TUM School of Medicine and Health

EMA Guideline on Computerised Systems and Electronic Data in Clinical Trials Highlights & Implications

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Hongkong 29 November 2023

MÜNCHNER STUDIEN ZENTRUM

EMA Guideline on Computerised Systems & Electronic Data in Clinical Trials

The guideline is intended to assist sponsors, investigators, and other parties involved in clinical trials to comply with the requirements of the current legislation as well as ICH E6 Good Clinical Practice (GCP), regarding the use of computerised systems and the collection of electronic data in clinical trials

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 March 2023
EMA/INS/GCP/112288/2023
Good Clinical Practice Inspectors Working Group (GCP IWG)

Guideline on computerised systems and electronic data in clinical trials

Adopted by GCP IWG for release for consultation	4 March 2021
Start of public consultation	18 June 2021
End of consultation (deadline for comments)	17 December 2021
Final version adopted by the GCP IWG	7 March 2023
Date of coming into effect	6 months after publication

Replaces: EMA/INS/GCP/454280/2010 Reflection Paper on Expectations for Electronic Source Data and Data Transcribed to Electronic Data Collection Tools in Clinical Trials

MÜNCHNER STUDIEN ZENTRUM

EMA Guideline on Computerised Systems & Electronic Data in Clinical Trials

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- Principles & definition of key concepts
- Computerised systems
- Electronic data

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EMA Guideline on Computerised Systems & Electronic Data in Clinical Trials
Legislation

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 April 2014

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

EU CTR 536/2014

Article 47 **Compliance with the protocol and good clinical practice**

The sponsor of a clinical trial and the investigator shall ensure that the clinical trial is conducted in accordance with the protocol and with the principles of good clinical practice.

HMA Heads of Medicines Agencies · European Commission · EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

RECOMMENDATION PAPER ON DECENTRALISED ELEMENTS IN CLINICAL TRIALS

Version 01, 13 December 2022

Draft agreed by DCT project team (experts from Clinical Trial Coordination Group, Clinical Trial Expert Group, EMA scientific committees, EMA working parties, and EMA staff)	December 2022
Draft agreed Clinical Trial Coordination Group	December 2022
Draft agreed by Clinical Trials Expert Group	December 2022
Draft agreed by GCP Inspector Working Group	December 2022
Adopted by ACT EU Steering Group	December 2022

Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

March 2023
Procedural
Revision 1

FDA

FDA 21 CFR Part 11
Equipment - Part III
C.4 (21 CFR 58.61 - 63)

Guideline for Good Clinical Practice E6(R2)

ICH E6 R2 (GCP)

5.5.3. When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

a) ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 December 2016
EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products

Guideline for good clinical practice E6(R2)
Step 5

Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	4 August 2015
End of consultation (deadline for comments)	3 February 2016
Final adoption by CHMP	15 December 2016
Date for coming into effect	14 June 2017

b) maintain SOPs for using these systems: The SOPs should cover system setup, installation, and use. They should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning.

The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

EMA Guideline on Computerised Systems & Electronic Data in Clinical Trials

Effective date:
09 September 2023

- Aims at understanding of regulatory expectations to validation, operation and safe use of IT systems in clinical trials.
- Clarifies further the requirements originating from GCP
  - to ensure data quality, reliability and integrity
  - to offer better advice to sponsors on how to demonstrate compliance and inspection readiness
- Stresses that they apply to all parties involved in clinical trials - sponsors, investigators and their service providers, irrespective of the services they provide
- Provides guidance for strategic considerations of sponsors

https://ispe.org/pharmaceutical-engineering/technology-transfer-pharma-one-size-does-not-fit-all

EMA Guideline on Computerised Systems & Electronic Data in Clinical Trials

- Overview of the evolution of the guideline, its scope & impact
- Requirements for establishing reliability & accuracy of computerised systems used in clinical trials
- Non-technology related perspectives for sponsors such as processes, people, project delivery, financial, vendors & investigators
- Guidance on systems e.g. eCRF, IRT, eCOA, ePRO* which are linked to the growing use of decentralised clinical trials
- Details on what is expected from sponsors to ensure longterm access & use of the trial master file (TMF) for 25 years
- All relevant computerised systems should be readily available with full, direct & read-only access (with a unique identification method e.g. username & password) upon request by inspectors from regulatory authorities.

* eCRF: electronic case report form, IRT: interactice response technology, eCOA: electronic clinical outcome assessment; *ePRO: electronic patient-reported outcome

Principles & Definition of Key Concepts

Data Integrity

- Data governance should address data ownership and responsibility throughout the data life cycle, and consider the design, operation, and monitoring of processes/systems to comply with the principles of data integrity including control over intentional and unintentional changes to data.
- Data governance systems should include staff training on the importance of data integrity principles and the creation of a working environment that enables visibility, and actively encourages reporting of omissions and erroneous results.
- Lack of integrity before the expiration of the mandated retention period may render the data unusable and is equivalent to data loss/destruction.

To achieve data integrity and ensure subject safety controlling of:

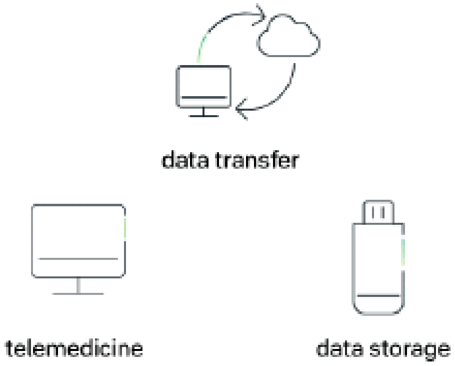
Hardware, software, procedures, facilities, people (sponsor, investigator, vendor and stakeholders)

throughout lifecycle of the clinical trial

Principles & Definition of Key Concepts

Data Integrity

- Validate computerised systems
- Authorise access (identifiable person), modification to and appropriate deletion of electronic records
- Avoid
  - data corruption to render the record inaccessible
  - loss of data, including metadata, during a process (e.g., transmission, archival, migration)
- Record the accurate time and date the data is modified (including capture of local time zones, when necessary, to distinguish between multiple sites)
- Retain original data
- Record reason for change

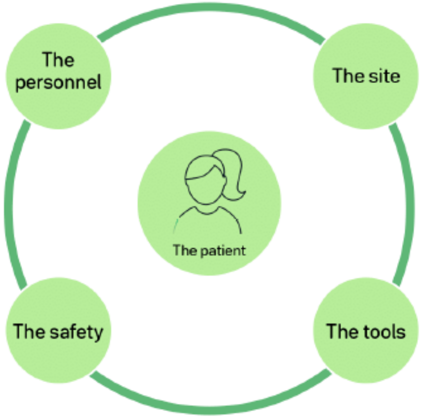


Principles & Definition of Key Concepts

Responsibilities

Annex I
Agreements

Roles and responsibilities in clinical trials should be clearly defined. The responsibility for the conduct of clinical trials is assigned via legislation to two parties, which may each have implemented computerised systems for holding/managing data:



- Investigators and their institutions, laboratories and other technical departments or clinics, generate & store the data, construct the record, and may use their own software & hardware (purchased, part of national or institutional health information systems, or locally developed).
- Sponsors that supply, store and/or, manage & operate computerised systems (including software & hardware) and the records generated by them. Sponsors may do this directly, or via service providers, including organisations providing systems that collect & store data on behalf of sponsors.

https://www.gmp-compliance.org/gmp-news/final-gcp-guideline-on-computerized-systems-and-data-integrity

Principles & Definition of Key Concepts

Data & Metadata

- Electronic data consist of individual data points. Data become information when viewed in context.
- Metadata provide context for the data point (e.g. variable name, unit, field value before & after change, reason for change, trial master file (TMF) location document identifier, timestamp, user):
  - are data that describe the characteristics, structure, data elements and inter-relationships of data e.g. audit trails.
  - permit data to be attributable to an individual entering or taking an action on the data such as modifying, deleting, reviewing, etc. (or if automatically generated, to the original data source).
  - without the context provided by metadata, the data of the original record have no meaning.
  - loss of metadata may result in a lack of data integrity and may render the data unusable.

Metadata: descriptive information about electronic data

https://blog.formedix.com/streamline-your-clinical-trials-with-automated-metadata-management

Principles & Definition of Key Concepts

Source Data

- original reported observation in a source document (e.g. hospital records, laboratory notes, emails, audio and/or video files, images, tables in databases)
- location of source documents and the associated source data they contain, should be clearly identified at all points within the data capture process
- should be processed as little as possible and as much as necessary
  - This process should be validated to ensure that the source data generated/captured is representative of the original observation and should contain metadata, including audit trail, to ensure adherence to the ALCOA++ principles.
  - The location where the source data is first obtained should be part of the metadata.

GCP

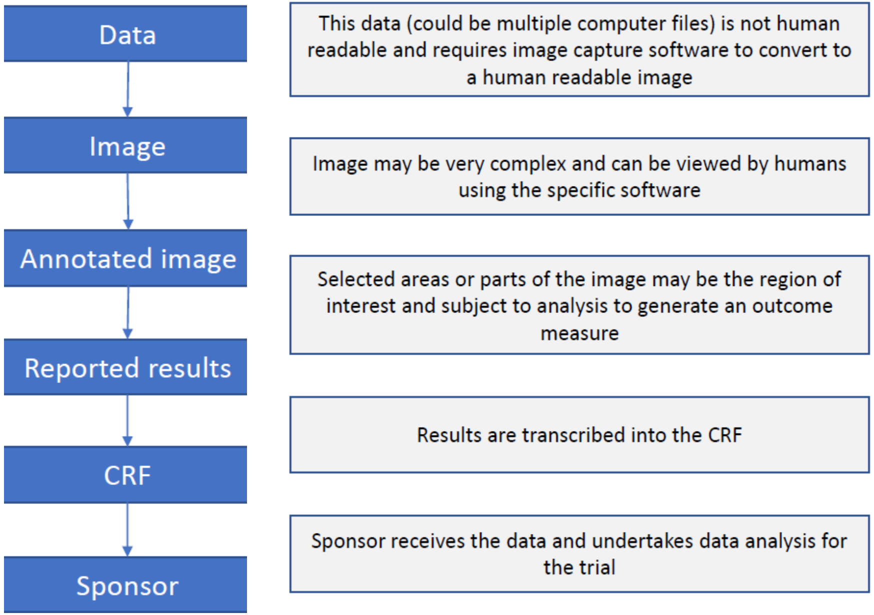
1.51. Source data
All information in original records & certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction & evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52. Source documents
Original documents, data, & records (e.g., hospital records, clinical & office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories & at medico-technical departments involved in the clinical trial).

Principles & Definition of Key Concepts

Source Data

From a practical point of view, the first obtainable permanent data from an electronic data generation/capture should be considered and defined as the electronic source data.



Example of the data processing stages, starting with the data capture. The correct identification of source data is important for adequate source data verification and archiving. Data at different processing stages can be considered source depending on the preceding processing steps.

Principles & Definition of Key Concepts

ALCOA++ as standard practice

- Any changes to the data should be documented as part of the metadata (e.g. audit trail).
- The process of data transfer between systems should be validated to ensure that data remain accurate.
- Data integrity is achieved when data are collected, accessed, and maintained in a secure manner, to fulfil the ALCOA++ principles.
- Data should be traceable throughout the **data life cycle**.

In short, this means that to maintain data integrity, the ALCOA++ principles must be followed for the entire lifecycle of clinical trial data, including during the 25 year retention period.

GCP

Attributable
(**L**egible)
Contemporaneous
Original
Accurate
Complete

Changes to source data:
Traceable (and explained if necessary (audit trial)

New:
Consistent
Enduring
Available when needed

https://www.gmp-compliance.org/gmp-news/final-gcp-guideline-on-computerized-systems-and-data-integrity

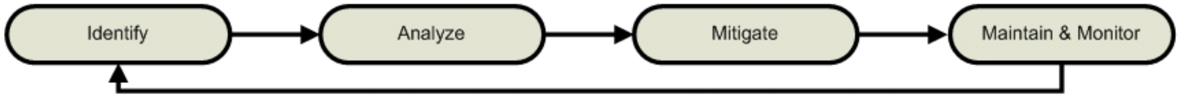
Principles & Definition of Key Concepts

GCP
ICH Q9 (R1)

RBQM system to identify risks affecting the rights, safety, well-being of trial participants or the reliability of trial results

Criticality and risks

- Risks should be considered:
  - at the system level (e.g. SOPs, computerized systems and staff) and
  - for the specific clinical trial (e.g. trial specific data & data acquisition tools or trial specific configurations or customisations of systems



- Risks should be identified, analysed, and mitigated or accepted, where justified, throughout the life cycle of the system:
  - Mitigation actions include e.g. revised system design, configuration or customisation, increased system validation, revised SOPs, training for use of systems, data governance culture
  - The approach used to reduce risks to an acceptable level should be proportionate to the significance of the risk (consideration: standard care, safety, primary efficacy data).
  - The sponsor should determine during site selection whether systems deployed by the investigtor/insitution are fit for purpose.

Principles & Definition of Key Concepts

Data capture

- The clinical trial protocol should specify data to be collected and the processes to capture them (who, when, which tools).
- Data fields should not be prepopulated or automatically filled (unless derived from other already entered data).
- The protocol should identify any data to be recorded directly in the data acquisition tools = source data.
- A detailed diagram and description of the transmission of electronic data (data flow) should be in the protocol or a protocol-related document.
- The sponsor should
  - describe which data (in which format) will be transcribed, the origin and destination of the data, the parties with access to the data, the timing of the transfer, and any actions that may be applied to the data (e.g. validation, reconciliation, verification, review), DMP encouraged
  - ensure traceability of data transformations and derivations during data processing and analysis.

Principles & Definition of Key Concepts

Electronic signatures

- The system should include functionality to
  - identify and authenticate the signatory
  - ensure non-repudiation, i.e. no later denial by the signatory
  - ensure an unbreakable link between the electronic record and its signatory, i.e. that the contents cannot later be changed by anyone without the signature being rendered visibly invalid
  - provide a timestamp, i.e. that the date, time, and time zone when the signature was applied is recorded.
- Electronic signatures can further be divided into two groups depending on whether the identity of the signatory is known in advance, i.e. signatures executed in
  - a closed system: system owner knows the identity of all users and signatories and grants and controls their access rights to the system.
  - an open system: the signatories (and users) are not known in advance.

Annex 5.3

Not all national regulations allow electronic signatures

Principles & Definition of Key Concepts

General Data Protection Regulation (EU) No 2016/679 (GDPR)

Data Protection

- The confidentiality of data that could identify trial participants should be protected, respecting privacy and confidentiality rules in accordance with the applicable regulatory requirement(s) [pseudonymisation].
- The requirements of GDPR should be followed (exception: trial participant does not have the right to be forgotten (and for the data to be consequently deleted) as this would cause bias to e.g. safety data (Regulation (EU) No 536/2014 recital 76 and Article 28(3)). Trial participants should be informed accordingly.
- If personal data of trial participants from an EU Member State are processed (at rest or in transit) or transferred to a third country or international organisation, such data transfer must comply with applicable EU data protection.

  In summary, this means that data transfer must be either carried out on the basis of an adequacy decision (Article 45 GDPR, Article 47 Regulation (EU) No 2018/1727 - EUDPR), otherwise the transfer must be subject to appropriate safeguards (Article 46 GDPR or Article 48 EUDPR) or the transfer may take place only if a derogation for specific situations apply (under Article 49 of GDPR or Article 50 of EUDPR).

Principles & Definition of Key Concepts

Data Protection

Safeguard personal data with GDPR

- Information in a clinical trial
  - must be fairly and lawfully processed
  - can only be processed for limited purposes and not in any way incompatible with those purposes
  - must be adequate, relevant and not excessive
  - must be accurate
  - can be kept for only as long as is necessary for its business purpose
  - must be processed in line with the individual's rights
  - must be kept secure
- If the information is going to be transferred to countries without adequate data protection laws, the transferring agent must demonstrate adequate mitigation
- Informed consent needs to contain references to data protection and data collection computerised systems that the subject will interact with (e.g., ePRO).

https://www.diaglobal.org/productfiles/25849/20110517/track3/02%20t3-1_earl%20w.%20hulihan.ppt
https://www.clinion.com/whitepapers/EMA_Guidelines_whitepaper.pdf

Principles & Definition of Key Concepts

Validation

Annex 2

GCP 1.65

'A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of clinical trial results.'

The sponsor and investigator are ultimately responsible for the validation and operation of the computerised system and for providing adequate documented evidence (to inspectors) that applicable processes have been followed and implemented…. „irrespective of who performed these activities (e.g. a vendor) ..."

Principles & Definition of Key Concepts

Validation

Annex 2

- Computerised systems used within a clinical trial should be subject to processes that confirm that they are fit for purpose.
- The processes used for the validation should be decided upon by the system owner (e.g. sponsors, investigators, technical facilities) and described, as applicable.
- System owners should ensure adequate oversight of validation activities performed by service providers to ensure suitable procedures are in place and that they are being adhered to.
- Documentation (including information within computerised systems used as process tools for validation activities) should be maintained to demonstrate that the system is maintained in the validated state. Such documentation should be available for both the validation of the computerised system and for the validation of the trial specific configuration or customisation.

Principles & Definition of Key concepts

Validation

Annex 2

- Validation of the trial specific configuration or customisation should ensure that the system is consistent with the requirements of the approved clinical trial protocol and that robust testing of functionality implementing such requirements is undertaken, (e.g., eligibility criteria questions in an eCRF, randomisation strata, dose calculations in an IRT system).
- If data is being held by a vendor, it should conduct their own validation of the system to ensure that it meets predefined requirements. It remains the responsibility of the sponsor and investigator to ensure that the vendor is validated and meets their specific requirements.
- If data is held in internal computerised systems, the sponsor and investigator are responsible for the validation and operation of said systems.
- With either solution, the responsible party must still provide sufficient documented evidence proving the relevant processes have been followed and implemented.

Computerised Systems

Description

The responsible party should maintain a list of physical & logical locations of the data e.g. servers, functionality & operational responsibility for computerised systems & databases used in a clinical trial together with an assessment of their fitness for purpose (clear overview, system interfaces, interaction, validation, methods, security measures).

Documented procedures

Documented procedures (e.g. SOPs) should be in place to ensure that computerised systems are used correctly. These procedures should be controlled and maintained by the responsible party.

Training

Each individual involved in conducting a clinical trial should be qualified by education, training, and experience to perform their respective task(s).
Computerised systems and training should be designed to meet the specific needs of the system users (e.g. sponsor, investigator, service provider, trial participants).

Computerised Systems

Security and access control

Computerised systems used in clinical trials should have security processes and features to prevent unauthorised access and unwarranted data changes and should maintain blinding of the treatment allocation where applicable.
Checks should be used to ensure that only authorised individuals have access to the system and that they are granted appropriate permissions (training, records of authorization & changes, protected password).

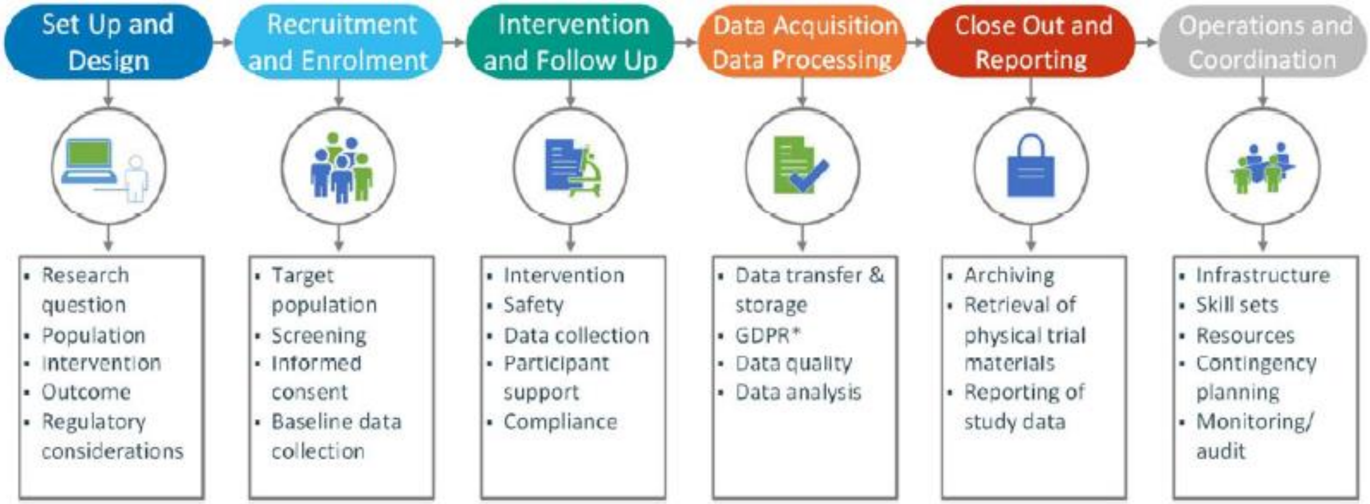
Timestamp

Accurate and unambiguous date & time information given in coordinated universal time (UTC) or time & time zone (set by an external standard) should be automatically captured. Users should not be able to modify date, time & time zone on the device used for data entry, when this information is captured by the computerised system & used as a timestamp.

Electronic Data

From Planning to Archiving: active, locked and archival systems

While the trial is live, data should be managed in an active system.
After it has closed, it must be secured in a locked system for reporting, submission and assessment.
For the archiving stage, data should be retained in such a state that the trial can be rebuilt if required.



Electronic Data

Data capture and location

The primary goal of data capture is to collect all data required by the protocol. All pertinent observations should be documented in a timely manner. The location of all source data should be specified prior to the start of the trial and updated

Transcription

Source data collected on paper (e.g. worksheets, paper CRFs or paper diaries or questionnaires) need to be transcribed either manually or by a validated entry tool into the eCRF or database(s).

Transfer

The process for file & data transfer needs to be validated & prespecified and should ensure that data & file integrity are assured for all transfers.
Transfer of source data & records when the original data or file are not maintained is a critical process (appropriate considerations expected to prevent loss of data & metadata).

Electronic Data

Direct data capture

- By using electronic data input devices and applications (e.g. electronic diaries, questionnaires, eCRFs) for direct data entry. Where treatment-related pertinent information is captured first in a direct data capture tool a documented procedure should exist to transfer information into the medical record, when relevant.
- By automated devices such as wearables, laboratory or other technical equipment (e.g. medical imaging, ECG equipment) that are directly linked to a data acquisition tool. Such data should be accompanied by metadata concerning the device used (e.g. device version, device identifiers, firmware version, last calibration, data originator, timestamp of events).

Edit checks

Manual and automatic data inputs should be validated to ensure a predefined set of validation criteria is adhered to. Edit checks should be relevant to the protocol, developed and revised as needed, implementation to be controlled and documented.

Electronic Data

Audit trail and audit trail review

An **audit trail** should be enabled for the original creation and subsequent modification of all electronic data.

- The audit trail should be secure, computer generated and timestamped; it should record all changes made as a result of data queries or a clarification process.
- Care should be taken to ensure that information jeopardising the blinding does not appear in the audit trail accessible to blinded users.
- Procedures for risk-based trial specific **audit trail reviews** should be in place and data review should be generally documented.
- Data review should focus on critical data and should be proactive and ongoing.
- Manual review as well as review by the use of technologies to facilitate the review of larger datasets is possible.
- The investigator should receive an introduction on how to navigate the audit trail of their own data in order to be able to review changes.

Electronic Data

Sign-off of data

- The sponsor should seek investigator endorsement of their data at predetermined milestones.
- The signature of the investigator or authorised member of his/her staff is considered as the documented confirmation that the data entered by the investigator & submitted to the sponsor are attributable, legible, complete, original, accurate, contemporaneous. Any member of the staff authorised for sign-off should be qualified.
- National law could require specific responsibilities, which should then be followed.
- The acceptable timing and frequency for the sign-off needs to be defined and justified (in a risk-based manner) for each trial by the sponsor.
- It is essential that data are confirmed prior to interim/final analysis and that important data related to e.g. reporting of SAEs, adjudication of important events & endpoint data, DSMB review, are signed off in a timely manner.

Electronic Data

Copying data

Data can be copied or transcribed for different purposes, either to replace source documents or essential documents or to be distributed amongst different stakeholders as working copies.

The method of copying should be practical and should ensure that the resulting copy is complete and accurate (including the relevant complete and accurate metadata).

Electronic Data

Certified copies

- When creating a certified copy, consider the nature of the original document:
  - content of the file is either static (e.g. PDF) or
  - dynamic (e.g. worksheet with automatic calculations) or
  - the copy tries to capture the result of an interpreter (e.g. a web page, where a web-browser interprets written HTML, JavaScript etc. programming languages).
- The result of the copy process should be verified either automatically by a validated process or manually to ensure that the same information is present —including data that describe the context, content, and structure — as in the original.
  - In case of dynamic files e.g. when a database is decommissioned and copies of data and metadata are provided to sponsors, the resulting file should also capture the dynamic aspects of the original file.
  - If files are the result of an interpreter, special care needs to be taken to not only consider the informative content the file, but also to capture & preserve aspects that are resulting from interactions of the used interpreter(s) & system settings
- Take special considerations whenever copies are to replace original source documents!

Electronic Data

Control of data

- Data generated at the trial site relating to trial participants should be available to the investigator at all times during & after the trial to enable investigators to make decisions related to eligibility, treatment, care for participants… and to ensure that he/she can fulfill the legal responsibility to retain an independent copy of the data for the required period.
- The sponsor should not have exclusive control of the data entered in a computerised system at any point in time (e.g. eCRF).
- Requirements above are not met if data are captured in a computerised system & stored on a central server under the sole control of the sponsor (or under control of a service provider not independent from the sponsor) or if the sponsor (instead of service provider) distributes data to the investigator.
- The investigator should be able to download a contemporaneous certified copy of the data (in addition to the record maintained elsewhere) and have sufficient time to review data before archiving.
- Any contractual agreements regarding hosting should ensure investigator control.
- IITs: degree of independence should be justified and pre-specified in agreements e.g. that it is a central IT department not otherwise involved in the operational aspects of the trial hosting the data and providing copies to the participating investigators.

Electronic Data

- .....
- Cloud solutions
- Backup of data
- Contingency plans
- Migration of data

from planning to archiving

IBM Watson Health Data Sheet IBM Clinical Development 2019

Electronic Data

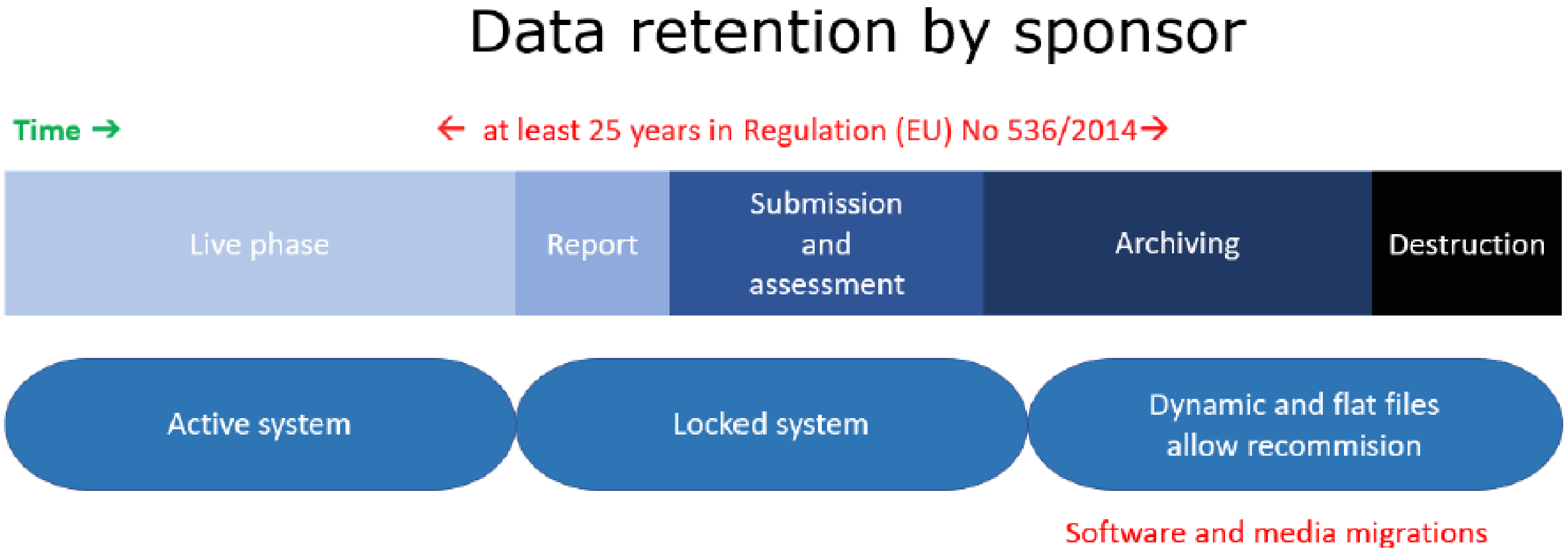
Archiving & database decommissioning

- Suitable archiving systems should be in place to safeguard data integrity for the periods established by the regulatory requirements including those in any of the regions where the data may be used for regulatory submissions, and not just those of the country where the data are generated.
- It should be ensured that the file and any software required (depending on the media used for storage) remain accessible, throughout the retention period of 25 years. This could imply e.g. migration of data.
- An inventory of all essential data and documents and corresponding retention periods should be maintained.
- Retention periods should respect the data protection principle of storage limitation.

Requirements for archiving electronic records include ensuring that

- records are accessible
&
- can be read throughout the retention period

Electronic Data



Annexes

6 Annexes on:

- **Agreements**
- **Computerised Systems Validation** (e.g. User Requirements, Validation and Test Plans, Periodic Review, Change Control)
- **User Management** (e.g. Segregation of Duties)
- **Security** (e.g. Ongoing Security Measures, Penetration Testing, Protection Against Unauthorized Back-End Changes)
- **Additional Consideration to Specific Systems** (e.g. IRT System, ePRO, Electronic Informed Consent)
- **Clinical Systems** (e.g. User Management, Trial Specific Data Acquisition Tools, Archiving)

Agreements

Annex 1

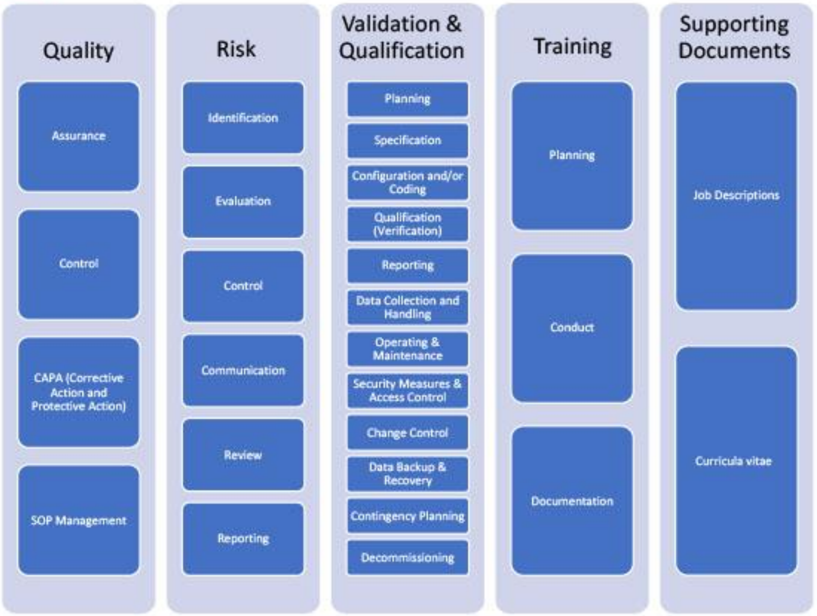
- It should be specified in agreements that the sponsor or the institution, as applicable, should have the right to conduct audits at the vendor site and that the vendor site could be subject to inspections (by national and/or international authorities) and that the vendor site shall accept these.
- Tasks transferred/delegated could include hosting of data. If data are hosted by a vendor, location of data storage and control (e.g. use of cloud services) should be described.
- To ensure reliable access to the data, the sponsor/investigator should employ measures to guarantee access to data for the sponsor and investigator in case of foreclosure (bankruptcy), shutdown, disaster of the vendor or for other reasons chosen by the sponsor/investigator (e.g. change of vendor).
- Agreements should ensure reliable, continued and timely access to the data in case of bankruptcy, shutdown, disaster of the vendor, discontinuation of service by the vendor or for reasons chosen by the sponsor/investigator (e.g. change of vendor).

Annex 2 Validation

Annex 2
Aligned with FDA 2018
Data Integrity Guidance

- Provides a detailed manual on computerised system validation as an essential component of ensuring the quality & integrity of clinical trial data
- It highlights a contemporary approach to the validation lifecycle of GxP & focuses on evaluating hardware, software, personnel, documenting during the valdation process
- It introduces some elements of agile methodology to the validation process, following a risk-based approach focussing on the most critical areas
- By following the guidance, stakeholders can ensure that they are meeting the high standards of quality and compliance

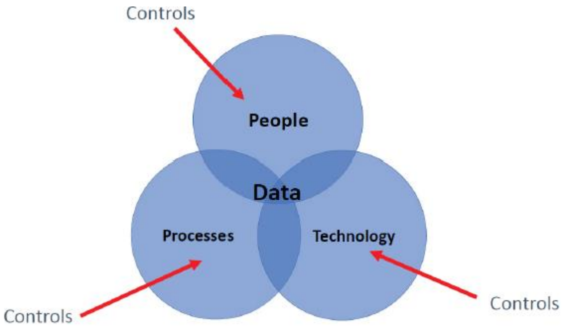
Figure 1: QMS expectations for detailed processes.



https://ispe.org/pharmaceutical-engineering/your-2023-state-validation-report-here
Oct 2023

Validation

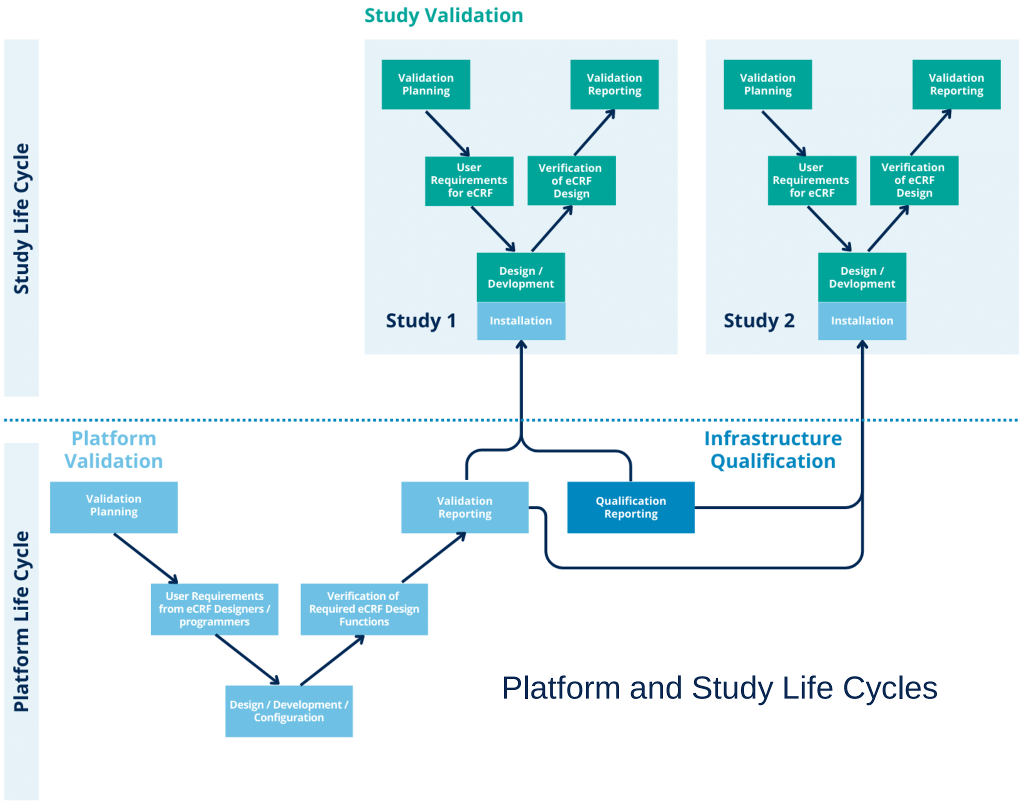
Annex 2



2022 GAMP 5 Sec. Ed. made for

- High-performance GxP- Processes,
- Computerised Systems and
- State-of-the-art Software Development

in the regulated world



Platform and Study Life Cycles

GAMP Good Practice Guide: Computerized GCP Systems & Data

Validation

Annex 2

Technical validation

Provide high level information on CE-marked medical devices

Usually performance data are needed

Check if CE-mark and intended use covers application

Clinical validation

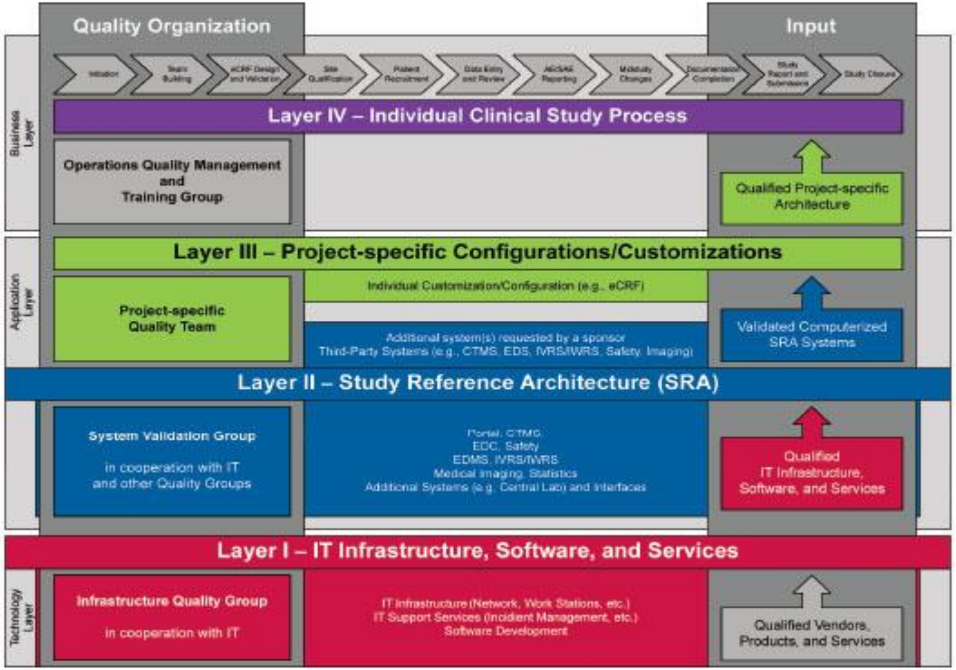
Separate clinical validation from technical validation

Context of Use should focus on specific application

Usually performance data in target population are needed

Performance in patients could differ from healthy volunteers

Figure 2: The validation layer model. (Reprinted from reference 7.)



https://www.ema.europa.eu/en/documents/presentation/presentation-regulatory-perspective-joerg-zinserling_en.pdf
https://ispe.org/pharmaceutical-engineering/september-october-2020/validation-clinical-trial-related-systems-smaller

Additional Consideration to Specific Systems

Annex 5

Digital health technology (DHT) aspects

Clinical performance evaluation

Relate performance evaluation to (specific) context of use and application (testing in clinical trial setting may be needed)

Will depend on importance/risks (primary endpoint vs. exploratory endpoint)

Tailor performance metrics and variables to Context of Use

Consider if reference standard is available

Considerations on devices

Ideally application of DHT should be device agnostic

Consider defining minimum requirements for technical performance

Publication of minimum requirements not sufficiently addressed so far

Performance of devices or software that do not require a CE-mark

Define criteria to ensure performance

Define limits for performance criteria

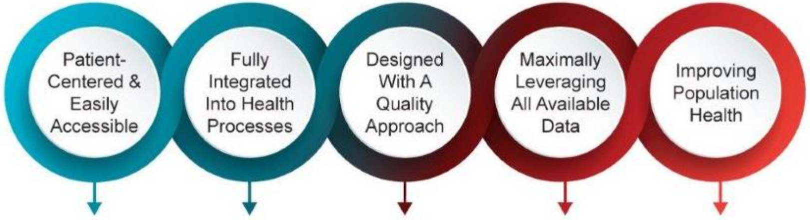
Use of layer model may be helpful (raw data → processing → derived device data → clinical endpoint data)

https://www.ema.europa.eu/en/documents/presentation/presentation-regulatory-perspective-joerg-zinserling_en.pdf

Take Home Message

- The EMA guideline on computerised systems and electronic data in clinical trials sets out clear requirements for the use of these technologies.
- Compliance with the guideline is essential to ensure the reliability, integrity, and security of clinical trial data.
- By following the guideline, sponsors, investigators, vendors etc. can ensure their compliance and take advantage of the many benefits that computerised systems and electronic data offer.

By 2030, clinical trials need to be



A critical part of the Evidence Generating System

https://ctti-clinicaltrials.org/who_we_are/transforming-trials-2030/

Thank you very much for your attention!

Outlook

work.
Thank You everyone
for your contributions to create t

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

N.B. TITLE PAGE to be DETERMINED.
This follows now the general structure of EMA Scientific Committees' reflection papers

[DATE]
EMA/83833/2023 – draft 6
<TBD/TBC (CHMP/CVMP)>

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Draft[1]

https://www.ema.europa.eu/en/documents/presentation/presentation-regulatory-perspective-joerg-zinserling_en.pdf