EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 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
ACRO (Association of Clinical Research Organizations)

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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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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)*
	The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our fourteen member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support the majority of all biopharmaceutical sponsored clinical investigations worldwide. With more than 200,000 employees, including over 60,000 in Europe, engaged in research activities in 114 countries the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. ACRO welcomes the opportunity to comment on the draft European Medicines Agency (EMA) guideline on computerised systems and electronic data in clinical trials. This is an important guideline that has been long-awaited by the stakeholder community, given the increased use of electronic systems in clinical trials over the last 10 years. In addition, the disruption caused by the COVID-19 pandemic highlights the increased	

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	urgency for the finalisation and release of this guideline. Specifically, the pandemic has compelled stakeholders in clinical research to consider new, innovative approaches to trial design and conduct that increasingly leverage electronic systems. The digitization of clinical trials began well before the COVID-19 pandemic – from recruitment and retention to electronic consent, and the use of mobile technologies such as sensors and wearables. The disruption caused by the pandemic is expediting and necessitating the embracing of digital innovations and solutions including but not limited to decentralized clinical trials; utilization within trials of patient devices (sensors, wearables); [remote] eConsent; and remote and centralized monitoring (including source data review / verification and remote review of investigator site files). Finalisation of this new guideline should therefore aim to provide stakeholders with assurance and confidence that innovative approaches being developed and adopted during these times will have longer-term applicability. Moreover, we hope that the release of the guideline will help to ensure that EU/EEA is viewed globally as a region that constructively and innovatively promotes and supports the wider utilization of advanced technology-based solutions for clinical research. Now, more than ever, it is important for guidance to keep pace with technological innovation.	

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	That said, there are a number of important practical issues around the use of computerized systems in clinical trials that are not addressed in the draft guideline. We strongly recommend that guidance on the following topics is added to the final version: • Enabling risk-proportionate remote source data review (rSDR) and source data verification (rSDV): European data protection laws are sometimes interpreted by member states as precluding remote SDR and remote SDV in the EU, even under exigent circumstances. ACRO emphasizes that it is important to distinguish between source data review and source data verification. While SDV focuses on identification of transcription errors, SDR is in many ways the more significant value-added activity because it enables verification of subject eligibility, safety and protocol compliance. Source data review is crucial because of the history in patient notes, which is so important. This is an important issue for ACRO member companies and, in order to facilitate the use of rSDR and rSDV in Europe, ACRO recommends that guidance is added that specifically assures stakeholders that remote review of unredacted data for purposes of	

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	source data review or source data verification (SDR/SDV) is permissible on the grounds of compliance with a legal obligation to which data controllers (sponsors and/or clinic-institution of the investigators/investigators) are subject under the requirements of GCP, encourages EU/EEA-wide agreement to the use of common monitoring and risk management plans incorporating rSDR and rSDV across all Member States, and stresses that remote monitoring and rSDR/rSDV must not result in confidential patient information being sent to the sponsor/CRO or being stored by the sponsor/CRO if this has not already been addressed in the participant information sheet. • There is no discussion of the process and documentation for uninstallation of applications or software installed on BYOD devices for the conduct of clinical trials at the conclusion of the study. We also noted that the draft guideline references GCP Q&As published on the EMA website. These do not have the same level of stakeholder input as this guideline in that the guideline is subject to public consultation before finalisation whereas the GCP Q&As are not. It	

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	would be very helpful if EMA could implement a mechanism to notify stakeholders of draft content for updates to the GCP Q&A page and provide a brief consultation period for input and feedback from stakeholders before finalization of the content. It would also be helpful to offer stakeholders a mechanism to propose specific new topics for inclusion on the GCP Q&A page. Additionally, we note that in several places the guideline emphasises that electronic capture of informed consent is acceptable only "when this is allowed according to national legislation." National legislative requirements on this are not always obvious and identifying which member states will/will not allow the electronic capture of consent creates a significant administrative burden for clinical trial sponsors. Consequently, we strongly recommend the inclusion of an appendix to the guideline that identifies the Member States that allow/do not allow electronic capture of informed consent. The lack of a harmonised EU position on this contrasts with the situation in other parts of the world where clinical trials are commonly conducted and adds to the burden and complexity of performing clinical trials in the EU. We therefore urge Member States that do not allow electronic capture of informed consent for clinical trial participation to consider changes to their	

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	legislation in order to improve the competitiveness of the EU and the perception of the EU/EEA as a region that constructively and innovatively promotes and supports the wider utilization of advanced technology-based solutions for clinical research. In this context, while we acknowledge that the guideline is designed to ensure GCP compliance and the maintenance of data integrity, it is disappointing that the opportunity has not been taken to use the guideline as a means to welcome and promote the use of innovative technologies to facilitate patient access to clinical trials and reduce the administrative burden on all stakeholders involved in clinical trials in the EU. The draft guideline, as currently written, does not reflect the aims of the EU Pharmaceutical Strategy to establish a competitive and resource-efficient EU pharmaceutical industry that can better respond to patients' needs. As noted in the European Commission's Communication of 25 November 2020 on the Pharmaceutical Strategy for Europe, the strategy draws on the digital transformation of health and care, driven by technological advances. It is our view that a major refocusing of the guideline is required in order to demonstrate its support of the EU Pharmaceutical Strategy's aims to support competitiveness, innovation and sustainability of the EU's pharmaceutical industry and enable new methods	

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	of evidence generation and support more patient-oriented design, planning *and conduct* of clinical trials (our italics). In revising the draft guideline, we strongly recommend that attention is paid to its presentation and useability. In order to be effective, its recommendations need to be more concisely and clearly stated. Computer validation has been practised for many years and international standards are now available (e.g., ISO 13485:2016). We believe the guideline text could be reduced considerably by replacing text on validation with references to appropriate international standards. We also strongly recommend that the final guideline should focus on principles rather than proscriptive and detailed requirements, as there are often different ways of achieving the same goal. Currently, the draft reads as if each section has been written by a different author and a thorough review is needed to ensure a concise, consistent style with alignment of terminology and recommendations throughout the document. We noted especially that, although the terms Qualification and Validation are defined within the document, the use of these terms throughout the document does not seem to be always consistent with the definitions. e.g. line 506 'The electronic signature functionality in these systems should be proven during system qualification to have	

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	the qualities mentioned above.' We would expect that validation would be required for an electronic signature system. As mentioned within the definition, qualification is part of validation, but it is often considered a less rigorous activity then validation. Commonly, qualification is the activity performed for a platform to ensure it is installed correctly and operating as required, while validation would encompass all of the activities necessary to ensure a computerized system is fit for purpose and is properly maintained throughout the system lifecycle Additionally, our member companies are reporting that some member state GCP inspectors are already referencing the draft guideline during inspections. This is completely inappropriate prior to completion of the public consultation and the issue of a final agreed guideline, and we urge the EMA to work with member states to stop this practice. Finally, we recommend that the EMA "future-proof" this guidance as much as possible, in alignment with the key aims and objectives of the EU Pharmaceutical Strategy. The European Commission "Combined Evaluation Roadmap/Inception Impact Assessment" for the EU Pharmaceutical Strategy (available here: https://ec.europa.eu/info/law/better-regulation/have-	

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	your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en) discusses the importance of "future-proofing" at many points in the document. A handle of examples are included here. ACRO believes it is vital for the Final Guidance to explicitly support the broader objective of the EU Pharmaceutical Strategy *"to make the European pharmaceutical system patient-centred, future-proof, and crisis-resistant."* On page 1, the document states: *The strategy is an ambitious, long-term project in the area of health. It is intended to make the European pharmaceutical system patient-centred**, future-proof** and crisis-resistant. The development and supply of medicines is a global operation. The EU pharmaceuticals system should ensure the quality and safety of medicines, while boosting the sector's global competitiveness and creating a regulatory environment, which is attractive for innovation and investment and supported by international harmonised standards and, where possible, regulatory convergence. As such, the strategy is a key pillar of the Commission's vision to build a stronger European Health Union [emphasis added].* On page 4 of the document, the Commission states— *Introduce elements of flexibility that allow **future proofing of the legislation** through adaptability to the new innovative ways medicines are developed and evidence is generated. This should take into account new possibilities in areas such as digital and personalised medicine and the interplay of medicines*	

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	and medical devices. Options shall consider adaptations to the current system of authorisations, the possibility of new regulatory pathways, the possibility to change the scope of the centralised application procedure for innovative products, as well as other adaptations of the regulatory requirements including for medicines containing GMOs [emphasis in original] On page 5, the document states— *The economic benefits to the European pharmaceutical sector in terms of reduction of administrative burden will be further enhanced through the **future-proofing** of the legislation and new possibilities for accelerated product development. Regulatory flexibility to use improved evidence generation techniques throughout the lifecycle of a medicine through the possibility to use real word data and artificial intelligence (AI) applications for evidence generation with the possibility to adjust decisions based on new evidence. SMEs stand to gain most from a simplified regulatory system and flexibilities related to modern developments. Start-ups and small companies are often responsible for basic R&D and are expected to benefit from a simpler regulatory environment [emphasis added].*	
	Finally, we note that the use of digital technology in clinical trials is expanding and developing rapidly. This is a very fast-moving field and we recognise the difficulty for regulatory staff in keeping up with	

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	developments. It is particularly difficult to keep up with the sophisticated capabilities and digital controls that safeguard data integrity and data accountability (for example, to ensure that data transmitted from a sensor or wearable is being transmitted from the actual trial participant). These safeguards exist but are not well understood by all stakeholders. ACRO would therefore like to propose the establishment of a regular forum for discussion involving experts from technology companies, CROs, sponsors and members of the EU regulatory network to provide awareness of technological developments and to aid the development of the necessary skills and understanding in the EU regulatory network. The continual advances in the sophistication of digital technology warrant establishing an annual, dedicated EMA meeting with industry – similar to the annual "Pharmacovigilance Platform Meetings" – to enable EMA to regularly hear from Industry experts with deep technology expertise	

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)*
122-237		Comment: The Glossary and Abbreviations sections cover a good list of abbreviations and definitions but for completeness we recommend further additions, as indicated below. The final guideline should ensure that all relevant definitions are aligned with the forthcoming revision (R3) of the ICH E6 guideline. Proposed change (if any): Addition of OQ (Operational Qualification) to the abbreviations and of definitions (aligned with respective legislation, where applicable) for Decentralised clinical trial (DCT), Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), Verification, Computerised System (e.g., "computer infrastructure, hardware, software or service and associated artifacts (e.g., manuals, SOPs) that create, modify, maintain, archive, retrieve, transmit information related to the conduct of the clinical trials in a digital form"), Computerised System types (e.g., cloud computing vs. on-premises software), Infrastructure as a service (IaaS), PaaS (Platform as a service), Software as a service (SaaS), Commercial off-the-shelf (COTS), User Requirements Specification, Functional Requirements Specification, Serious Adverse Event (SAE), Data and Safety Monitoring Board (DSMB), electronic Patient Reported Outcome (ePRO),	

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		Institutional Review Board and Independent Ethics Committee (IRB and IEC), and Notified Body.	
124-126 and 137-140		Comment: The definition of "data" for purposes of the guideline stated in lines 124-126 differs from that stated in lines 137-140. Proposed change (if any): Ensure alignment throughout the guideline.	
127-128		Comment: We recommend that the final guideline should make clear that vendor/supplier direct compliance obligations under the guideline pertain solely to those trial-related duties which the vendor/supplier has specifically assumed under a written contract with the sponsor. Proposed change (if any): Revise the text to read as follows: "All references to a sponsor in this guideline also apply to a contract research organisation (CRO), and to suppliers/vendors to the extent to which the suppliers/vendors have entered into a contract with the sponsor or CRO to assume specific trial-related duties and/or functions of the sponsor that have been specifically delegated to them."	
154-156		Comment: The definition of CRF is verbatim per ICH GCP.	

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		Proposed change (if any): Add an additional statement to clarify that the reference to 'electronic' document is inclusive of other electronic data capture systems such as ePRO, systems used to derive data directly from electronic health records and any devices used to collect clinical data to report to the sponsor.	
166-168		Comment: For clarity, we recommend use of an alternative definition of data governance that provides more details. Proposed change (if any): Replace the definition with "The total of activities, processes, roles, policies and standards used to manage and control the data during the entire data life cycle."	
172-174		Comment: Dynamic data allows interaction between the user and record content. However, spreadsheets that have been validated will have fixed calculations. A system that provides "automatic processing" is typically validated and is not the same as interactivity of the resulting electronic record / data. Also, once data is reported it becomes static because interaction should no longer be possible. Proposed change (if any): We recommend replacing the sentence with the following: "Dynamic data allows interaction between the user and the record content. For example, electronic records in database formats allow the user to	

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		track, trend and query data; chromatography records maintained as electronic records allow the user or reviewer (with appropriate access permissions) to reprocess the data and expand the baseline to view the integration more clearly."	
180-181		Comment: The requirement for pages in notebooks to be numbered will be very difficult to enforce in practice. Proposed Change: Remove the reference to notebooks.	
201-206		Comment: The User Requirements Specification (URS) is a planning document, created when a business is planning on acquiring a system and is trying to determine specific needs. When a system has already been created or acquired, or for less complex systems, the user requirement specification may be combined with the functional requirements specification. This is consistent with the International Society for Pharmaceutical Engineering (ISPE) GAMP 5 document: A risk-based Approach to Compliant GxP Computerized Systems. It would be helpful to include text to this effect in the guideline. Proposed change (if any): Add "When a system has already been created or acquired, or for less complex systems, the user requirement specification may be combined with the functional requirements specification."	

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		Regarding Line 205 specifically: Traceability to specification - Grouping of requirements should also be allowed. Leveraging of a Computer Software Assurance (CSA) approach and User Acceptance Testing (UAT) where groups of requirements or specifications could be verified as part the verification of an entire process or function.	
237 and 977		Comment: Typographical error. Proposed change (if any): Under COTS, change "commercial of the shelf" to "commercial off the shelf".	
249-254		Comment: We strongly recommend that the Introduction to the guideline should note the need to ensure the use of computerised technology in clinical trials does not disadvantage or reduce access to clinical trials for those participants who are unable or unaccustomed to use the technology. Proposed change (if any): Add the following text: "The use of electronic methods may unintentionally discriminate against people who are not comfortable with or who cannot use such technology, and this could introduce bias into the clinical trial. Alternative methods for provision of information and documentation should be available for those unable or unwilling to use electronic methods."	

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255-302		Comment: The Scope section defines a list of computerised systems used in the conduct of clinical trials but lacks clarity around categorization. We recognise that systems often have elements of various different categories and therefore the categorization alone cannot be used to drive the decision for the required activities, and we recommend that this is stated in the final guideline. Proposed change (if any): Align the guidance with the (ISPE) GAMP 5 guide on Compliant GxP Computerized Systems and with relevant medical device terminology (instruments, machines, apparatus etc.) where appropriate and ensure consistency on use of the terms products, systems, tools, and devices throughout the guideline. Also, add text to make clear that systems often have elements of various different categories and therefore the categorization alone cannot be used to drive the decision for the required activities.	
256 and 294		Comment: Line 256 defines the scope as "computerised systems, (including instruments, software and services)" whereas Line 294 refers to "computerised systems and medical devices". Proposed change (if any): Ensure consistency on use of terms throughout the document.	

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269-271		Comment: The term eSource is becoming widely used. A definition for eSource vs eCRF may be useful for all to understand when source data is directly entered into an electronic tool. eCRFs can then be transcribed data or data transferred from other sources. Proposed change (if any): Add a new bullet point in 2. Scope "eSource e.g., desktop or mobile device-based programs or access to web-based applications, which contain source data directly entered" and remove this aspect from the 'eCRF' bullet point.	
280		Comment: Electronic capture of informed consent is acceptable only "when this is allowed according to national legislation." National legislative requirements on this are not always obvious and it would be extremely helpful to stakeholders to include an appendix to the guideline that identifies the Member States that allow/do not allow electronic capture of informed consent. Proposed change (if any): Include an appendix to the guideline that identifies the Member States that allow/do not allow electronic capture of informed consent.	
285-287		Comment: The systems that exchange information with the sites may not be Sponsor portals.	

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		Proposed change (if any): Revise the text to read: "Systems/ applications for supplying information from/ to the Sponsor and Sites,"	
295-298		Comment: The current text could imply that computerised systems are less reliable in producing data, and therefore their use to generate primary efficacy data is discouraged. We therefore recommend rewording the sentence "The risk-assessment should consider ….. of derived clinical trial data" as indicated below. Proposed change (if any): Replace the sentence with "The risk assessment should take a holistic approach to identify and assess all potential risks relevant to system use for the safety of the participant and the integrity of derived clinical trial data."	
299-302		Comment: This sentence is confusing and seems to imply that only medical devices used in the setting approved by a notified body may not require in-depth validation. More explanation is needed as to what forms a critical/less critical system and validation expectations for computerised systems that are not approved as medical devices. We also recommend adding examples to help with clarity and understanding and suggest, as a minimum, that examples are given for the following: (1) 'well-established computerized systems', (2) when 'certification by a notified	

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		body' would suffice, (3) what constitutes a 'notified body'. We also recommend that the phrase "justified pre-trial" is clarified to indicate whether this means prior to implementation of the trial specific configuration or prior to protocol approval. Proposed change (if any): Provide more explanation as to what forms a critical/less critical system and validation expectations for computerised systems that are not approved as medical devices, include examples and clarify the meaning of "justified pre-trial".	
329-331		Comment: "Traceable" is added to the ALCOA ++ list, which is notable because the MHRA guidance on GxP Data Integrity (March2018) adds "Available" to the same list but does not specify traceability. While the concept of traceability is not new, the draft guideline could here be construed as emphasizing the need for traceability at the expense of availability. However, section 4.5 specifies both traceability and availability. Proposed change (if any): Align the text and expectations throughout the guideline.	
337		Comment: The scope for data changes should be clarified, e.g. it is not clear whether this applies only to changes to the source data or also includes post-processing such as	

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		normalizing laboratory values for analysis. Proposed change (if any): Clarify the scope for data changes.	
341-342		Comment: Expectations for data integrity in cases where the vendor decommissions the system prior to the end of the record retention period should be clarified and the documentation to be retained made clear. Proposed change (if any): Add text to confirm that, in the event that a Sponsor/CRO contracts with an IT service provider, any continuous access by sponsors is the obligation of the Sponsor/CRO unless agreed to specifically in the vendor agreement, and that the need for continuous access may be met by offline copies of records, in particular following trial completion and decommissioning of applicable computerized systems.	
355		Comment: The section is headed "Electronic Data" whereas the Index (line 29) states "Electronic Data and Documents". Proposed change (if any): Align section heading and Index.	
367		Comment: For clarity, it would be helpful to insert an additional sentence after "laboratory notes". Propose change (if any): Add "This guidance is not intended	

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		to displace relevant guidance on validation of hospital EHR systems.”	
368		Comment: We recommend adding the following to the list of examples. Proposed change (if any): Add “raw data files generated from equipment”.	
376-377 (Figure 1)		Comment: Figure 2 clearly indicates that the data on the central server is the source data but there is no such indication in Figure 1, although there is wording associated with the 'Reported results' that indicates that this is often incorrectly regarded as the source data. Proposed change (if any): Amend the text within the boxes to indicate the source data.	
381 (Figure 2)		Comment: The requirement that the source data contains the full metadata creates a risk of site staff entering Personal Health Information (PHI) data in the audit trail and the audit trail then not allowing removal of the data from the certified copy transferred to the Sponsor. Proposed change (if any): Include text to confirm that the audit trail metadata should not contain personal health information.	

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384		Comment: Figure 2 indicates that data on an electronic device such as an ePRO or wearable is only temporary storage until pseudonymised data is uploaded to the central server where permanent storage is achieved and then considered as source data. This implies that retention of these devices is not required after the relevant data have been uploaded. Proposed change (if any): Provide additional clarification to confirm that ePRO and wearable devices are not considered permanent repositories of source data and so do not need to be retained.	
394-396		Comment: The definition of Legible is " Data should be maintained in a readable form to allow review in its original context. Therefore, changes to data, such as compression, encryption and coding should be completely reversible to facilitate this." We agree that one approach to ensure legibility should compression, encryption or coding be required would be to ensure there is a process to reverse these activities. However, another approach that is often used is to maintain the original data. Proposed change (if any): Include text to confirm the use of multiple approaches to ensure legibility is acceptable.	

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401-402		Comment: The automatic capture requirement would need to be applied across each system and vendor in use for a study and be documented centrally in trial documentation. Additionally, section 4.5 states the time captured should be linked to an external standard such as UTC. However, for the electronic signature the time is noted to be logged with the signature's time zone and not UTC. In section A4.17 again it is noted to have a standard of UTC. Taken together, the expectations for recording time are unclear. Proposed change: Align the text and expectations throughout the guideline.	
404-405		Comment: It would be helpful to confirm that the phrase "Certified copies can replace original data" means that the original data can be discarded once the certified copy is created. Proposed change (if any): Include text as above.	
459-460		Comment: It is not clear what is meant here. If, for instance, the aim is for on-going effective assessment of mitigations to determine the most effective and efficient risk-based control, we recommend that this is stated explicitly. Proposed change (if any): Add text as above.	

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464-469 and 477		Comment: The level of detail required to define the tools/procedures is not clear, e.g. whether there is a need to specify the vendor who will supply the ePRO tool or simply state that the data will be collected via ePRO. Proposed change (if any): Provide examples of the level of detail required to define the tools/procedures.	
471-473		Comment: This sentence does not recognize the role of Site Management Organizations in clinical trials. Some technology may also capture data other than data explicitly listed in the protocol when the technology is supporting Site Operations. Data necessary to use the technology, such as participant name, email address and telephone number may be required to interact with the participant if the technology is functioning as site support technology. Proposed change (if any): Revise the sentence to read as follows: "Tools used to generate, capture, transfer, manipulate, or store data should be configured to capture and transfer only the minimum data required to manage the clinical trial effectively as described in the protocol."	
480		Comment: The level of detail required to document format is not clear, e.g. whether a statement of file type is sufficient or data types/values should be documented in a similar way to a data transfer agreement.	

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		Proposed change (if any): Add text to confirm that, while full details of document format may be documented elsewhere, the protocol may specify document formats using a generic term (e.g., pdf).	
484-485		Comment: As written, this sentence would prevent CROs and other third parties from functioning in site support functions, such as performing home health nursing, participant education, or offering technology support through a help desk. These are all legitimate business functions that utilize technology that will collect data required to effectively and efficiently run the study in the capacity in which the CRO is functioning, with appropriate processes and safeguards to separate CRO and Site Operations functions. As an example, a help desk employee of a CRO or third party may access the name, phone number, and country of residence of a study participant when answering a participant request for technology support, or a home health nurse employee of a CRO or third party may access the participant name and address in order to reach the home of the participant. Proposed change (if any): Revise the text to read as follows: "Any data generated/captured and transferred to the sponsor that is not stated in the protocol or related documents is considered GCP-noncompliant. Any system that generates/captures and transfers data to a CRO beyond the	

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		minimal data necessary to perform the protocol-related tasks delegated to the CRO by the sponsor or the site is considered GCP non-compliant, and the data generated/captured and transferred in excess of the minimum data necessary is considered GCP non-compliant."	
507		Comment: We recommend the addition of more information on expectations for the validation of eSignature functionality. Proposed change: Add text to confirm that it is appropriate for the sponsor to rely on the supplier's validation report.	
510-512		Comment: The EU Electronic Identification and Trust Services (eIDAS) Regulation EU No. 910/2014 is adopted on the basis of Article 114 of the Treaty of the Functioning of the European Union and is intended to ensure the approximation of national laws and the achievement of the objectives of the EU internal market. In particular, the eIDAS Regulation aims at the approximation of laws governing EU Member States' rules governing electronic identification schemes and trust service providers. The eIDAS Regulation does not, however, apply or even refer to the rules governing the conduct of clinical trials in the EU, nor does Regulation (EU) No. 546/2014 refer to the eIDAS Regulation to provide any basis to require the use of an eIDAS-compliant system in the context of a clinical trial. Additionally, it is impractical to expect (and therefore to state the need for) compliance with	

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		the eIDAS Regulation. There are two reasons for this: (1) eIDAS requires a qualified e-signature and there are currently over 40 qualified e-signature system providers (with different systems) operating in the EU that, depending upon the member state, a sponsor may need to work with. This would add significantly to the complexity and administrative burden for sponsors operating in the EU, and (2) if a clinical trial, or part of a clinical trial, is performed outside the EU and its results are used for regulatory purposes in the EU, it is not appropriate to expect compliance in third countries with a specific EU regulation that could potentially conflict with local law. Rather, the final EU guideline should set out an internationally accepted approach for the use of qualified e-signatures in an open system. Proposed change (if any): Replace the reference to eIDAS with internationally accepted principles on the use of e-signatures and verification of the signatory for clinical trial purposes.	
513-514		Comment: We are concerned that the guidance regarding the "hashcode" and enforcing the participant wait time will end hybrid eConsent use by print-to-sign sites, as this will necessitate that sites print only after the participant and the person taking consent have reviewed the document together. This is time-consuming and many clinical trial sites do not have printers available at the consenting site. In a worst case	

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		scenario, there may simply be no printer on the ward or near the consent site. If the consent would be taken remotely, certainly we cannot expect for participants to print the consent themselves. Additionally, alternative methods such as QR code or barcode can improve efficiency and convenience. Proposed change (if any): State explicitly in the final guidance that two copies of the document for each expected participant may be printed prior to the informed consent discussion and be available in the patient files during the visit so that they can be signed after the interactive review on the computer system is finished, and that other methods such as QR code or barcode may be used. In the event when the consent is taken place remotely, to allow electronic signature to minimize burden to participants and sites.	
515-516		Comment: Some systems are not capable of providing an unbreakable link between the electronic record in the computerised system and the signature page on paper. Proposed change (if any): Include examples of how this can be achieved.	
521-536		Comment: We recommend that the guideline should note the need for the sponsor to ensure that the technology used is compliant with the requirements of Regulation (EU) No.	

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		2016/679, including, without limitation, that system architecture does not frustrate the exercise of data subject rights and is configurable to allow for data minimization of both data collection and access to data. We also recommend the final guideline should confirm that Personal Identifiable Information (PII) should be encrypted at rest. Proposed change (if any): Add appropriate text.	
524-528		Comment: The following sentence is incorrect: "The requirements of Regulation (EU) 2016/679 (General Data Protection Regulation) on the protection of individuals with regard to the processing of personal data and on the free movement of such data should be followed except when specific requirements are implemented for clinical trials e.g. that a trial participant does not have the right to be forgotten (and consequently data deleted) as this would cause bias to e.g. safety data (Regulation 536/2014 recital 76)." It is always necessary to follow the requirements of Regulation 2016/679 and perform the assessments described in it to determine if an exception to the data rights request may be exercised by the data controller in order to retain the data despite the request. Other conditions also apply. Proposed change (if any): Revise the text to read as follows: "The requirements of Regulation (EU) 2016/679 (General Data Protection Regulation) on the protection of individuals	

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		with regard to the processing of personal data and on the free movement of such data should be followed. Should a trial participant request the deletion of data, the data controller should assess whether the request should be granted. The bias to the study data that approval of such a request would cause is recognised as grounds for refusal in Regulation (EU) No. 536/2014 recital 76."	
528-529		Comment: As noted above, should a trial participant request the deletion of data, the data controller should assess the request in order to determine if there are grounds for refusal as deletion would cause bias to the study data. It would be good practice to highlight this restriction in any informed consent information. This conflicts with the sentence "Trial participants should not be asked to waive their rights by informed consent processes", which should therefore be rephrased to ensure the position is presented accurately. Proposed change (if any): Amend the text as appropriate.	
530-531		Comment: The sentence "In accordance with Union data protection legislation, the location of personal data processed (both at rest and in transit) must be within the EU/EEA" is inaccurate. Specifically, the use of the word "must" in line 532 contradicts the ability to use adequacy decisions, appropriate safeguards or derogations to facilitate data transfer. As subsequently stated in the draft guideline,	

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		personal data may be exported from the EU provided the conditions laid down in Regulation (EU) No. 2016/679 are met. Proposed change (if any): Revise the text to read as follows: "In accordance with Union data protection legislation, the location of personal data processed (both at rest and in transit) must be within the EU/EEA or within third countries that have suitable safeguards, or otherwise made subject to adequacy agreements or other measures in compliance with the provisions of Union data protection legislation."	
535		Comment: The word "place" is omitted. Proposed change (if any): Revise the text to read: "… or the transfer may take place only if a derogation…"	
537-554		Comment: This section does not address the need for ongoing validation. Proposed change (if any): We recommend adding that a risk-based assessment should be performed whenever a new version of the computerised system is released.	
542-545		Comment: The current sentence is misleading in that the system owner, while responsible for all aspects of validation, may rely on third party experts to determine the actual	

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		processes used for validation. Proposed change (if any): Revise the sentence to read "The system owner (e.g. sponsors, investigators, technical facilities) is accountable for the processes selected for the validation. These processes should be fully documented."	
555-559		Comment: The draft guideline does not address access expectations (including training on the system, where appropriate) for regulatory inspectors. We recommend that this information is added. We also recommend that any direct access to IT vendors by a regulatory body or auditor in respect of a specific clinical trial or trials should be addressed by a request made to the sponsor or CRO, as opposed to a direct request to the IT vendor. We further recommend that the guideline should clarify that providing inspectors direct access to computerized systems does not remove the requirement for the inspector to accept an End User License Agreement to establish agreed use of the computerised system. Also, after a system is decommissioned it is no longer available for normal user access but re-enabling of the system would be required and it would be helpful to address expectations for re-enabling access during inspections. Proposed change (if any): Add text on access expectations for regulatory inspectors, including use of a "guide" when the technology is such that an inspector cannot access or	

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		navigate the system without training, requests for access to IT vendors, the need for acceptance of an End User Licence Agreement by inspectors, and confirmation that re-enabling access to decommissioned systems will not be required when offline copies of records have been retained following trial completion and decommissioning of applicable computerized systems.	
563-569		Comment: The recommendations are appropriate for investigator and sponsor/CRO computerised systems but do not address "bring your own device" (BYOD) use. Proposed change (if any): Add text the following text to address best practice for BYOD use: "It is recommended to "containerize" the applications on BYOD devices by using a mobile device management or container apps to separate and secure a portion of the BYOD device from the rest of it."	
571-572		Comment: The guidance specifies "SOPs", which may hinder flexibility to maintain written procedures in other forms. We also recommend that it is important to clarify that these procedures should be controlled and maintained at a central location. Proposed change (if any): Replace the text with the following: "Written procedures (e.g., SOPs, Work Instructions, job aids, etc, as applicable) should be in place.	

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		These procedures should be controlled and maintained at a central location."	
577-578		Comment: The reference to Annex 5 should also include the section on Electronic patient reported outcome (ePRO). Proposed change (if any): Revise the text to read "Special considerations should be considered regarding training of trial participants where they are users (see also Annex 5, sections A5.1.1 and A5.3)."	
583-584		Comment: Training of developers of technology does not apply to a single clinical trial and therefore is not appropriately filed in the investigator or sponsor TMF. However, we recommend that the final guideline should recognise that the sponsor should be responsible for ensuring such training records are available. Also, it is not clear if this statement includes training for trial participants. Again, it may be appropriate for participant training records to be stored directly within participants' accounts in the system itself rather than in the site file/sponsor TMF. Assuming that participant training records are excluded from this statement, we suggest revising it for clarity. Proposed change (if any): Replace the sentence with "All such study-specific training for study staff on the use of the technology should be documented and the records retained in	

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		the appropriate part of the investigator or sponsor TMF. Documented training records for trial participants should be retained in the TMF or within participants' accounts in the training system. The sponsor is responsible for ensuring that training for those involved in developing, building, and managing trial-specific computerised systems is documented, and the records retained by the system developer."	
585 and 1145		Comment: Guidance on security related to User Accounts is missing from these sections, nor are off-boarding procedures addressed. Proposed change (if any): Add text to confirm that offboarding procedures should exist to ensure system access is revoked when individuals leave an organisation, and add text to line 585 that notes it is important to ensure User Accounts are secure and managed by the appropriate Administrator, and refer to Annex 3, which should include appropriate access controls.	
589		Comment: We recommend the addition of text to confirm that user access checks should be regularly performed. Proposed change (if any): Replace "Checks…." with "Regular checks…."	
593-594		Comment: For certain groups that maintain the computer	

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		system, a common group identification code/password may be established. To cover this scenario, it would be helpful to clarify the need to protect and not to share passwords to individual accounts. Other regulations do not prohibit the establishment of a common group identification code/password for read-only access purposes. It would also be helpful to include guidance on specific security expectations for Open and Closed systems. Proposed change (if any): Clarify the need to protect and not to share passwords to individual accounts, and include guidance on specific security expectations for Open and Closed systems.	
597-601		Comment: We recommend adding the changes below in order to emphasise the use of secure systems and the maintenance of data integrity. In addition, it should be noted that, where consent under Regulation (EU) No. 2016/679 is used as the legal basis for data processing, systems must be capable of rectification and erasure of the subject's data. Proposed change (if any): Change the phrase "how they are retrieved and transmitted" to read "how they are securely retrieved and transmitted" and add the following text: "The computer system used to access trial data should be designed in such a way that retrieved data regarding each individual subject in a study is attributable to that subject."	

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		In addition, it should be noted that, where consent under Regulation (EU) No. 2016/679 is used as the legal basis for data processing, systems holding trial data must provide functionality enabling data controllers to process requests for rectification and erasure of the subject's data.	
599-601		Comment: These lines specify that audit trails should be directly accessible to investigators, monitors, auditors and inspectors without compromising confidentiality. However, section 6.2.1 specifies required fields for audit trails such as previous/current value fields. This contradicts the confidentiality clause as these fields may contain personal data on study participants. Proposed change (if any): Ensure consistency of expectations.	
618		Comment: Guidance does not indicate where transfers are to be pre-specified. Proposed change (if any): Transfers should also document data being transferred from where and to whom and frequency of transfers.	
621-624		Comment: We recommend that, in the event that a Sponsor/CRO contracts with an IT service provider, any continuous access by sponsors is the obligation of the Sponsor/CRO unless agreed to specifically in the vendor	

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		agreement. Additionally, we recommend that the final guideline should confirm that the need for continuous access may be met by offline copies of records, in particular following trial completion and decommissioning of applicable computerized systems. Proposed change (if any): Add appropriate text.	
625-626		Comment: The text emphasises the importance of this process but provides no guidance on what is expected. We recommend the guidance should confirm that a risk-based approach may be taken and that practical examples are included. Proposed change (if any): Revise the text as above.	
629-632		Comment: The phrase "treatment related pertinent information" requires clarification. Proposed change (if any): Add examples to clarify meaning.	
656-660		Comment: Compliance with the statement "Audit trails should be visible at data-point level" is challenging for systems such as equipment and other analysis software used in laboratories where the audit trail is visible at an event level rather than a data-point level. Additionally, the widely accepted definition of an audit trail is that of the US National	

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		Institute of Standards and Technology (NIST), which defines a security audit trail as "A set of records that collectively provide documentary evidence of processing used to aid in tracing from original transactions forward to related records and reports, and/or backwards from records and reports to their component source transactions." In other words, it does not include being able to export an audit trail specifically as a dynamic record for tracking and trending purposes. For example, there are systems that only allow export of the audit trail in PDF format or for an individual patient record vs all patient records in a single export. Moreover, when an audit trail is exported from a system it is no longer a "dynamic data file". Also, the phrase "in a GCP compliant manner" is superfluous as GCP requirements will be met when the preceding instructions are followed. Proposed change (if any): Replace the statement "Audit trails should be visible at data-point level in the live system and the entire audit trail should be available as an exported dynamic data file…." with "Audit Trails should be visible at data-point level or task/event level as applicable. A risk-based assessment should determine whether it is appropriate that the entire audit trail should be available as an exported dynamic file….". Delete the phrase "in a GCP compliant manner."	
656		Comment: Depending on the complexity of the system and	

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		associated data, it may not be feasible logistically to export the entire audit trail (the export could be overly cumbersome such that the required information cannot be readily located or reviewed in any meaningful way). Proposed change (if any): We recommend noting the critical aspect of being able to search the audit trail and export according to search parameters so that the audit trail is easily reviewed and understood. This should facilitate the ability to discern patterns or concerns in the data by allowing the user to drill down to the pertinent information.	
669		Comment: Typographical error. Proposed change (if any): Replace the reference with "See Annex 5 section A5.1.1.4 for further details."	
671		Comment: Typographical error. Proposed change (if any): Replace "temporally" with "temporarily".	
673		Comment: Some apps record only to the primary server's time zone. We therefore recommend that dates and times are recorded using a single consistent time zone for each computerised system, and not necessarily the UTC. The insistence on use of UTC for electronic capture of informed	

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		consent (line 1625) should be aligned with this section. Proposed change (if any): Replace the text with "The date of entry into the capture tool (e.g., eCRF) and date of data saved to a hard drive should be recorded as part of the metadata, using a single consistent time zone (which may be UTC) for each computerised system," and align with line 1625.	
691-705		Comment: We recommend that a statement is added to the text to make clear that an audit trail generated by a third party should be made available to the investigator or sponsor, as appropriate, as a component of the record of the relevant data and events. Additionally, where consent forms the legal basis for data processing under Regulation (EU) No. 2016/679, the systems holding trial data should be designed in such a way that, if needed, they enable the data controller to erase the data record for an individual or subject. It would be very helpful to stakeholders for the guideline to provide advice on how this situation should be managed in a GCP-compliant manner. Proposed change (if any): Add a statement to make clear that an audit trail generated by a third party should be made available to the investigator or sponsor, as appropriate, as a component of the record of the relevant data and events. Add guidance on managing the need for the data record for	

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		an individual or subject to be erased if consent forms the legal basis for data processing under Regulation (EU) No. 2016/679.	
698-699		Comment: Audit trail review will not necessarily detect unauthorised accesses, which are more likely to be detected by metadata review. We note that the listed audit trail requirements in line 658 do not include "view" activities. Proposed change (if any): Delete "detect unauthorised accesses".	
709-723		Comment: Line 707 references 'other EDC tools' whereas lines 709-723 address only the eCRF. This could be misinterpreted as meaning that only the eCRF system needs evidence of oversight from the investigator. However, increasingly, key efficacy and safety data is captured in other direct data entry tools and it is important to demonstrate investigator oversight of this data. Proposed change (if any): Add additional text to clarify the need for investigator oversight of data from any direct data capture tool.	
758-759		Comment: There is a conflict between the requirement to ensure the dynamic aspects of an original file can be captured when systems have been decommissioned and the	

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		statement in line 877 that "Data should be archived in a read only state". At some point, the data output must be "fixed", reported, and then archived as reported. Proposed change (if any): Explain how to archive dynamic data in a read only state while maintaining the dynamic functionality.	
767-796		Comment: ACRO supports the use of an independent third party as described. However, we recommend that the text should state clearly that the independent third party may not assume any other Sponsor-related responsibilities (e.g. data management or monitoring) for a specific clinical trial. Proposed change (if any): Add text to clarify that the independent third party may not assume any other Sponsor-related responsibilities (e.g. data management or monitoring) for a specific clinical trial.	
809-810		Comment: It is not clear why cloud computing systems are considered to pose a greater risk. It can be argued equally that they pose less of a risk because of the secure nature of the hosting and system architecture. Proposed change (if any): Delete the sentence.	
813-815		Comment: We agree that data jurisdiction is complex given	

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		the global nature of public cloud solutions and services being deployed across several sites, countries and continents. We recommend that the guidance should include examples of how the use of multiple assessments from regulatory, data classifications, business risk, security, technology risks can inform contractual obligations. Proposed change (if any): Include examples of how the use of multiple assessments from regulatory, data classifications, business risk, security, technology risks can inform contractual obligations.	
816		Comment: Typographical error. Proposed change (if any): Replace “choses” with “chooses”.	
816-817		Comment: The creation of an identical test environment may present an architectural challenge considering the size, scalability, business continuity requirements, data volume, etc. in a non-production environment. Consequently, we recommend that a risk-based approach is taken to ensure a production-equivalent test site is available for testing, when required. However, it is not always efficient to base a modern system on multiple environments which then leads to the need to copy environments and verify the copy. Another way of achieving this qualification could be through a test site in the production environment. We therefore recommend the	

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		use of the term "test site" rather than "test environment", and that the guideline should confirm the need for full support from the cloud system provider. Proposed change (if any): Revise the text to allow for a risk-based approach to determine if a production-equivalent test site is necessary for testing, and to ensure that, when required, the cloud service provider facilitates the qualification process fully.	
833-835		Comment: We recommend moving the text on disaster recovery from the section on Adequate Back-up of Data to a new section headed Disaster Recovery. Proposed change (if any): Move the text as described.	
848-850		Comment: It would be helpful to provide guidance on expectations for data sampling relative to data verification. It is recognised that a statistical approach will be required, e.g., if there are 10 million records to migrate, 10% of these records may be verified during data migration verification; as the record counts decreases the percentage of verification can increase. Proposed Change (if any): Add guidance as above on expectations for data sampling relative to data verification.	

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855-860 and 877		Comment: Where legacy audit trail data is archived, it may not be practical to migrate the archived audit trail data into a new system due to space limitations. Further, the statement (line 877) that "Data should be archived in a read only state" appears to conflict with the concept of archiving in a dynamic format. At some point, the data output must be "fixed", reported, and then archived as reported. Proposed change (if any): Explain what is meant by archiving dynamic data in a read only state while maintaining the dynamic functionality.	
883-885		Comment: The ability to restore to a transactional state decommissioned computer systems (whether originally hosted as cloud services or as on-premise installations) becomes increasingly challenging (and a significant financial burden) with the passage of time due to the availability of supporting hardware, middleware, software and knowledge. This would be particularly the case if inspectors were to interpret the 25-year trial master file retention period (as detailed in the Regulation (EU) 536/2014) to include the ability to restore database/application files held by sponsors/CROs. We propose that the focus of the proposed text is changed to concentrate on the extraction of all necessary files before decommissioning. Additionally, we recommend including a reference to ICH GCP 1.65: "In case of decommissioning, the sponsor should ensure	

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		(contractually if done by a contracted party) that archived formats provide the possibility to restore the database(s)" Proposed change (if any): Revise the text to read as follows, and include a reference to ICH GCP 1.65: "In case of decommissioning, the sponsor should ensure that all the clinical data, associated audit trails and other relevant information, as determined by a risk assessment, are extracted prior to decommissioning (in a format that can be interrogated and queried i.e. dynamic). The sponsor may elect to retain all necessary files to enable the computer system to be restored to a transactional state with recognition that such restoration may be feasible for a limited post-trial period due to technology aging considerations."	
887		Comment: We recommend adding additional guidance as follows. Proposed change (if any): Provide guidance on how to accomplish retaining static data as dynamic data files as well as how to retain dynamic data in a read only state.	
906-909		Comment: It would be helpful to expand on the concept of "contractually obligated" as some systems that are used to fulfil investigator responsibilities may be contracted by the sponsor (e.g., PRO systems). Currently, the draft text could be read as requiring each individual investigator to have a	

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		contract in place with the vendor of a system managing records that are the responsibility of the investigator under GCP. This is clearly impractical and would lead to a significant additional burden on investigators. The text should state clearly that, although the sponsor can contract directly some activities belonging to the Institution/Investigator, the contract between the sponsor and the Institution/Hospital/Investigator should mention the involvement of this external organization or personnel and that the contract should specify that the investigator is responsible for the oversight of the external party if allowed under the sponsor agreement with the external party. The involvement of external parties should be submitted to and approved by the Ethics Committee before the start of such contracted activities, as required by local regulations. Proposed change (if any): Include relevant text as above.	
954-956		Comment: The instruction to "restore the database(s) to full functionality" is not practical or even possible in a SaaS multitenant production environment. Proposed change (if any): As stated above with reference to lines 883-885.	
970-1021		Comment: There is inconsistent use of the terms "Validation" and "Qualification" throughout the draft	

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		guideline. We propose leveraging the definitions within the EMA 'Notice to Sponsors on validation and qualification of computerized systems used in clinical trials' and to reinforce that there is a hierarchy with qualification being a part of validation. In addition, we recommend that the term "Verification" is used specifically for software development related activities. Proposed change (if any): Ensure alignment and accurate use of terminology throughout the guideline.	
977-981		Comment: Trial level configuration is typically confirmed via a user acceptance testing process as opposed to validation. Also, we recommend the need for ongoing validation is addressed. Proposed change (if any): Replace "validation" with "UAT" in regard to trial level configuration testing, and add that a risk-based assessment should be performed whenever a new version of the computerised system is released.	
984-987		Comment: We recommend that the term "Verification" is used specifically for software development related activities performed by vendors. The guidance does not make clear what would be regarded as "adequate" verification by the vendor.	

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		Proposed change (if any): Include text to confirm that the vendor may take a risk-based approach to verification to ensure that the software meets all of its requirements.	
1011-1012		Comment: This sentence omits the need for Operational Qualification (OQ) and is not consistent with standard practice. Proposed change (if any): Replace the sentence with "Where the system depends on trained users, the responsible party (Sponsor/CRO) is ultimately accountable to ensure all required qualification is performed; the (qualified) vendor may perform Installation Qualification/Operational Qualification (IQ/OQ) but the responsible party is responsible for Performance Qualification (PQ)."	
1021		Comment: Typographical error. Proposed change (if any): "A.2.8" should read "A2.8".	
1022-1050		Comment: For clarity, we recommend adding the following text, which is based on the ISPE GAMP 5 document: A risk-based Approach to Compliant GxP Computerized Systems, to this section of the guideline. Proposed change (if any): Add the following text: "A User Requirement Specification (URS) is typically required when	

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		Performance Qualification (PQ) is required. Otherwise, the Functional Specification and Operational Qualification (OQ) will suffice. The responsible party (Sponsor/CRO) must be in possession of a Design Specification in case of customization."	
1045		Comment: We recommend adding a sentence at the end of the paragraph to clarify that current standard practice may be followed. Proposed change (if any): Add a final sentence that reads "If contractually delegated by the responsible party, a third party may approve the documentation on behalf of the responsible party, who remains accountable for decisions made."	
1054-1057		Comment: Some requirements may not necessarily be traced to a qualification activity but to processes such as training, onboarding, disaster recovery, etc. It would be helpful to include some guidance on traceability requirements tied to non-qualification activities. Also, the statement "ensure for every requirement, there is at least one corresponding test case" is not consistent with a risk-proportionate approach to validation. Proposed change (if any): Add guidance on traceability requirements tied to non-qualification activities, and revise	

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		the text to make clear that a risk-proportionate approach should be taken to validation.	
1059-1061		Comment: The guidance provided around test procedures and test evidence is very prescriptive and does not allow for a risk-based approach to the testing approach and documentation. The goal of testing is to ensure that the computerized system is fit for purpose. Often, overly prescriptive testing procedures lead to more of a documentation exercise then to testing that ensures the system is fit for purpose. Also, given current developments in the software industry towards robust design and development practices and tool usage, it would be helpful to include guidance on automatic installation of software builds. Proposed change (if any): Revise the text to allow for a more risk-based approach to testing procedures and documentation in alignment with the guidance in the (ISPE) GAMP Records and Data Integrity Good Practice Guide: Data Integrity by Design, and add guidance on automatic installation of software builds.	
1075		Comment: We recommend that the text should make clear that a risk-based approach should be taken to determine if a production-equivalent test site is necessary for testing. Proposed Change: Add text to allow for a risk-based	

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		approach to determine if a production-equivalent test site is necessary for testing.	
1080		Comment: Typographical error. Proposed change (if any): "difference" should read "different".	
1107-11		Comment: We recommend adding text to clarify that the review period should be determined by a risk-based approach. Proposed change (if any): Add appropriate text.	
1134-1136		Comment: We recommend specifying the need for testing / validation of changes in an appropriate test site before deployment. Proposed change (if any): Add appropriate text.	
1145		Comment: We recommend adding a section on password policy requirement recommendations, e.g. characters that must be used, minimum length, expiration period, password history reuse, etc. Proposed change (if any): Add appropriate text.	

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1156-1170		Comment: It would be helpful to provide specific guidance relative to Cloud computing systems in this section. In particular, we recommend adding text to confirm that cloud providers should have clear policies and procedures in place explaining how they control infrastructure and system access by their employees. Proposed change (if any): Add specific guidance relative to Cloud computing systems.	
1205		Comment: We recommend adding text to specify that a disaster recovery plan should be in place and tested for the data. Proposed Change: Add appropriate text.	
1220		Comment: We recommend adding text to specify that the record of security patches that have been applied/installed should be maintained for future reference. Proposed change (if any): Add appropriate text.	
1239		Comment: We recommend revising the sentence as follows. Proposed change (if any): Revise the sentence to read "Mitigation using updated antivirus software scans on a regular basis should be attempted."	

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1268		Comment: It would be helpful to clarify whether the term "serious breaches" refers to serious breaches of good clinical practice or to personal data breach under Regulation (EU) No. 2016/679, or both. Proposed change (if any): Clarify as above.	
1275		Comment: The challenges listed are not specific to cloud-based systems. Proposed change (if any): Delete the text ", e.g. to cloud-based systems,".	
1301-1305		Comment: Platforms with offline capabilities will require extended timeout periods and only prompt users for authentication upon reconnecting online. We therefore recommend adding clarification that this section applies only to online activities. Proposed change (if any): Include clarification as recommended.	
1308		Comment: The current sentence is clumsily worded. Proposed change (if any): Revise the text to read "….procedures should be in place to ensure consistency	

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		irrespective of…."	
1321		Comment: Typographical error. Proposed change (if any): "method relatively" should read "method is relatively".	
1349-1353		Comment: The 'EDC' tool is mentioned throughout this eCOA section. However, an EDC tool is not always the tool used for eCOA capture, and is often not suited to an EDC vendor capabilities. We recommend keeping the eCOA tool as a separate offering and not including it in the EDC definition. This applies also to the A5.1.1.1 section for ePRO. Proposed change (if any) Replace EDC reference in the eCOA section with 'eCOA tool' or 'eCOA'	
1356-1358		Comment: UAT is usually performed before or in parallel to site selection, so site staff and trial participants may not yet be available. We also recommend the use of a risk-based assessment to determine whether, after the initial release, UAT is required for any subsequent release. Proposed change (if any): Revise the text to read as follows: "….involve representatives of potential site staff and of the intended trial participant/patient population,,,," and add text to recommend the use of a risk-based assessment to	

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		determine whether, after the initial release, UAT is required for any subsequent release.	
1367		Comment: Only one "e.g." is required. Proposed change (if any): Revise the text to read "e.g. just requires input once daily but event-driven."	
1376-1383		Comment: As data on an electronic device such as an ePRO or wearable is considered only temporary storage until pseudonymised data is uploaded to the central server where permanent storage is achieved and then considered as source data, this implies that retention of these devices is not required after the relevant data have been uploaded. Proposed change (if any): Provide additional clarification to confirm that ePRO and wearable devices are not considered permanent repositories of source data and so do not need to be retained.	
1434-1436		Comment: We believe that these lines are ambiguous in two ways. First, as used in this section entitled "user name and password," the term "authentication information" is ambiguous. As used in this manner it should be something more than just user name or password alone to be consistent with the remainder of the document, including the section on "authentication methods." (lines 1269-1273). This is an	

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		important point since a reasonably secure system might use one token or another in a manner that would preserve confidentiality and yet contain some of the associated personal information. By way of example, a user could select a version of their name as a password but such password could nevertheless be encrypted and thus not "allow breach of confidentiality." Second, the guideline should clearly state the principle that the system should not use user name and password in a way that itself could breach the confidentiality of a user. Like the first point, a reasonably secure system might allow a user to use an email as a valid user name, but protect the confidentiality of the user by not revealing it to others without an obligation of confidentiality to that user. Proposed change (if any): Revise the text to read: “"The user name and password should not be used in a manner that would breach a trial participant's confidentiality.”	
1471-1472		Comment: It would be helpful to include examples of Terms of Service that conflict with ICH GCP and local (legal) requirements. Proposed change (if any): Include relevant examples.	
1570-1572		Comment: This additional burden for the sponsor/CRO is not necessary if, as recommended above (see comment on line 280), an appendix that identifies the Member States that	

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		allow/do not allow electronic capture of informed consent is added to the guideline. Proposed change (if any): Add an appendix that identifies the Member States that allow/do not allow electronic capture of informed consent.	
1575-1577		Comment: As noted above, it would be helpful to include an appendix to the guideline that identifies the Member States that allow/do not allow electronic capture of informed consent. Proposed change (if any): Add an appendix that identifies the Member States that allow/do not allow electronic capture of informed consent.	
1588-1590		Comment: This is not specific to eConsent and applies to all forms of computer technology. Proposed change (if any): As noted in our comment on lines 249-254 above, this is best addressed in the Introduction to the entire guideline.	
1593-1595		Comment: As noted in the text, this will depend on the situation relating to a specific clinical trial. For clarity, we therefore recommend that the text is revised as stated below. Additionally, it is important to note that in many cases	

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		satisfactory face to face communication can be achieved using digital methods and does not necessarily need to be physical. Proposed change (if any): Revise the text to read as follows: "There may be some specific situations (e.g., due to the characteristics of the disease or trial) where physical face to face communication between one or more members of the research team and the potential trial participant is considered mandatory; this will form part of the assessment of the clinical trial application. In other situations, face to face communication using digital means may be appropriate."	
1634-1637		Comment: It is not clear that verification of identity can be confirmed remotely, e.g. via a telehealth or other video conferencing platform. Proposed change (if any): Include text that confirms identity can be confirmed via telehealth or other video conferencing platform.	
1641		Comment: It is not appropriate for a guideline of this nature to state simply that "a biometric method may be considered." We recommend that the principles associated with the use of biometric verification be included. Proposed change: Add text to confirm that biometric methods	

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		should minimise the amount of personal information stored, limit the number of submission attempts, and authenticate the user, and that an alternative means of verifying user identity should be available.	
1645-1646		Comment: The sentence "Remote access by the sponsor to personal identifiable information in the electronic consent system should not be permitted" may prevent remote verification of informed consent and therefore hinder the uptake of decentralised clinical trials, thereby reducing patient access to clinical trials in the EU. Proposed change (if any): Revise the sentence to read as follows: "The sponsor may access the electronic informed consent system to confirm that consent has been given, but the system should provide functionality to ensure that personal information is not available to the sponsor.	
1621-1622		Comment: As noted above, it would be helpful to include an appendix to the guideline that identifies the Member States that allow/do not allow electronic capture of informed consent. Proposed change (if any): Add an appendix that identifies the Member States that allow/do not allow electronic capture of informed consent.	

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1665		Comment: Typographical error. Proposed change (if any): "A.5.3.3" should be "A5.3.3"	
1674-1676		Comment: The ability to grant access to computerized systems should be restricted to authorized and trained staff qualified to manage the systems. Generally, the site staff, including the Investigator, are not qualified to manage system access. Proposed change (if any): Revise the text to clarify that the Investigator should be able to request or authorize access for inspection without requiring approval from the sponsor.	
1685-1686		Comment: For clarity, we recommend revising this sentence as shown below. Proposed change (if any): Revise the text to read: "Release of electronic trial participant information and informed consent forms to the sites prior to IRB/IEC approval should be prevented at the start of the trial and whenever any subsequent updates to the information and informed consent forms are finalised."	
1688-1691		Comment: The requirement for all the documents regarding informed consent to be made available in the Investigator TMF needs clarification, e.g. it is not clear whether this means the core informed consent document	

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		should be retained in the Investigator TMF. Proposed change (if any): Include specific guidance on expectations for informed consent documents to be retained in the Investigator TMF.	
		ACRO thanks the Agency for the opportunity to provide feedback on this guidance. Please contact ACRO (knoonan@acrohealth.org) if we can answer any questions or provide additional details.	

Please add more rows if needed.