ICH E6 R3 Data Governance

SCDM Brussels

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Disclaimer

- This presentation is based on the ICH E6 (R3) step 5 version published in January 2025 by the EMA
- The slides are a mixture of official ICH E6 (R3) slides produced by the EWG (in the official ICH template) and slides produced by me for the purpose of this or other meetings. The opinions expressed on the latter are my own and not to be seen as those of ICH or the EMA
- The focus here will be on selected, significant changes with focus on data governance
- In the ICH EWG we have published a slide deck where a more systematic high-level review of the changes can be found: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step%204_Presentation_2025_0123.pdf
- I recommend you to watch the recording from the recent ACT EU meeting when it becomes available

Sub-agenda data governance

Selected glossary terms

Principle 9

New data governance section (4) and how it fits with the investigator section (2) and the sponsor section (3)

Selected topic 1: computerised system responsibility

Selected topic 2: data and metadata review

Selected topic 3: data endorsement

Selected topic 4: data management steps prior to analysis and statistical programming

Data Governance

- Data Governance considerations starts with the planning of the trial and the initial risk assessment
- Know and define your internal and external:
  - systems,
  - data,
  - data flows,
  - interfaces
  - decision points
- A good description in the protocol with elaboration in a data management plan, as appropriate, increases the common understanding of key processes and points of awareness

Selected glossary terms

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ICH E6 R3 – selected glossary terms

Data Integrity

Data integrity includes the degree to which data fulfil key criteria of being attributable, legible, contemporaneous, original, accurate, complete, secure and reliable such that data are fit for purpose

Data Acquisition Tool (DAT)

A paper or electronic tool designed to collect data and associated metadata from a data originator in a clinical trial according to the protocol and to report the data to the sponsor

The data originator may be a human (e.g., the participant or trial staff), a machine (e.g., wearables and sensors) or a computer system from which the electronic transfer of data from one system to another has been undertaken (e.g., extraction of data from an electronic health record or laboratory system)

Examples of DATs include but are not limited to CRFs, interactive response technologies (IRTs), clinical outcome assessments (COAs), including patient-reported outcomes (PROs) and wearable devices, irrespective of the media used

ICH E6 R3 – selected glossary terms

Metadata

The contextual information required to understand a given data element. Metadata is structured information that describes, explains or otherwise makes it easier to retrieve, use or manage data. For the purpose of this guideline, relevant metadata are those needed to allow the appropriate evaluation of the trial conduct

Audit Trail

Metadata records that allow the appropriate evaluation of the course of events by capturing details on actions (manual or automated) performed relating to information and data collection and, where applicable, to activities in computerised systems. The audit trail should show activities, initial entry and changes to data fields or records, by whom, when and, where applicable, why. In computerised systems, the audit trail should be secure, computer-generated and time stamped

Service provider

A person or organisation (commercial, academic or other) providing a service used by either the sponsor or the investigator to fulfil trial-related activities

Principle 9

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Principle 9 (selected parts)

Clinical trials should generate reliable results

9.1 The quality and amount of the information generated in a clinical trial should be fit for purpose and sufficient to provide confidence in the trial's results and support good decision making

9.2 Systems and processes that aid in data capture, management and analyses, as well as those that help ensure the quality of the information generated from the trial, should be fit for purpose, should capture the data required by the protocol and should be implemented in a way that is proportionate to the risks to participants and the importance of acquired data

9.3 Computerised systems used in clinical trials should be fit for purpose (e.g., through risk-based validation, if appropriate), and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes to ensure the integrity of relevant trial data

9.4 Clinical trials should incorporate efficient and robust processes for managing records (including data) to help ensure that record integrity and traceability are maintained and that personal information is protected, thereby allowing the accurate reporting, interpretation and verification of the relevant clinical trial-related information

How all data governance parts fit together

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Revised Structure

E6(R3) Guideline

E6(R3) Principles and Annex 1 replacing E6(R2)

I. INTRODUCTION

II. PRINCIPLES OF ICH GCP

III. ANNEX 1

1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
2. Investigator (2.12)
3. Sponsor (3.16.1 and 3.16.2)
4. Data Governance – Investigator and Sponsor

APPENDICES

Appendix A. Investigator's Brochure
Appendix B. Clinical Trial Protocol and Protocol Amendment(s)
Appendix C. Essential Records for the Conduct of a Clinical Trial

GLOSSARY

ANNEX 2 – *under public consultation from November 2024 to March 2025*

The new section 4

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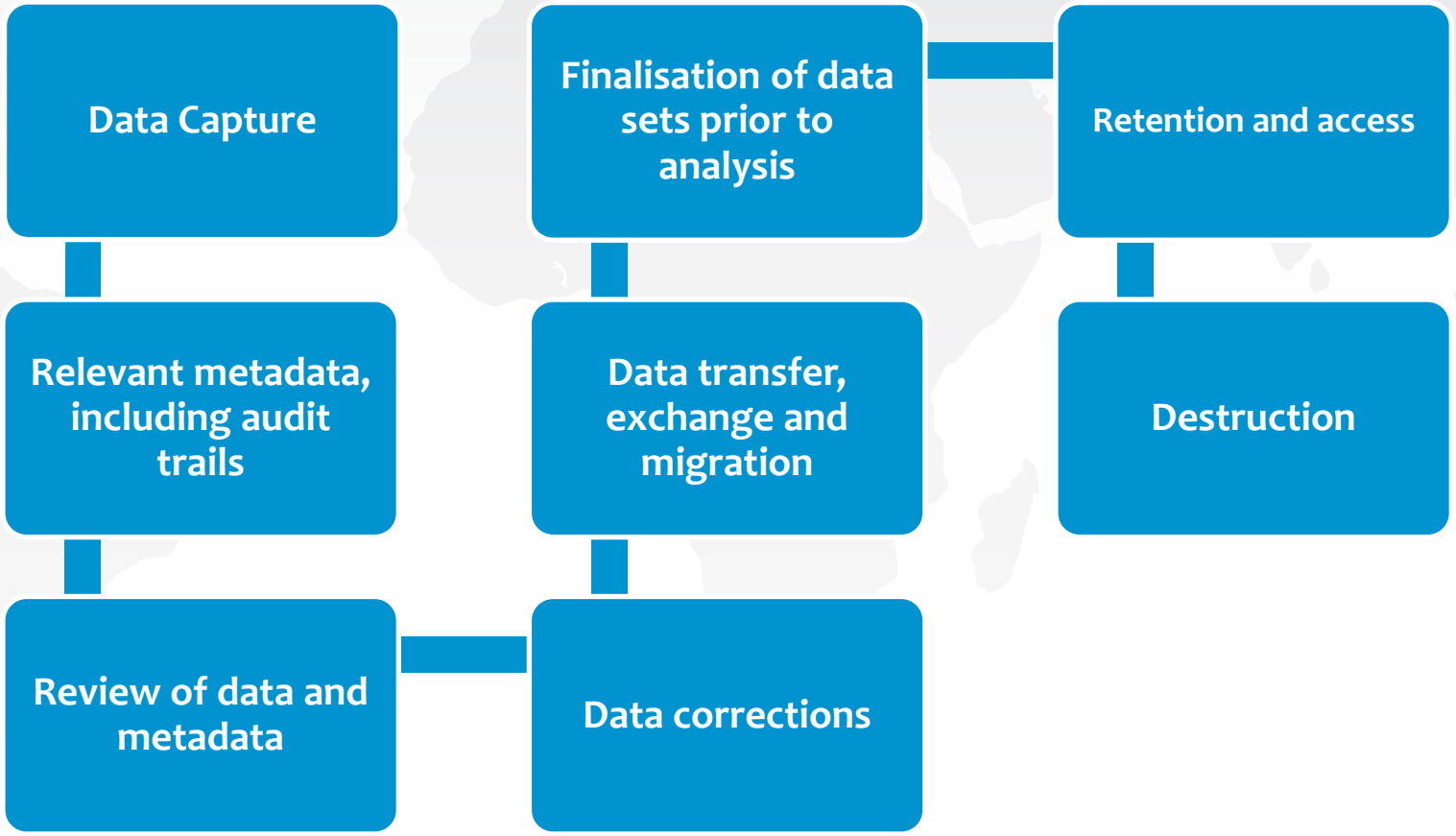
Data Governance

- Introduced a new section that provides guidance to the responsible parties (i.e., investigators and sponsor) on appropriate management of data integrity to allow accurate reporting, verification and interpretation of clinical trial-related information.
- Defined **key processes** that should be addressed across the full data life cycle:
  - **data protection,**
  - **management of computerised systems,**
  - essential elements such as **randomisation, dose adjustments and blinding**
  - processes to support key decision making such as **data finalisation, unblinding and IDMC activities**
- Specified that processes should focus on the criticality of the data and be **implemented proportionately and documented appropriately**.
- Described **data lifecycle elements** from data capture to data destruction.
- Clarified the meaning of **metadata**.

Data Governance (2)

Procedures should be established to cover the full data life cycle.



- Some activities may occur in a different order or in parallel, depending on the trial design, e.g., data transfer.

ICH E6 R3 New section 4 - section overview

Definition of key processes

4.1 Safeguard Blinding in Data Governance

4.2 Data Life Cycle Elements

4.3 Computerised Systems

- 4.3.1 Procedures for the Use of Computerised Systems
- 4.3.2 Training
- 4.3.3 Security
- 4.3.4 Validation
- 4.3.5 System Release
- 4.3.6 System Failure
- 4.3.7 Technical Support
- 4.3.8 User Management

Please refer to the EU e-guideline for our more detailed expectations for points 4.3.1 to 4.3.8

Selected topic 1: Responsibility for computerised systems

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Computerised systems responsibilities

NB! This is just a private visual aid to facilitate understanding on how responsibilities are divided in both the EU e-guideline and ICH E6 R3

Responsibility Matrix	Systems deployed by the investigator/Institution	Systems deployed by the sponsor
System designed for clinical trial purposes	Examples: • e-Investigator Site File • AI algorithm designed to screen patients or measure trial endpoints	Examples: • bespoke systems (Examples: sponsor-build CRF, ePRO or IRT) • systems designed to be configured or managed (Example: licens ed eCRF)
System used for clinical trials but designed for other purposes	Examples: • electronic medical record • imaging equipment e.g. x-ray, DEXA	Examples: • systems where no alterations are needed (Examples: wearables or sensors or questionnaires not specifically developed for a clinical trial)

Focus on proportionality and risk

ICH E6 R3 Investigator

Investigator records section (2.12) – selected sections

2.12.10 When using computerised systems in a clinical trial, the investigator/institution should do the following:

(a) For systems deployed by the investigator/institution, ensure that appropriate individuals have secure and attributable access

(b) For systems deployed by the sponsor, notify the sponsor when access permissions need to be changed or revoked from an individual

(c) For systems deployed by the investigator/institution specifically for the purposes of clinical trials, ensure that the requirements for computerised systems in section 4 are addressed proportionate to the risks to participants and to the importance of the data

(d) Where equipment for data acquisition is provided to trial participants by the investigator, ensure that traceability is maintained and that participants are provided with appropriate training

(e) Ensure that incidents in the use and operation …may have a significant and/or persistent impact on the trial data or system security, are reported to the sponsor and, where applicable, to the IRB/IEC

ICH E6 R3 Sponsor

3.16.1 (x) When using computerised systems in a clinical trial, the sponsor should:

For systems deployed by the sponsor:

(i) Have a record of the important computerised systems used in a clinical trial…

(ii) Ensure that the requirements for computerised systems (e.g., requirements for validation, audit trails, user management, backup, disaster recovery and IT security) are addressed and implemented and that documented procedures and adequate training are in place …proportionate to the importance of the computerised system and the data or activities…

(iii) Maintain a record of the individual users who are authorised to access the system, their roles and their access permissions

(iv) … in accordance with delegations by the investigator and visible to the investigator

(v) Ensure that there is a process in place for service providers and investigators to inform the sponsor of system defects identified

ICH E6 R3 Sponsor

For systems used or deployed by the investigator/institution:

(vi) Assess whether such systems…are fit for purpose or whether the risks from a known issue(s) can be appropriately mitigated. This assessment should occur during the process of selecting clinical trial sites and should be documented

(vii) In situations where clinical practice computerised systems are being considered for use in clinical trials (e.g., electronic health records or imaging systems used or deployed by the investigator/institution), these systems should be assessed for their fitness for purpose in the context of the trial

Question(s) received

- Following on from "fit for purpose" what is expected for sites with poor esystem process but high subject needs. Should these sites be eliminated from studies or will inspectors accept a pragmatic approach with some risk mitigation to ensure that the study can reach as many as possible?
- For investigator-deployed computerised systems, to what extent should the sponsor be involved in validation and testing, given the responsibility to demonstrate their oversight over these systems?
- Regarding the sponsor assessment of systems implemented by the investigator - what type of documentation could evidence this assessment during inspection?
- Computerised systems should be fit for purpose in a risk based context to ensure reliable data. Is “fit for purpose” equal to the EMA Guidance on computerised systems and electronic data in clinical trials?
- Direct access to investigators’ system is a challenge. What mitigation is acceptable?

Selected topic 2: Data and metadata review

Metadata review, expectations

E-guideline 6.2.2.

Data review can be used to (among others):

- identify missing data
- detect signs of data manipulation
- identify abnormal data/outliers and data entered at unexpected or inconsistent hours and dates (individual data points, trial participants, sites)
- identify incorrect processing of data (e.g. non-automatic calculations)
- detect unauthorised accesses
- detect device or system malfunction
- detect if additional training is needed for trial participants /site staff etc.
- detect situations where direct data capture has been defined in the protocol but where this is not taking place as described

ICH E6 R3 Data review Investigator

2.12.3 The investigator should be provided with timely access to data by the sponsor (see section 3.16.1(k)) and be responsible for the timely review of data, including relevant data from external sources that can have an impact on, for example, participant eligibility, treatment or safety (e.g., central laboratory data, centrally read imaging data, other institution's records and, if appropriate, electronic patient-reported outcome (ePRO) data). The protocol may provide exceptions for access, for instance, to protect blinding

ICH E6 R3 Data review Sponsor

3.16.1

(b) The sponsor should apply quality control to the relevant stages of data handling to ensure that the data are of sufficient quality to generate reliable results. The sponsor should focus their quality assurance and quality control activities, including data review, on data of higher criticality and relevant metadata

(k) The sponsor should ensure that the investigator has timely access to data collected in accordance with the protocol during the course of the trial, including relevant data from external sources (e.g., central laboratory data, centrally read imaging data and, if appropriate, ePRO data)… The sponsor should not share data that may unblind the investigator and should include the appropriate provisions in the protocol

(n) The sponsor should ensure that the investigator receives instructions on how to navigate systems, data and relevant metadata for the trial participants under their responsibility

Metadata review, expectations

ICH E6 R3:

4.2.3 Review of Data and Metadata

Procedures for review of trial-specific data, audit trails and other relevant metadata should be in place. It should be a planned activity, and the extent and nature should be risk-based, adapted to the individual trial and adjusted based on experience during the trial

These requirements are similar to requirements in the EU e-guideline

Metadata review, expectations

ICH E6 R3:

4.2.2 Relevant Metadata, Including Audit Trails

The approach used by the responsible party for implementing, evaluating, accessing, managing and reviewing relevant metadata associated with data of higher criticality should entail:

(a) Evaluating the system for the types and content of metadata available to ensure that:

(i) Computerised systems maintain logs of user account creation, changes to user roles and permissions and user access

(ii) Systems are designed to permit data changes in such a way that the initial data entry and any subsequent changes or deletions are documented, including, where appropriate, the reason for the change

(iii) Systems record and maintain workflow actions in addition to direct data entry/changes into the system

ATR/Metadata review, expectations

(b) Ensuring that audit trails, reports and logs are not disabled. Audit trails should not be modified except in rare circumstances (e.g., when a participant's personal information is inadvertently included in the data) and only if a log of such action and justification is maintained

(c) Ensuring that audit trails and logs are interpretable and can support review

(d) Ensuring that the automatic capture of date and time of data entries or transfer are unambiguous (e.g., coordinated universal time (UTC))

(e) Determining which of the identified metadata require review and retention

Questions received

Can you please advise in what type of document the study-specific strategy for the audit trail review of the systems used in the trial is expected?

Where is it possible to find guidance on how to perform the audit trail review?

Selected topic 3: Data endorsement

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ICH E6 R3 Data endorsement

Investigator

2.12.1 In generating, recording and reporting trial data, the investigator should ensure the integrity of data under their responsibility, irrespective of the media used

2.12.5 The investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the data acquisition tools completed by the investigator site (e.g., case report form (CRF)) and in any other required reports (e.g., SAE reports). The investigator should review and endorse the reported data at important milestones agreed upon with the sponsor (e.g., interim analysis) (see section 3.16.1(o))

Sponsor

3.16.1 (o)

The sponsor should seek investigator endorsement of their reported data at predetermined important milestones

Please also read Q&A # 13 at the EMA/GCP IWG website

Question received

– Can you please elaborate on what would be the acceptable way to show endorsement by the investigator of the eCOA, ePRO data which is going directly to the database. Would a service provider be expected to build-in the capability of approving eCOA/ePRO data?

Selected topic 4: Data management steps prior to analysis

ICH E6 R3 Sponsor

3.16.1

(p) The sponsor should determine the data management steps to be undertaken prior to analysis to ensure the data are of sufficient quality. These steps may vary depending on the purpose of the analysis to be conducted (e.g., data for IDMC, for interim analysis or

(q) For planned interim analysis, the ability to access and change data should be managed depending on the steps to achieve data of sufficient quality for analysis

(r) Prior to provision of the data for final analysis and, where applicable, before unblinding the trial, edit access to the data acquisition tools should be restricted.

Examples of expected data management steps

Finalising

- Monitoring
- Review of data and metadata
- Data cleaning
- Import of external data
- Query resolution
- Coding of AEs, MH, CM
- PD documentation
- PI sign-off of data

ICH E6 R3 Sponsor 3.16.2

Statistical Programming and Data Analysis

Bridging to ICH E9 on Statistical Principles for Clinical Trials

(a) The sponsor should develop a statistical analysis plan that is consistent with the trial protocol and that details the approach to data analysis, unless the approach to data analysis is sufficiently described in the protocol.

(b) The sponsor should ensure that appropriate and documented quality control of statistical programming and data analysis is implemented (e.g., for sample size calculations, analysis results for IDMC review, outputs for clinical trial report, statistical or centralised monitoring).

(c) The sponsor should ensure the traceability of data transformations and derivations during data processing and analysis

ICH E6 R3 Sponsor 3.16.2

(d) The sponsor should ensure that the criteria for inclusion or exclusion of trial participants from any analysis set is pre-defined (e.g., in the protocol or the statistical analysis plan). The rationale for exclusion for any participant (or particular data point) should be clearly described and documented

(e) Deviations from the planned statistical analysis or changes made to the data after the trial has been unblinded (where applicable) should be clearly documented and justified and should only occur in exceptional circumstances… should be reported in the clinical trial report

(f) The sponsor should retain the statistical programming records that relate to the output contained or used in reports of the trial results, including quality control/validation activities performed. Outputs should be traceable to the statistical software programs, dated and time stamped, protected against any changes, and have access controls implemented to avoid inappropriate viewing of information that may introduce bias

Questions or comments?

Thanks for your attention and for the networking!

ICH E6 R3: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

ICH Step 4 release slides: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step%204_Presentation_2025_0123.pdf

EU e-guideline: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-and-electronic-data-clinical-trials_en.pdf

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