertise in clinical and PV auditing, QMS implementation and computer systems validation projects. She is currently the GCP Compliance Operation Manager at PQE Group.

Laura has a masters degree in pharmaceutical chemistry and technology and had her first experience in Fidia Farmaceutici S.p.A. Here she covered the role of Corporate R&D Quality & Compliance Coordinator and gained experience in GCP and GVP compliance, especially for vendor management and validation on computerised systems used in clinical studies and for pharmacovigilance processes. Laura currently covers the role of CSV and Data Integrity Consultant for QStep srl, providing consultancy services to pharma companies on computerised system validation projects for GMP, GVP and GCP compliance.

Anna has a degree in pharmacy and more than 30 years' experience in pharma companies covering the role of Head of QA for GLP, GCP, GVP. She also worked in project management and science information during her career. Anna is currently a freelance GxP auditor, coordinator of the Italian Group of Research QA (GIQAR) and Vice-president of the Italian Society of Medicinal Farmacy (SIMeF).

Massimo is a GLP/GCP Senior Specialist and Auditor at Chiesi Farmaceutici. He has 19 years' experience in Research Quality Assurance across GLP and GCP areas. He started working as QA Auditor in a toxicology test facility in 2004 and in 2016 joined Chiesi where he is responsible for preclinical quality assurance activities. Massimo is involved in the implementation and maintenance of the GCP quality system in R&D projects.

We recently ran a webinar on this topic with members of our GCP and IT Committees which is available in the Community Hub for members to view.