EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<03-Dec-2021>

Submission of comments on ' Guideline on computerised systems and electronic data in Guideline on computerised systems and electronic data in (draft)' (EMA/226170/2021 GCP IWG 10 June 2021)

Comments from:

Name of organisation or individual
Association for Clinical Data Management

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)*
	These comments are provided herewith on behalf of the Association for Clinical Data Management. They have been extensively discussed withing dedicated focus groups, with participation from multiple UK-based and international member companies. They represent the consensus reached within the Association, but not necessarily the views and opinion of every member organisation. If you have any question, please contact ian.pinto@astrazeneca.com, chair of the ACDM.	
	More clarification is needed around the requirement of involving Investigators in the approval and validation of computerized systems. Investigative sites do not routinely have access to technology experts, who are able to drive specifications or audit Cloud and other complex State-of-the-Art systems. Further and more specific guidance will also be needed for Investigator-sponsored versus regular MAA clinical trials by pharmaceutical sponsors.	

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)*
122		Comment: Please consider adding definitions for System vs Software; and Validation vs Qualification. Of note is the previous EMA guidance on this topic, which should be referenced and reconciled with the draft guidance herewith: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf Proposed change (if any):	
174-175		Comment: The definition of Dynamic file formats is not consistent with the FDA one on the same term. "Dynamic" per the FDA and long-standing practice describes the ability to access and analyse study-wide table contents (records, i.e. in SDTM, ADaM, Excel, SAS formats), which is clearly not possible from a certified electronic copy of Case Report Form (line 160). Proposed change (if any):	
341		Comment: Record retention should also be a foundational concept of data integrity.	

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		Proposed changed (if any):	
360-362		Comment: This sentence causes confusion between Metadata and Audit Trails. In current standard practice and literature, metadata is a key ***subset*** of the audit trail. Proposed change (if any):	
363-387		Comment: This section seems to ignore national Privacy restrictions, which prevent Sponsors from having any direct access to electronic health records (EHR, which are in many cases our Electronic Source). Investigators have no legal basis to obtain, review, approve or challenge contractual provisions between their institutions and the EHR software and infrastructure service providers (i.e. Clouds) and the data owners or custodians, which can be States or Regions. Please consider adding guidance on this problem - as recently done by MHRA, FDA and other national regulatory bodies around the world. Proposed change (if any):	
466-467		Comment: Even for smaller trials (let alone multi-country, multi-site ones) it is impossible to trigger protocol amendments for all local system changes (i.e. EHR/EMRs). Kindly consider maintaining this information as site-specific essential records instead. Proposed change (if any):	

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474-475 and 483		Comment: The Data Management Plan is usually a centrally located document, which describes data collection and review activities by the Sponsor. Although we strongly agree that the location of source data, should be part of essential documentation for the sites at all times, please provide a more practical template for this purpose. Proposed change (if any):	
503		Comment: With regards to the sentence – "the identity of the signatory is known in advance or not". We cannot anticipate any situation in a protocol conduct where the originator is not an already known clinical trial participant. Please clarify or provide examples. Proposed change (if any):	
510-512		Comment: As above. In our experience, data originators are always known and authorised before they generate any records or reports. Please provide additional information to help us understand this requirement. Proposed change (if any):	

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521-527		Comment: Could you please clarify how Data Protection section and the "right to be forgotten" will be linked to the new data retention periods? We are looking forward to EMA guidance clarifying the interplay with GDPR. Proposed change (if any):	
538-540		Comment: Please consider rewording for clarity. We recommend aligning this CSV section with established guidelines - or to simply reference them, to avoid conflicting concepts or an impression thereof. Proposed change (if any):	
548-549		Comment: This section seems to imply that Investigators are expected to assert the validation of their computerized system. We have a very hard time imagining that Investigators will be able to actively participate in complex IT tasks. They are system users, not system architects or auditors. In the case of Electronic Health Records and in many European and *Rest of the World* countries, sponsors and their delegates cannot have any direct unsupervised access, as per GDPR. In the case of trusted third parties which are system, technology, platform or service providers, trial-specific validation is routinely provided -- but not the CSV and system architecture, which is considered proprietary.	

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		Proposed change (if any):	
558-559		Comment: it is technologically and financially impossible to assert that multitenant systems of today could be restored back to full operation 20 years from now. There are so many proprietary components to today's systems (source code etc.) that are subject to frequent upgrades, with no possibilities for Sponsors and Investigators to prevent or obtain working copies when the software owners change them drastically or retire them. We hope for a risk-based approach which will allow GCP trial participants to establish how the data and their audit trail will be preserved for legal purposes - i.e. via certified copies. Expecting the original systems, browsers, operational systems, cloud storage etc. to be maintained and available for such long periods is disconnected from reality. Proposed change (if any):	
574-575		Comment: Please clarify which types of systems and study participants should be exempted from that requirement. In the case of eCOA systems for example, basic training is indeed given to trial subjects (patients) but we cannot require "training" and "qualifications" records from them. Proposed change (if any):	

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625-626		Comment: This section seems to describe Certified Copies. If so, please clarify your expectations for long term Record Retention. Proposed change (if any):	
635-636		Comment: Please be more specific about these minimal metadata requirements. Proposed change (if any):	
646-648		Comment: In this section you are limiting the concept of audit trail to computer generated history of modified data points (i.e. CRF entries). What about other components of the clinical trial which are also electronic? (i.e. Protocols and Protocol Amendments in document authoring systems or eTMFs, the Electronic Edit Checks that Data Management Specifies, Data Review listings and their logics etc.). Proposed change (if any):	
675-676		Comment: Although the timing of capturing study observations or events is driven by the protocol and enforced by the computerised systems - which will prevent belated data uploads or will treat them as protocol deviations -- such delays could be triggered by factors that have nothing to do with study participant intent (i.e. network downtimes). In most of our risk assessments, an exhaustive review of those timestamps is never deemed as	

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		a key performance indicator, nor has it ever revealed compliance issues or data fabrication. Proposed change (if any):	
679-680		Comment: Please note that not all systems allow that. For example, when we use SAS to extract data. There is no audit trail, but the programming group is generating a standard form to document the extracts. Another example of non-computerised audit trails are data transfer logs, that are recording import/export events between distinct databases, functional units or companies. We hope that you consider those records as equally critical components of the clinical trial audit trail. Also see comment below. Proposed change (if any):	
686		Comment: "… are in some cases" Proposed change (if any): "… are in all cases"	
691		Comment: This section doesn't provide clarity on how and why we could use audit trail reviews efficiently. Example or major review objectives are not provided (i.e protocol deviations, data fabrication - which are the risks you are expecting us to mitigate via audit trail reviews? Please provide additional clarity on the scope of audit trail reviews and any ramifications to risk-based monitoring, and	

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		allowances for sponsors to take a risk based approach to this piece of work. We hope to avoid sterile reviews of system logs (data dumps) with thousands of records. Proposed change (if any):	
704-705 and 733-735		Comment: Which is the scope and added value of investigators reviewing the audit trail of their own entries? We are concerned with the ethical basis of adding such resource-intensive activities to already overburdened sites. If your concern is unauthorised changes by Sponsors to Investigator data, there are other ways to identify, prevent and capture those. Proposed change (if any):	
724-726		Comment: We hope for more alignment on requirements across regulatory bodies. For example, the FDA requires sign offs only in view of database locks. Proposed change (if any):	
750 - 762		Comment: This section adds to the confusion between certified copies of source data and certified copies of analysis datasets (dynamic data). It is not possible nor	

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		efficient to try to create a copy of the entire EDC system at the level of patient records. Proposed change (if any):	
770-779		Comment: Trusted 3rd party hosted systems, do not allow the sponsor to have exclusive control of the data entered by sites. This wording and expectation for an "independent" investigator copy, which we had seen in EMA reflections in 2010, has not been retained in ICH E6 R2. It was never feasible in any EDC system and is very unlikely to ever become technically feasible. Proposed change (if any):	
807-808 and 811-812		Comment: In current practice, it is unheard off to expect an Investigator or their delegates to "qualify" a cloud. Even large sponsors will need to hire and involve highly skilled engineers, in order to review the portion of the System Qualification that the vendors allow them to review - per signed non-disclosure agreements. Proposed change (if any):	
817		Comment: This is simply not possible nowadays, given how large systems grew. Proposed change (if any):	
823-827		Comment: What is the technology standards source or reference for these recommendations? They seem very disconnected from today's realities.	

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		Proposed change (if any):	
828-830		Comment: "Human readable data" is no longer a secure approach for cloud-based systems, where the raw data are usually encrypted. Proposed change (if any):	
833-835		Comment: The concepts of Back-up and Disaster Recovery, are clearly separated in state of the art on computerized system design and validation. Please split into 2 sections to match current established technology standards and to provide clearer requirements. Proposed change (if any):	
838		Comment: Should Audit Trail also be part of planned data migrations? Proposed change (if any):	
851-854		Comment: Please discern between migration in view of decommission system and migration of data from the source system to analysis reporting repository. Proposed change (if any):	
861		Comment: This section does not take into account nor even mention GDPR in Europe. Proposed change (if any):	

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883-885		Comment: We have no guarantees that components outside the control of data originators or custodians would not prevent integral system recommission - even in a near future. Such "components" are source code of applications, web browsers, internet protocols etc. We support a risk-based strategy, with planned data migrations ("certified/validated copies") in order to meet record retention requirements by the CT Regulation. Proposed change (if any):	
886-888		Comment: please ensure consistency of the terms "dynamic" and "static" record formats. Dynamic record formats allow user interaction and data analysis (i.e. SAS or XML/CDISC datasets). EDC system contents are not "dynamic". This section needs to be re-written in order for us to understand your requirements on decommission and recommission.	
898-900		Comment: None of these requirements could govern EHR systems and contracts, as those systems are not designed with clinical research in mind - albeit they contain Source data. Investigators cannot drive system specifications for EHRs that are owned by their government, state or region. Proposed change (if any):	
904-905		Comment: It is inefficient to link protocol with site specific systems, as it will increase exponentially the need for site-specific amendments. Please propose another essential document template in order to document systems and changes thereof.	

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		Proposed change (if any):	
939-944		Comment: Please consider that this would not be possible for EHRs in certain countries (for instance, in Germany). Proposed change (if any):	
945		Comment: sponsor Proposed change (if any): sponsor or designee	
959-960		Comment: Please clarify that this is not the physical location for cloud systems. (Also covered by GDPR). Logical locations are the current de facto standard. Proposed change (if any):	
961		Comment: We recommend a risk-based approach to establish acceptable methods for data access. Proposed change (if any):	
962		Comment: We agree that a disaster recovery plan and business continuity plan are needed at minimum. Please create a predicate requirement for them. Proposed change (if any):	
982		Comment: Investigators cannot possibly be ultimately responsible for system validation. They can only be accountable for the systems that they select. Proposed change (if any):	

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1006		Comment: Please add reference here about confidentiality disclosure agreements and intellectual property. Proposed change (if any):	
1007		Comment: Instead of full configuration management, we recommend establishing proportionate configuration management against risk and known requirements, with a clear focus on data integrity. Proposed change (if any):	
1011		Comment: The responsible party Proposed change (if any): The responsible party or designee	
1036		Comment: It seems that there is some confusion between responsibility and accountability throughout this document. URS can be created by a service provider, and the sponsor would review and approve. Proposed change (if any): The Sponsor/Investigator or Designee	
1101		Comment: Please clarify when defects become serious breaches Proposed change (if any):	
1104-1105		Comment: We recommend moving this concept to the top of the annex.	

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		A validation report is providing evidence that the system is ready for production release. This implies a risk management approach, which we strongly support. Proposed change (if any):	
1121		Comment: Please add to this list: new requirements, new system intended usage. Proposed change (if any):	
1151-1155		Comment: Please clarify the periodic nature of these reviews. At minimum, the process must describe review intervals and triggers in order to manage user access and guarantee data integrity. Proposed change (if any):	
1163		Comment: Audit trails must not be modified; this example is confusing. Please consider replacing the word "edit" (i.e., by the word "corrupt" or "alter"). Proposed change (if any):	
1182		Comment: Logical security should be part of CSV for each critical system component. It could then warrant distinct validation efforts for each such system node or element. Security measures (i.e. user access reviews, firewalls, patches, antivirus) however, can be implemented across all components of a given infrastructure.	

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		Proposed change (if any):	
1202		Comment: This whole section implies use of archaic systems and processes. Cloud and rack computing create no risk for physical unauthorised access by competitors - the risk of hacking or data breaches is much more realistic. Proposed change (if any):	
1215		Comment: Please clarify the scope of this section and define your recommendations (or assess impact on known regulatory references and technology standards). Proposed change (if any):	
1232		Comment: Beyond software, every system component must have the same security measures in place. Proposed change (if any):	
1240		Comment: This is just one form of logical security. We recommend merging with section 4.1 for improved readability. Kindly consider also covering social engineering and phishing. Proposed change (if any):	
1247		Comment: As above, please consider merging section into 4.1 Proposed change (if any):	

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1255		Comment: As above, please consider merging section into 4.1 Proposed change (if any):	
1272		Comment: Multifactor authentication would be recommended upon criticality of data risk assessment Proposed change (if any):	
1274		Comment: Please define what you mean by Remote Authentification and address the repetition in the title? All system connections will basically be "remote" and "authenticated". Proposed change (if any):	
1336-1337		Comment: Please clarify this statement. Do you expect the coded and verbatim entries to be maintained? (systems largely impose this already). Proposed change (if any):	
1349-1353		Comment: This section does not provide any additional guidance compared to pre-existing regulatory requirements or reflections. Proposed change (if any):	

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undermine 1356-1358		Comment: ePRO usually employs scientifically/psychometrically validated data collection instruments - which are protected by copyright in all languages used and must remain comparable across studies and development projects. Involving site staff and trial participants may sound tempting but will invariably hurt the validation and comparability of ePRO instruments. Proposed change (if any):	
1362-1363		Comment: Therefore, the length of time that data are viewable by the participant should be considered when designing the EDC tool Proposed change (if any): Therefore, the length of time that data are viewable by the participant should be considered when **configuring** the EDC tool	
1363-1367		Comment: Investigators have access to the entire history of patient entries both via the ePRO system and via the transcript to the EDC system. In current ePRO implementations however, the patient does not have such access - not because of technical restrictions, but in order to collect unbiased patient responses. Direct access to patients of their entire history of PRO records in one or more clinical trials, would then undermine the psychometric validation of ePRO standard copyrighted instruments. Moreover, it will have uncontrollable consequences to the Privacy Impact Assessments (PIA). Proposed change (if any):	

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1385		Comment: It should be clarified subject responses must never be "corrected" (unless by the subject themselves at the time of entry); such corrections are only acceptable on metadata (i.e. visit ID, response date if erroneously captured or derived etc.) Proposed change (if any):	
1393		Comment: Important actions .... Proposed change (if any): All actions	
1407-1408		Comment: Please clarify how patient should initiate the process of changing data. If this is limited to metadata, this needs to be better described. Proposed change (if any):	
1417-1418		Comment: Please clarify and substantiate concerns around data fabrication by sites on patient questionnaires. That said, forcing the patient to become a signatory/formal data originator is neither practical nor reasonable. Proposed change (if any):	
1449-1450		Comment: Please rephrase and clarify. In our experience, Clinician Reported Outcome requirements should not differ from other CRF/EDC original entries. Proposed change (if any):	

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1495-1497 and 1501-1503		Comment: Please provide additional clarity on ramifications with Informed Consents and GDPR. Proposed change (if any):	
1541		Comment: The process for emergency unblinding should be tested. Proposed change (if any): The process for emergency unblinding should be tested. A back-up process needs to also be present in case the online-technology emergency unblinding is unavailable.	
1563		Comment: Please reword and clarify- do you mean "Feed" when you talk about "Seed"? Proposed change (if any):	
1615		Comment: General comment for this section (Annex 5.3). How does this section differ from earlier guidance by the EMA on ICF and eICF? Proposed change (if any):	

Please add more rows if needed.