EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 November 2021

Submission of comments on 'Guideline on computerised systems and electronic data in clinical trials' (EMA/226170/2021)

Comments from:

Name of organisation or individual
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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The guideline is highly appreciated. Where appropriate it is recommended, that definitions and terms should be based on ISO standards or similar standards	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Guideline 142-148		Comment: The section is relevant, but terminology should be aligned with AI terms from ISO22989:20 Proposed change: Artificial Intelligence (AI) as a system is a set of methods or automated entities that together build, optimize and apply a model (physical, mathematical, or otherwise logical representation of a system, entity, phenomenon, process or data) so that the system can, for a given set of predefined tasks, compute predictions (output of a machine learning model when provided with input data), recommendations, or decisions. Machine learning (ML) is a subset of AI and includes computer algorithms which are trained to classify or predict data, without actually being programmed to do so. ML is divided into supervised and unsupervised learning. Deep learning (DL) is a subset of ML and contains algorithms which allow software to train itself by exposing multi-layered neural networks to vast amounts of data.	
238		Comment: The increased usage of Cloud services and SaaS should be mentioned here as well Proposed change:	

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240		Comment: Abbreviation of "ePRO" should be defined Proposed change: Add to line 237 the following "ePRO - Electronic patient-reported outcome"	
242		Comment: "The latter ... in a future Annex." This sentence does not make it clear if AI is covered by this guidance or not. Plans for future guidance should not be included in existing guidance, despite the fact it is highly appreciated. If possible, the guidance should be coordinated with EU proposal for "Regulation of The European Parliament and of The Council Laying Down Harmonised Rules on Artificial Intelligence (Artificial Intelligence Act) and Amending Certain Union Legislative Acts" Proposed change: Remove sentence, or if possible, link to EU legislation if approved	
243		Comment: Term "Computerised System" could be defined to prevent different interpretations Proposed change: Add the following "Computerised System - A computer system includes hardware and software components interacting to automate tasks that are programmed or	

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		configured specifically to meet user requirements. In most cases this definition excludes commercially available embedded controllers often found in field instruments and peripherals. A computer system includes documentation (e.g., specifications, manuals, validation documentation, and instructions) and training of personnel. The term "computer system" in this definition includes all types of computer systems ranging from small systems to enterprise systems. The term "computer hardware" includes components such as CPU, memory, network, and peripheral equipment acting as input output devices (e.g., keyboards, displays, and printers). Based on interpretation from FDA Glossary of Computer System Software Development Terminology (8/95)."	
272, 274, 470		Comment: The term "Tool" should be defined to avoid confusion with computerised system as defined in requirements from EudraLex GMP Annex 11 Proposed change: Add the following "Tool - Tools are characterized by their semi- ad-hoc use in tight interaction with the operator, in contrast to systems that are designed and configured to automate user defined processes. Examples of tools include network loading and diagnostics, and engineering tools such as test automation tools, editors, compilers, and linkers. Tools should be carefully selected and risks from their use to continuing operation of computer systems must be	

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		assessed.”	
324		Comment: Editorial comment – link to be inserted or a reference with a link to the GCP Q&A’s published on the EMA website Proposed change: Please add the following link https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp	
335		Comment: This paragraph should include access control to data as an important aspect of Data Integrity Proposed change:	
357		Comment: The term “metadata” should be defined to avoid misunderstanding Proposed change: Add the following “Metadata – Data that describe the attributes of other data and provide context and meaning. Typically, these are data that describe the structure, data elements, inter-relationships and other characteristics of data. It also permits data to be attributable to an individual (or if automatically generated, to the original data source).	

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		Source MHRA GxP Data Integrity Definitions and Guidance, Revision 1, March 2018 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf	
439		Comment: Link to guidance on Risk Management would be beneficial Proposed change: Add the following sentence. "Risk Management should be applied in accordance with ICH guideline Q9 on quality risk management"	
501		Comment: Requirements applied to electronic signatures are not complete – the "meaning" related to approval is missing Proposed change: Add the following "…..5) The meaning (such as review, approval, responsibility, or authorship) associated with the signature."	
537		Comment: ICH E6 R2 requires that the sponsor "Maintains SOPs for using these systems. The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures,	

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		change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use." This section does not make it clear that documented SOPs are needed for the validation and operation of the systems. Proposed change: Section 5-2 would be a good place to elaborate on the need for such SOPs	
226 / 564		Comment: The terms "responsible party" and "contracted party" are not clearly defined within the draft guideline. Definition should be provided in the glossary to the guideline to ensure clear understanding and delineation of roles and responsibilities Proposed change:	
569		Comment: Section 5.1 gives good guidance, but alignment to requirements stated in EU GMP Annex 11 would be beneficial. Proposed change: Add the following "For critical systems an up-to-date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security	

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		measures should be available."	
573		Comment: Section 5.3 should also include the training of IT personnel and support staff…this could be made clearer… Proposed change:	
589		Comment: The word "Checks" should be clarified indicating whether it refers to periodic reviews or "Checks" as tests in the context of validation or both? Proposed change:	
619-621		Comment: Please provide some risk-based approach context in the sentence starting with "Qualification/Validation..." Proposed change: Add the following ".. committees) based on a justified and documented risk assessment.	
624		Comment: Any requirement for built-in checks and potential failures is missing. Proposed change: Add the following "Computerised systems exchanging data electronically with other systems should include appropriate	

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		built-in checks for the correct and secure entry and processing of data, in order to minimize the risks"	
650-651		Comment: Terms like "normal users" and "admin users" should be defined under glossary and abbreviations. Proposed change: Add the following under glossary and abbreviations End User: End User is a person who uses a computer system as opposed to those who develop or support it Individual, authorized to access a system. Admin User: The Admin User supervises the day-to-day usage, operation, and maintenance of the computer system. Admin User normally have privilege access to the Computerized System	
705		Comment: Examples of types of Audit Trail review could be added to clarify what is expected. Proposed change: Add the following text "There are three main types of audit trail review: 1. Review of data audit trails as part of normal operational data review and verification, second person verification and approval, usually performed by the operational area which has generated the data (e.g., a laboratory), i.e., using the	

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		audit trail routinely. 2. A tool to be used for investigation (e.g., of deviations or data discrepancies) as and when required, i.e., using the audit trail as and when needed. 3. Review of audit trail functionality (as part of normal periodic review or audit) to check that they remain enabled and effective, i.e., checking the audit trail." Reference. ISPE GAMP® Guide: Records and Data Integrity	
812		Comment: Link to EMA Q&A section 8 could be provided Proposed change: Add the following sentence "For considerations regarding contractual arrangements with vendors for electronic systems in connection with clinical trials see EMA Q&A: Good clinical practice (GCP) Q&A, question 8 https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp	
835		Comment: Requirement for validation must be included Proposed change: Add the following sentence "Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically."	

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891		Comment: Consideration of the approach for exit of usage of cloud service providers and cloud services could be described Proposed change: N/A Please add additional detail in Annex 1 that recognises the inclusion of consideration for decommissioning of cloud-based databases	
915		Comment: The paragraph is hard to understand for non-English speakers and recommend it is changed for clarity Proposed change: Please change the text in lines 915 to 917 to "If appropriate contracts cannot be put in place due to the inability or reluctance of a contracted party (based on potential intellectual property concerns) to allow access to key aspects supporting information, for example qualification documentation / records (e.g., systems requirements specifications), or the contracted party is unwilling to support pre-qualification audits or access for GCP inspectors, then use of systems from such a contracted party shall not be used in clinical trials."	
918		Comment: "…this includes vendors of computerised systems" may be true, but the statement is misleading as vendors of computer systems are not necessarily required to comply with GCP. E.g., a vendor of a LMS system may only provide the software for implementation on premise at a sponsor/CRO/investigator site. In such a case the	

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		sponsor/CRO/investigator must ensure the GCP compliance and validation, the vendor is not directly involved. Proposed change: The sentence in lines 918 and 919 should be replaced by "All parties involved in the conduct of the clinical trial should be aware of and comply with ICH-GCP as appropriate to their responsibilities. Vendors of computerised systems, while not expected to directly comply with ICH-GCP, will be required to provide support the responsible party to ensure compliance to ICH-GCP".	
938		Comment: Consideration to cloud services should be included Proposed change: Add the following "This also applies for Cloud Services like SaaS solutions"	
967		Comment: Link to EMA Q&A section 8 could be provided Proposed change: Add the following "For considerations to be aware of regarding contractual arrangements with vendors for electronic systems in connection with clinical trials see EMA Q&A: Good clinical practice (GCP) Q&A, question 8 https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp	

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1028 - 1032		Comment: Regards the statement "For example, the use of the software for a trial specific build or configuration will also require specification documentation to be produced. This should make reference to the clinical trial protocol and version for which it was designed." As a recommendation it is suggested that a sufficiently detailed and structured Protocol would be suitable as an alternative to a separate specification. As mentioned in line 464 "The approved clinical trial protocol should specify which data is to be generated/captured by whom and when and which tools or procedures are to be used. The protocol should identify any data to be recorded directly into the eCRFs and considered to be source data (ICH-GCP 6.4.9)." The generation of an additional specification could be unnecessary when using "configurable" EDC systems rather than "programable" ones. This recommendation would support a justified and documented risk-based approach to be taken. The last sentence (1031 – 1032) does not make sense and requires clarification please. Proposed change:	
1036		Comment: "The sponsor/investigator should take responsibility for the	

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		URS. This document should always be reviewed and approved by the sponsor/investigator." In this whole section we should differentiate carefully between - Study-specific specifications - System-specific specifications While the sponsor/investigator should take responsibility for the Study-specific URS and review and approve those, this is not true for a system-specific URS. Proposed change: It is recommended that the section text be revised to take into consideration the differing responsibilities based on type of specifications.	
1038		Comment: "The responsible party should ensure availability of qualification documentation." Does this include software development documentation as this includes a lot of functional testing? Proposed change: The responsible Party should ensure availability of all appropriate qualification documentation to demonstrate the validation status of the system, including assessments of vendor generated documentation.	
1059 - 1061		Comment: "Validation activities should be planned and documented, for example validation plan and test plan. Test cases and	

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		individual test steps should be pre-approved and conducted accordingly. This is required for validation of both core software and trial specific configurations/builds." This is not aligned with the Computer Software Approach as currently considered by the FDA. This proposes informal testing with basic documentation and without preapproval for low-risk functions. It is recommended that the EU also accepts a risk-based approach. Proposed change: We recommend that the sentence in lines 1059 – 1061 is replaced by "Indicate that validation activities should follow a risk-based approach and that testing should be managed and controlled as appropriate in line with this approach."	
1102		Comment: "Defects/issues should be fixed in a timely manner." This should be documented and the records kept according to a pre-defined process. Proposed change: Defects/issues should be fixed in a timely manner. The fix should be documented and records kept according to a pre-defined process.	
1121		Comment: Other topics should be included in periodic review to evaluate the validated state.	

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		Proposed change: Add the following "- where appropriate, the current range of functionality, - deviation records, - incidents, - problems, - performance, - reliability, - and validation status reports."	
1284		Comment: Password managers often create complex passwords and users of password managers are more willing to accept and use these passwords, thereby creating more security compared to the "one-size-fits all" passwords that users often use for all sorts of accounts. The vast majority of cyber-security specialists agree that password managers are indeed the most secure way to protect your passwords see https://www.cnet.com/tech/services-and-software/password-managers-a-little-pain-for-a-lot-better-security-world-password-day/ Proposed change: We recommend that this section is rewritten to allow the use of appropriate password managers if supported by suitable risk-based qualification procedures commensurate with the complexity and novelty of the application used.	
1354		Comment: It would be important to state that there needs to be access controls to ensure that entries come from the study	

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		participants. The system also needs to capture/transmit who is the data originator and the date/time data was transferred to the sponsor's database and date/time data was entered by the participant. Additionally, the system should restrict who can access or modify the patient's data. Proposed change: We recommend that the text is modified to include our suggestions	
1380		Comment: "The data saved in the device are considered source data. After the data are transferred to the server via a validated procedure, the data on the server are considered a certified copy." This statement does not align line with the statements in line 384 and figure 2. Proposed change: Please clarify the requirements and amend either Figure 2 or line 1380. Our preference is that Figure 2 is changed.	
1524		Comment: We recommend adding the reference. Proposed change:	

Please add more rows if needed.