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ANALYSIS OF THE EMA DRAFT GUIDANCE ‘GUIDELINE ON COMPUTERISED SYSTEMS AND ELECTRONIC DATA IN CLINICAL TRIALS’

THIS ARTICLE WAS WRITTEN BEFORE THE RECENT EMA UPDATE OF THIS GUIDELINE. AN UPDATE WILL BE AVAILABLE IN DUE COURSE.

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 like remote monitoring and remote inspections. Still, it is not all rosy. The digital environment can 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 be also challenging. With perfect timing, in June 2021 EMA opened the public consultation for the draft guideline 'Guideline on computerised systems and electronic data in clinical trials'. The document was released by the GCP 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, meaning that the inspectors' attention in this area is high (and probably inspections findings are common). 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'. While the old reflection paper was only 13 pages long and with a narrow scope, this new guideline is an impressive 47 page document, highly detailed and demanding. 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 'current hot topics' like electronic Clinical Outcome Assessment (eCOA), electronic Patient Reported Outcome (ePRO), electronic Informed Consent (eIC), cloud systems and Artificial Intelligence (AI). The recipients of the guideline are sponsors, CROs, investigators but also other parties like 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' and examples of common but incorrect identification of source data are provided. Details on requirements for computerised systems are given. A full chapter is dedicated to electronic data (and audit trail) and the challenges of their management during the whole life cycle. Finally, five annexes provide detailed requirements on topics like contracts, validation, user management, security and specific types of systems. An outline of the guideline structure is provided in Figure 1.

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.

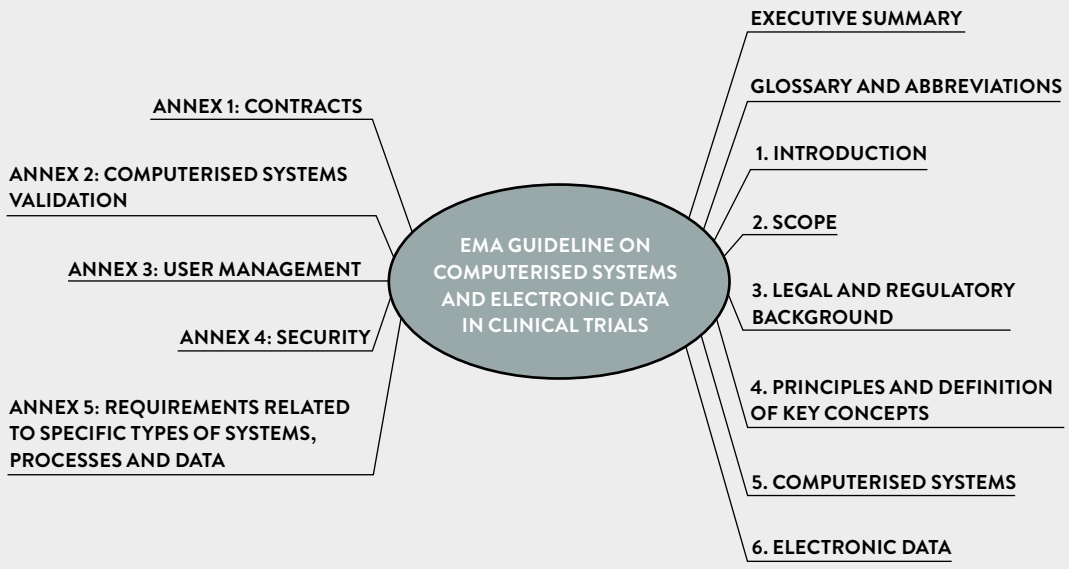
Our team analysed the draft guideline and sent comments, requests for clarification and suggestions on different aspects of the document to EMA. From this analysis we came up with some topics that, unmistakably, will be posing new challenges to sponsors, CROs and mostly to clinical sites. We summarised them in the following points:

NEW COMPUTERISED SYSTEMS IN SCOPE

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 programming pharmacovigilance databases, statistical software, document management systems and central monitoring software
- Artificial intelligence (AI) used in clinical trials.

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



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 the investigator is ultimately responsible for the validation of the computerised systems implemented by the investigator's institution as it is the sponsor for all the remaining systems used in each clinical trial. However, while sponsors and CROs are generally accustomed with concepts and techniques of validations and, have specific procedures and resources in place, this requirement may be challenging for clinical sites. Indeed, investigators/institutions will need dedicated personnel and/or consultants to validate their systems, to plan periodic reviews and to implement change control processes.

Finally, the guideline requires that in case of regulatory inspections, the validation documentation for all the systems in scope 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.

ELECTRONIC DATA TRANSMISSION AND eSOURCE 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, the timing of the transfer and any actions that might be applied to the data, for example, validation, reconciliation, verification and review. This also applies when data are captured by an electronic device and are 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, are they 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).

'The sponsor should never have the exclusive control of data entered in a computerised system.'

All these electronically captured source data must be precisely identified in the study protocol. The guideline clearly states that any data generated/captured and transferred to the sponsor or CRO that is not stated in the protocol or study related documents will be considered GCP non-compliant. ePRO data should not be kept on servers under the exclusive control of the sponsor until the end of the study but they must be made available to the investigator in a timely manner, since he/she is responsible for the oversight of safety and compliance of trial participants' data.

CONTROL OF DATA AND MANAGEMENT OF DYNAMIC DATA

The sponsor should never have the exclusive control of data entered in a computerised system. 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, he/she 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 its performance 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, for example, 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.

AUDIT TRAIL AND AUDIT TRAIL REVIEW

As anticipated, the guideline really highlights the importance of audit trails. The extension of ALCOAC principles to ALCOAC+, with the addition of the 'traceable' requirement, is easy proof of where the focus is and it explicitly requires that all changes must 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 ahead with the requirements for audit trail review and specifies that 'the entire audit trail should be available as an exported 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
- Implausible dates and times
- Incorrect data processing
- Unauthorised access
- Malfunctions
- Direct data capture not performed as planned.

Therefore, the raising questions are: do we have the resources to deeply review the audit trail to the extent required? 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?

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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.

Whether or not technical providers are always up-to-date and aware of all the applicable legislations and guidelines is the main concern. Indeed, such vendors often provide systems for different industrial sectors and are not limited to the pharma industry. Therefore, while 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.

For investigators and site staff competence, the guideline states that 'all training should be documented, and the records retained in the appropriate part of the Investigator Site File/sponsor TMF'. It is clearly indicated that investigators should receive training on how to navigate the audit trail of own data to be able to review changes and that such training needs to be documented; however, the guideline does not clarify if non-study specific training (on systems used in multiple studies, such as training on CTMS, PV database, etc.) and training on IT security and serious breaches management should also be retained in ISF/TMF.

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 SOP 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-viral software
- Task manager monitoring
- Regular penetration testing
- Intrusion attempts detection system
- Effective system for detecting any unusual activity from a user (e.g. excessive file downloads, copying or moving or backend data changes).

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 to be able to fully satisfy the above requirements.

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 really 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 enforce providers and site compliance.

Nevertheless, through the analysis performed, we can conclude that not all the requests are clear and some of them are deeply technically challenging (e.g. retention of data preserving their dynamic state). A great deal of work will be needed to achieve full compliance when the guideline comes into force, especially for trials already ongoing. Additionally, some requirements could be really complex for clinical sites and they will require a totally new approach.

Electronic systems and data are here to stay and it is important that the compliance requirements are clear and feasible. GIQAR, as stated, has requested several clarifications on the document and we assume that many more questions and suggestions must have been received by the stakeholders in the pharma industry and maybe investigators. We hope that EMA will take them into account and will respond with a clear and well-applicable final guidance.

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PROFILES

Mario has 23 years of experience in Clinical Research. During his career he has worked as Clinical Monitor, Project Leader, Quality Assurance and Auditor. Mario leads the Quality Assurance Unit of the CROs Alliance Group. For seven years he 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 professional life in the pharmaceutical environment with extensive experience in GCP/ GCLP/GVP/CSV compliance and Quality Assurance (QA). She possesses wide knowledge of ICH guidelines, European pharmacovigilance regulations, 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 Master's 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 on GCP and GVP compliance, especially for vendor management and validation on computerised systems used in clinical studies and for pharmacovigilance processes.

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