<Date of submission>

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

Comments from:

Name of organisation or individual
Parenteral Drug Association

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Comment: The term "data quality" is used several times in the guidance. It would be helpful to the reader if the term were defined in the Glossary. Proposed Change: "Data Quality" "Data that is fit for its intended purpose"	

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)*
220		Comment: An example of a file type such as a text file that may be both dynamic or static based on their use would be helpful for the reader. Propose Change: Add "Some file types, for example text files, many be dynamic or static dependent on their design within a system and the ability/control to change information once entered."	
226-227		Comment: To be consistent with the contents of published guidance (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf.) recommend the text be modified: Proposed Change: "2) the project phase where a contracted party is selected, a risk-assessment is made **(which includes the vendors qualification/validation)**, **any additional qualification and validation required performed**, and the system is implemented and qualified,"	
237		Comment: Recommend including Interactive Web Response System (IWRS) in the list of abbreviations and its inclusion in line	

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		352 for completeness. See line 352 comment for proposed change.	
256		Comment: The term "services" is unclear in this text based on the examples provided. recommend the use of "processes" in its place. Proposed Change: "The scope of this guideline is computerised systems, (including instruments, software and ~~services~~ **processes**) used in clinical trials	
329		Comment: A reference to Annex 4 should be made in the text. Proposed Change: At the end of the section add the following sentence. "**See Annex 4 for additional information on this topic."**	
347-350		Recommend the addition of the word "store" as this is an important function as well. Proposed Change: "Investigators and their institutions, laboratories and other technical departments or clinics, **generate and store** data,"	
352		Comment: For completeness recommend adding IWRS to this line of text.	

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		Proposed Change: "…., including organisations providing ePRO, eCRF **(including IWRS)**, or interactive voice response system (IVRS) specialists …."	
355		Comment: To better reflect the context of this section we suggest the title be changes to Metadata, Proposed Change "4.2. ~~Electronic Data~~ **Metadata "**	
356		Comment: To better reflect the type of data suggest adding "Electronic" before "Data" at the start of the paragraph. Proposed Change: "**Electronic** ~~D~~**d**ata consists of collected…"	
361		Comment: To ensure the term "individual" is correctly interpreted in this sentence recommend adding "entering or taking an action on the data such as modifying, deleting, reviewing, etc." after "individual" Comment: "...to an individual **entering or taking an action on the data such as modifying, deleting, reviewing, etc**…."	
373-375		Comment: The end of the sentence "or it is not ensured that it is	

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		retained" is not needed as it is not relevant to the example being provided distracts from the points being made about source data. Proposed Change: Proposed change: "Below is an example (Figure 1) of a situation where the true source data (e.g., imaging) is often not used for source data verification ~~it is not ensured that it is retained~~."	
Fig.1		Comment: In figure 1, it is recommended that "metadata" be included in the top box for completeness. Proposed Change: "This data **with the exception of some Metadata** (could be …"	
383		Comment: Providing an example after the end of the sentence on line 384 would be very helpful. Proposed Change: Add to the end of the sentance **"for example the logical location data where the source data is first obtained could be the device ID and Serial Number."**	
384 – 385		Comment: Clarification of what is considered "source data" is needed in the text to resolve a conflict in terminology.	

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		The sentence "From a practical point of view, the first obtainable permanent data from an electronic data generation/capture should be considered and defined as the electronic source data." and the text in the example "Once Permanent storage is achieved, this is considered source data" clearly indicated that once transferred to permanent storage this is considered the "source data". The statements above are in a conflict with lines 1377-1380 "Since the data stored in a temporary memory are at higher risk of physical loss it is necessary to transfer the data to a durable server at an early stage, by a validated procedure and with appropriate security methods during data transmission. Data should be transferred to the server by a pre-defined timing and procedure. 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 text indicates the data in the device is the "source data" and the data in permanent storage is "a certified copy".	
396		Comment: Based on the general term "coding" used with "Completely reversible" in this sentence clarification is needed. For the above-mentioned scenario (imaging in a MR-scanner) this might be impossible if coding is interrupted as reversing the programming used to transform the raw data into a DICOM	

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		image file. Some reconstruction algorithms are not completely reversible by nature (e.g. matrix inversions) using linear regression methods.	
403-406		Comment: Clarification is needed as this sentence seems to indicate that it is necessary to maintain the initial dynamic state in which the information was originally captured which is not always feasible.	
429-430		Comment: To better clarify this text the following wording is recommend: Proposed Change: "Data should be accessible and available in a timely manner for review, audit or inspection over the record lifetime."	
432		Comment: The use of ALCOA ++ creates unneeded confusion. Recommend aligning this document and this section with the recognized ALCOA+ terminology. The various aspects of traceability is already covered by the ALCOA+ terms and the addition of a separate "Traceable" term is not needed.	
444		Comment: Complexity is an important consideration when evaluating risk. Recommend text be changes to include this term. Proposed Change: "...risks should be determined based on system used, **its**	

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		complexity, operator,"	
459-460		Comment: Recommend "The identification of the most effective and efficient risk-based control, including periodic review of the data and metadata can be determined and implemented." be removed. Its phrasing and use of "can be" is confusing and the sentence is repetitive of line 440 and 441, "Risks in relation to the use of computerised systems and especially those related to the assurance of data integrity should be identified, analysed and mitigated or accepted throughout the system life cycle"	
464-467		Comment: The clinical protocol is typically not the governing document where details of data generation and data capture are identified. At the time the protocol is written all data systems and data tools may not be identified. Data systems development and data handling are covered in Data Management Plan and other protocol related documents at the time of systems development. Proposed change (if any): "The approved clinical protocol **or related protocol documents (e.g. Data Management Plan)** should specify which data are to be generated/captured by whom and when and which tools or procedures are to be used. The protocol **or protocol related documents** should identify any data to be recorded directly into the eCRFs and considered to be	

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		source data (ICH-GCP 6.4.9).”	
468-469		Comment: The statement “Any data generated/captured and transferred to the sponsor or CRO that is not stated in the protocol or related documents is considered GCP-noncompliant” the term “Any Data” is too far reaching as it is possible that data of relevance that could not been foreseen become available. Proposed Change. “Any Data” should be replaced with “Patient Data”	
479		Comment: For clarity it is recommended that the sentence be modified to indicate that the diagram is intended for the transmission electronic data during the conduct of the clinical trial. Proposed Change: “A detailed diagram and description of the transmission of electronic data **expected during the conduct of the clinical trial** should be available.”	
484-485		Comment: As noted in the comment for line 468-469, the use of “Any Data” is to far reaching. Change Proposed: “Any Data” should be replaced with “Patient Data”.	
494/497/515		Comment: Recommend the term “Unbreakable link” be replaced with	

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		"permanently linked to their respective record" to align with the language used in EU GMP Volume 4 Annex 11.	
504		Comment: "Closed Systems" used but not defined recommend a definition be provided. Proposed Change: Add in definitions: "Closed System" "A Computer system whose user access is controlled by the company responsible for its contents, i.e., the company can confirm the identity of all users prior to providing access to the system"	
495-501		Comment: It is suggested that the system should also capture the 'reason for Signature' when an electronic signature can signify more than interpretation like certifying the content, reviewing the content, or approving the content etc. Proposed change: "… 4) provide a *timestamp*, i.e., that the date, time and time zone when the signature was applied is recorded**, 5) reason for signature**."	
513		Comment: The term 'hybrid electronic signature" is confusing. The process describes one where the signature itself is a wet ink signature. This term is expected to create confusion.	

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		Proposed Change: Recommend removing of this paragraph or the use a term that better reflects the action.	
518-519		Comment: The statement assumes biometrics replaces e-signature (i.e., instead). As biometrics can be used to record/input e-signature. To avoid confusion the use of the term "to record" is recommended in place of "instead" Proposed change: "If using biometrics **to record** ~~instead of~~ e-signature, investigator and sponsor should ensure that these fulfill the above-mentioned requirements and local legal requirements."	
537		Comment: For clarity if is recommended that "CRO" be added to the example list of system owners. Proposed Change: "…e.g. sponsors, **CROs**, investigators, technical facilities) …"	
555		Comment: It is important that the access provided is "Read-Only" (Guest/Auditor Account). Where it is not possible access should be provided in a way that protects the data from accidental modification. Proposed change:	

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		"All relevant computerised systems should be readily available and directly accessible **by providing a "Read Only"** (this requires a unique username and password) upon request by inspectors of regulatory authorities. If a computerised system is de-commissioned, direct access (with personal username and password) **with a "Read-Only" account** to the data should be still ensured (see section 6.11). **In cases where a read only account can not be provided due to system limitations access should be provide to the data in a manner that ensures the data is protected from accidental modification."**	
570		Comment: Greater specificity/clarity would be helpful in this text regarding requirements for ownership/reporting of documents.	
583-584		Comment: The sentence "All training should be documented, and the records retained in the appropriate part of the investigator site file/sponsor TMF" would indicate that all records need to be retained in the TMF. Per Regulation EU No 536/2014 and the EMA "Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)" there is not a requirement that the training records be maintained in the TMF as this will be impractical. The training does need to be documents and retained.	

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		Proposed Change: "All training should be documented, and the records retained ~~in the appropriate part of the investigator site file/sponsor TMF"~~	
613-618		Comment: Clarification is needed in this sentence if transfer of data is required outside of a pre-defined period. There are occasions where an unscheduled data transfer needs to occur due to regulatory requests or potential safety assessment needs. Propose change. It is recommended that the following sentence be added after the sentence on line 618. "In cases where a transfer is needed during the conduct of a clinical trial due to an unforeseen request (i.e., request from a regulatory authority, part of an assessment related to a potential safety issue, etc.) the specific transfer details must be pre-specified and the transfer and transfer protocol to be used approved prior to its occurrence."	
645		Comment: As audit trails may be designed as part of the individual record or as a log linked to its respective record. To add clarity on this point it is recommended that it be capture in the text. Proposed Change: After the end of the sentence on line 648 add the following	

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		text "The audit trail should be part of the actual record or a separate log file that is linked to its respective records."	
650		Comment: The term "Normal" used in this line of text could be improved. The more common term used is "non-admin Proposed Change: Use the term "non-admin" for "Normal"	
653		Comment: The sentence "The audit trail should not be stored outside the system" is incorrect: A backup should be stored outside of the system. Additionally in some data retention scenarios audit trails must be exported and stored elsewhere. Recommend this sentence be removed.	
656-658		Comment: The use of the term "entire" in line 656 may be miss interpreted. This could be interpreted as the audit trail for the entire study must be available as an export. Recommend "entire" be removed. Recommended Change: "…and the ~~entire~~ audit trail should be available as an exported dynamic file..."	
659		Comment: In the description of the data to be captured in the audit trail the information provided for "by whom" specifically "(username, role, organisation)" is significantly different then	

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		current expectations in other published guidance documents. The acceptable standard is the capture of the unique user identifier alone. Based on the unique user identifier the information if needed as to their role and organization at the time of the change can be determined. Proposed change: "…whom (**unique** user identifier ~~name, role, organisation~~)…"	
665-666		Comment: The term "clarification process" in this sentence is unclear. If this term could be defined or explained with additional text it would be very helpful to the reader.	
702-703		Comment: Line 702-703 is a repeat of line 684-685. As the text is related to audit trail review, recommend line 684-685 be removed.	
704-705		Comment: Clarification is requested as to whether the expectations is that sponsors should require investigators to review the audit trails in systems and document their review (and train them on how and when to do this) or if it is sufficient for sponsors to show investigators on how to access and navigate the audit trails *should* they want/need to review them.	
770		Comment: Clarification of the term "data" is needed to reflect that is it	

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		referring to patent data. Proposed change: "The sponsor should not have exclusive control of the **patient** data entered in a computerised system at any point in time. All **patient** data held by the sponsor…"	
792		Comment: The rationale for the investigator having control of hosting is unclear. It is suggested that this refers instead to access. Proposed change: "Any contractual agreements regarding hosting should ensure investigator ~~control~~ **access**."	
823-825		Comment: The use of different firewalls is too restrictive. Recommend changing it to "strongly recommended". Proposed Change: "Back-ups should be stored in separate physical locations and logical networks, and it is **strongly recommended** that they are not behind the same firewall as the original data to avoid simultaneous destruction or alteration."	
850		Comment: In situations where tools used for data migration get qualified/validated using mock data, there should not be a need to perform additional data verification post migration, it should be acceptable to rely on a qualified/validated tool to	

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		perform data migration. A risk-based approach is recommended, as suggested below. Proposed change: "A data verification focused on key data, **may** ~~should~~ be performed post migration**, depending upon outcome of risk-assessment**."	
857-858		Comment: This area of the text is unclear and appears as if some text was left out or accidently inserted. If the text is as intended consideration should be given to rewriting the text so it can be better understood.	
875		Comment: Typo "4.6." was written instead of "4.11." Proposed change: To change line to be "their regulatory obligations. For direct access please refer to section ~~4.6~~ **4.11**."	
875		Comment: This appears to cross refer incorrectly to Section 4.6. Proposed change: "For direct access please refer to section **4.11** ~~4.6."~~	
879		Comment: More clarifications is needed in regards to which data retention strategies are allowed or if the strategy used should be a risk-based decision and including data exports to ensure	

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		the content is preserved in a way that allows for the trial reconstruction.	
917		Comment: Certain Cloud Providers do not allow for pre-qualification audits or access for GCP inspectors; however, they could still be assessed for compliance through Public Information Assessments and review of publicly published information. Suggest including provisions, as suggested below, for such IAAS/PAAS providers. Proposed change: "If appropriate contracts cannot be put in place, e.g., because a contracted party does not allow provision of e.g., access to system requirements specifications, pre-qualification audits or access for GCP inspectors, **or in case of cloud providers when vendor suitability cannot be confirmed through other equivalent means such as Public Information Assessments**, systems from such a vendor shall not be used in clinical trials."	
977 to 981		Comment: The decision to perform additional validation and the amount of additional validation required is dependent on the changes made. Clarification in the text is needed to capture this important point. Proposed Change: "A further validation may be required where **based on the**	

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		requirements of a specific trial the installed software ~~is then used for specific~~ **requires changes in the** ~~requiring~~ a configuration or build. **The need for further validation and the amount of additional validation required should be made based on an assessment of the changes made."**	
982		Comment: The sponsor has the ultimate responsibility for the validation of the computerized system used in the clinical trial process. While the authority may be delegated to the investigators institution the ultimate responsibility still resides with the sponsor. Propose change: "The sponsor ~~(or the investigator in case of a system implemented by the investigator's institution)~~ is ultimately responsible for…"	
1000-1003		Comment The sponsor is responsible, as part of the vendor qualification audit, to review and document the vendor's qualification documentation and be able to navigate through… Proposed change: Instead of "should have a detailed knowledge about the qualification documentation and should be able to navigate through it and explain the activities as if they had performed the activities themselves" recommend using, "sponsor should be able to show knowledge of and navigate	

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		through the documents if access to the documentation is requested during inspections or upon request by the authorities"	
1030		Comment: The requirement for referencing protocol version within specification document should also apply when changes are made to specification documents due to protocol amendments. It is recommended that any changes to trial specific build due to protocol amendments be clearly identified in the specification documents, as suggested below. Proposed change: "This should make reference to the clinical trial protocol and version for which it was designed**, including any clinical trial protocol amendments."**	
1031-1032		Comment: The last sentence of the text is unclear and appears as if some text was left out or accidently inserted. If the text is as intended consideration should be given to rewriting the text so it can be better understood.	
1074 to 1091		Comment: The section on testing only considers testing performed by human operators. It is suggested that the possibility of automated testing be addressed also. Proposed addition in line 1078 after "…documented."	

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		"Automated testing tools may be part of the testing strategy and are considered as appropriate."	
1093-1098		Comment: It is unclear why the release of a system into production would require a regulatory approval of the clinical trial. If the trail is not approved the system would not be used. Based on timing of the approval and when the clinical trial is to begin release of the system and training on it may be advantageous while the study awaits approval. Proposed Change Removal of line 1093 through 1098.	
1147		Comment: Text should be added that the process used should be an approved process Proposed Change: "Organisations should grant, change and revoke system accesses **using an approved process** in a timely manner…"	
1221-1222		Comment: In specific cases patches to systems must be evaluated as to their potential unintended impact on the systems function as the patch may impact how the system interacts with other programs on which it depends. In some cases, a risk assessment must be conducted and other actions take to resolve the potential threat.	

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		Proposed change: Removal of line 1221 and 1222	
1230-1231		Comment: When platforms and operating systems are no longer supported by their vendors a risk assessment and action may be needed to ensure they can still be operated in a secure manner. In cases were a platform or operating system is no longer supported a review should be conducted to determine if and how the system or operating system can continue to be used. Proposed Change: Removal of line 1230 -1231	
1363-1367		Comment: Clarification of this text is suggested below to improve readability. Proposed change: "Decisions about 'view-period' ~~for participants~~ should be based on considerations regarding risk for bias on data to be entered**.** ~~but also considering that if~~ **If** view of recently entered data is not possible by the participant, then there is a risk that the participant could forget if relevant data have been collected**. This is** – especially **the case** if the planned entry is not foreseeable ~~and~~ e.g., ~~just~~ requires ~~e.g.,~~ input	

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		once daily **and is** ~~but e.g.,~~ event-driven."	
1368		Comment: Clarification of this text is suggested to improve readability. Proposed Change: "Logical checks should be in place to prevent **unreasonable** data changes ~~unreasonable~~ **i.e.,** "time travel" ~~e.g.~~ **such as** going back (months, years back in time) or forth into the future based on the protocol design."	
1380-1382		Comment: There is a conflict in the document related to the definition of source data that needs resolution. The text in the sentence "The data saved in the device are considered source data" is in conflict with the definition in line 378-379 "From a practical point of view, the first obtainable permanent data from an electronic data generation/capture should be considered and defined as the electronic source data."	
1409-1412		Comment: Clarification of this text is suggested to improve readability. Proposed Change: "Data reported should always be reliable. ~~and it is not acceptable that~~ **D**data clarification procedures introduced by the sponsor or vendor**,** whether or not described in the protocol**,** ~~do~~ should not ~~allow for~~ **prohibit** changes in trial participant data when justified e.g. if the trial participant	

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		realises that data has not been entered correctly."	
1547-1558		Comment: This guidance is focused on computerized systems. The text on lines 1547-1558 while important is clearly for paper systems. As such to avoid confusion the text should be removed.	
1593-1595		Comment: It is not clear from the text if this is an absolute requirement for all studies or is dependent on portion of the clinical trial the potential participant is in and the type of study being conducted. Obtaining the consent remotely would be appropriate in specific cases such as for initial consent for pre-screening activities, low interventional trials (under EU 536/2014, Clinical Trial Regulation,) or informed consent amendments or addenda that may not warrant the patient being on-site. Proposed Change: Add the following text after the last sentence on line 1595. "There are instances where remote communication may be acceptable such as for initial consent for pre-screening activities, low interventional trials or for informed consent amendments or addenda that may not warrant the participant being on-site."	
1661-1662		Comment: Based on the wide audience of this document the term "directly" present in the last word of the last sentence many	

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		be unclear, suggest using, "immediately after signing or as soon as practically possible" Proposed Change: "The copy should be available ~~directly~~ **immediately after signing or as soon as practically possible**."	

Please add more rows if needed.