ICH E6 R3 Information meeting

The Danish Medicines Agency 27 and 28 February 2025

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Disclaimer

- This meeting and the presentations are local Danish (DKMA) initiatives that aim at supplementing the ACT EU meeting on E6 R3 and any official ICH training material. The opinion expressed are therefore not to be seen as those of ICH or the EMA
- 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

Content disclaimer

- This will not be a complete walk through the guideline, nor a complete list of changes from R2 to R3
- 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
- We recommend you to watch the recording from last week's ACT EU meeting last week when it becomes available
- The focus here will be on selected, significant changes (selected by me) with an extra focus on data governance
- Some selected questions from last week's ACT EU E6 R3 event has been inserted in this presentation as they may be of common interest. The opinion expressed are not opinions discussed in an ACT EU setting, and the opinions are my own

Logistics/house keeping

- There is streaming possibility, but focus will be on the room
- People online are muted and cameras are turned off
- We are monitoring questions from the chat using the Q&A function. These will be monitored both to potentially address a few after the breaks but also to guide us to things you find difficult/challenging and which may require Q&As from our side
- The sessions will be recorded for internal (EU regulator) e.g. inspector training purpose
- We will publish the presentation on our website (but not the recording)

Agenda

Background for the revision and the work of the ICH expert working group (EWG)
Scope and revised structure
Key concepts
Principles
Glossary
Annex 1,
- selected changes (IRB/IEC, Investigator, Sponsor)
  - Informed consent
  - End of participation
  - Qualification and training
  - Safety
  - IMP
  - Protocol deviations
- Data Governance, more in-depth (next slide)

Appendices, selected changes

And in between there will be breaks, cases and time for questions

We are aiming for a longer break around 16 DKMA time

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

Selected topic 5: data corrections

Background for the revision and the work of the EWG

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Initial Takeaways from Feedback and Comments on ICH E6(R2)

Concerns about the following:

- The clinical trial ecosystem is rapidly evolving and this was not reflected in the guideline.
- The academic community were concerned about a lack of proportionality.
- The R2 guidance was seen as a “one-size-fits-all” approach to clinical trials.
- The ability of clinical trials to meet all GCP requirements in different situations (e.g., during public health emergencies).
- GCP requirements were being applied where they were not applicable.

ICH-E6(R3): Background to this Revision

E8 – integrating QbD into study design and conduct

↕

E6 – Applying the foundation of E8 to the conduct of clinical trials

Do not read E6(R3) in isolation

- **E6: Good Clinical Practice (GCP) – finalised in 1996**
  - Described the responsibilities of investigators and sponsors and expectations of interested parties in the conduct of clinical trials;
  - Covered aspects of monitoring, reporting, and archiving of clinical trials; and
  - Included sections for essential documents and investigator brochures
- **E6 (R2) – finalised in 2016**
  - Included integrated addendum to encourage implementation of improved and more efficient approaches to GCP, while continuing to ensure human subject protection; and
  - Updated standards for electronic records.
- **E6 (R3) – finalised in 2025**
  - Grounded in the foundational principle of Quality by Design (QbD)
  - Involves critical thinking
  - Utilises proportionate, risk-based approaches
  - Recognises that a one size does not fit all.

GCP renovation E8 and E6

ICH E8 (R1) was adopted by the CHMP 14 October 2021 and date for coming into effect was 14 April 2022

ICH E6 (R3) was adopted by the CHMP 12 December 2024 and date of coming into effect is 23 July 2025

We (the expert working group for E6 R3) had our first meeting in November 2019

Do not read E6 in isolation!

E6(R3) Development Process

Gap Analysis: Utilising inputs from:

- Articles (including open letter to ICH & EMA)
- Responses to Clinical Trials Transformation Initiative (CTTI) survey
- Regional stakeholder engagement (such as public workshops, surveys)
- ICH guidelines

Stakeholder Representative Engagement

- E6(R3) EWG engaged with academic stakeholders in a series of meetings to seek input on the draft guideline.
- The EWG sought their views throughout the guideline development process.

Summary of Stakeholder Engagement to Support the Development of ICH E6(R3), 21 April 2020
https://database.ich.org/sites/default/files/E6-R3_PublicEngagemenSummary_2020_0421.pdf

Increased Transparency

- New approaches to enhance transparency (published draft principles in April 2021 and held a 2-day public web conference in May 2021).

Public Consultation - May to Nov 2023

- Over 7000 Comments received and reviewed.

Final Principles and Annex 1 document adopted - January 2025

Scope and revised structure

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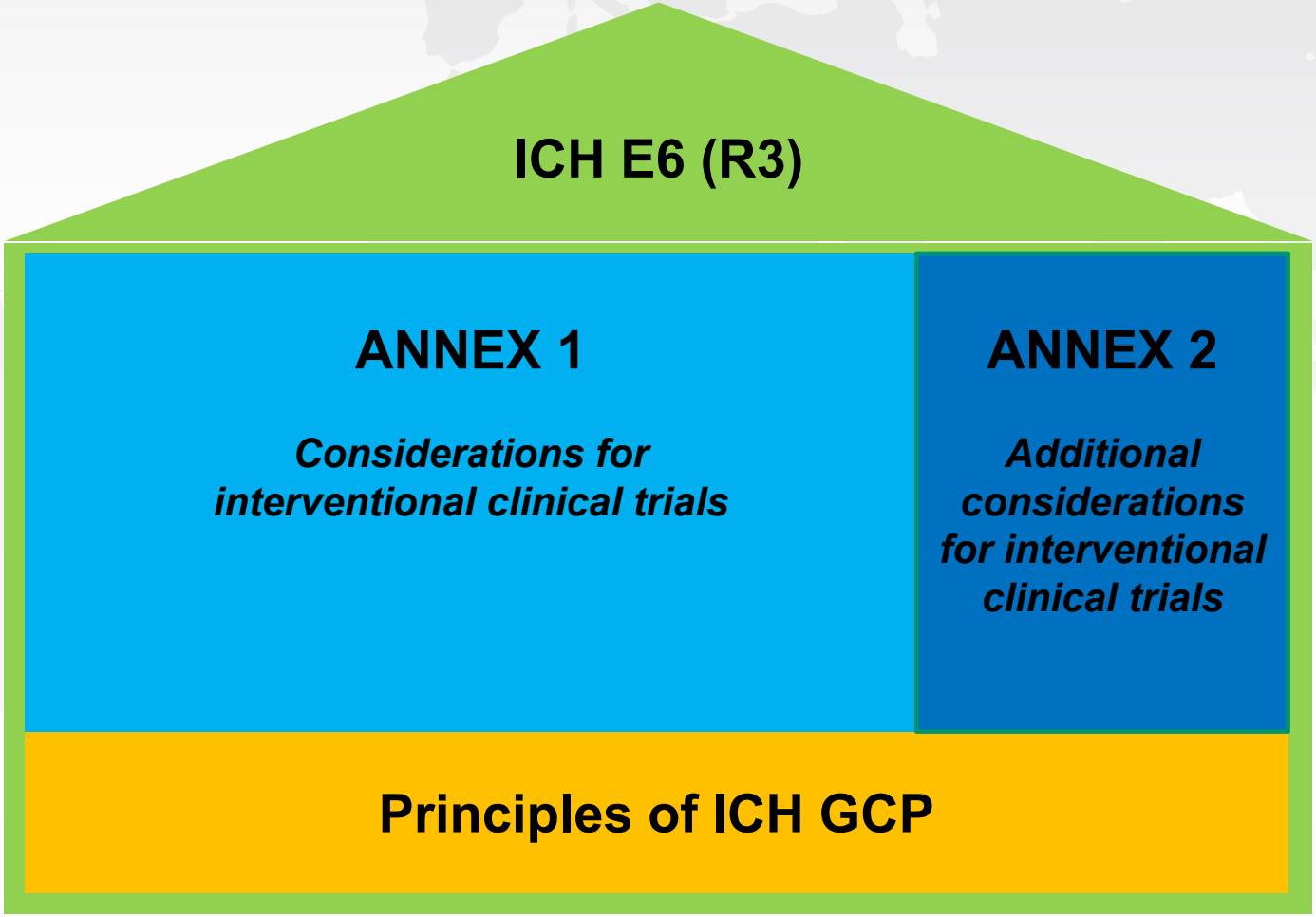
Scope

- This guideline applies to interventional clinical trials of investigational products that are intended to be submitted to regulatory authorities. The Principles of GCP in this guideline may also be applicable to other interventional clinical trials of investigational products that are not intended to support marketing authorisation applications in accordance with local requirements.
- The Annexes provide the basis for the appropriate interpretation and application of the principles and should therefore be appropriately considered; however, various approaches to the provisions in the Annexes may be considered provided they are justified and achieve the intended purpose of the application of the principles.
- This guideline encourages a risk-based and proportionate approach to the conduct of a clinical trial.

OVERVIEW OF ICH E6 (R3)



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
3. Sponsor
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*

Key concepts in E6 (R3)

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Focus on fit for purpose clinical trial quality (QbD and proportionate, risk-based approaches)

- This guideline builds on key concepts outlined in ICH E8 (R1) General Considerations for Clinical Studies. This includes fostering a quality culture and **proactively designing quality into clinical trials** and drug development planning, identifying factors critical to trial quality, and engaging interested parties, as appropriate, using a proportionate risk-based approach.
- Clinical trials vary widely in scale, complexity, and cost. Careful evaluation of **critical to quality factors** involved in each trial **and risks** associated with the priorities will help ensure efficiency by focusing on activities critical to achieving the trial objectives.

Focus on fit for purpose clinical trial quality (QbD and proportionate, risk-based approaches) (2)

- QbD should be implemented to identify the factors (i.e., data and processes) that are critical to ensuring trial quality and the risks that threaten the integrity of those factors and ultimately the reliability of the trial results.
- **Clinical trial processes and risk mitigation strategies** implemented to support the conduct of the trial should be **proportionate** to the importance of the data being collected, the risks to trial participant safety and the reliability of trial results.
- Trial designs should be **operationally feasible and avoid unnecessary complexity**.

Innovation, Efficiency & Engagement

- Encouraging the exploration of technology:
  - The principles are intended to **support efficient approaches to trial design and conduct**. For example, **innovative digital health technologies**, such as wearables and sensors may expand the possible approaches to trial conduct.
  - Such technologies can be incorporated into existing healthcare infrastructures and enable the **use of a variety of relevant data sources** in clinical trials.
  - The use of technology in the conduct of clinical trials should be **adapted to fit the participant characteristics and the particular trial design.**
- Encouraging engagement and inclusivity:
  - The use of **innovative trial designs** and technologies may enable the inclusion of a **wider and more diverse population of participants** and thereby broaden the applicability of trial outcomes.
  - The design and conduct of the clinical trial may be supported by **obtaining the perspectives of interested parties**, such as patients and their communities, patient advocacy groups and healthcare professionals. Their input can help to. **reduce unnecessary complexity, improve feasibility and increase the likelihood of meaningful trial outcomes**

Risk-based

”Risk-based’ is not about taking risks but about identifying and mitigating risks”

Questions for your consideration

Who do you bring to the table for your initial protocol drafting and risk assessments?

Do you have experience with engaging stakeholders such as patient representatives and researchers?

Do you find that you sometimes/often have to initiate the trial and then soon after have to adapt the protocol or the systems used?

Examples of wording in the principles

“6.1 Quality of a clinical trial is considered in this guideline as fitness for purpose“

“6.2 Factors critical to the quality of the trial should be identified prospectively”

“7.4 Trial processes should be operationally feasible and avoid unnecessary complexity, procedures and data collection”

“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”

“9.3 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”

Examples of wording in Annex 1

”2.3.1…The level of investigator oversight of the delegated activities should depend on the nature of the delegated activities and be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability”

“2.3.2 Trial-related training to persons assisting in the trial should correspond to what is necessary to enable them to fulfil their delegated trial activities that go beyond their usual training and experience”

“2.3.3 Documentation of delegation should be proportionate to the significance of the trial-related activities. In situations where the activities are performed as part of clinical practice, delegation documentation may not be required”

“2.7.2 b. In accordance with applicable regulatory requirements, the protocol may identify SAEs not requiring immediate reporting; for example, deaths or other events that are endpoints…”

Examples of wording in Annex 1

“3.6.10 Trial-related activities performed by service providers should be conducted in accordance with relevant GCP requirements, which may be fulfilled by a service provider’s existing quality management processes that were not designed specifically to be GCP-compliant but are fit for purpose in the context of the trial”

“3.13.2. (d) The reporting of SUSARs to investigator(s)/institutions(s) and to the IRB(s)/IEC(s) should be undertaken in a manner that reflects the urgency of action required and should take into consideration the evolving knowledge of the safety profile of the product and should be performed in accordance with applicable regulatory requirements. In some regions, periodic reporting of line listings with an overall safety assessment may be appropriate”

In general, absolutes such as “each”, “any”, “all” etc. have been replaced, except in the cases where the EWG retained it deliberately

Question received

What is your position on 2 sponsor camps existing:

1) R3 not differing much from ICH R2 - we are doing most of it already (e.g. risk-based approach) and doesn't have much impact on our processes.
2) R3 is a total rewrite having impact on our operating procedures requiring a formal gap analysis

Sponsor requirements are challenging for academic sponsors. What do you suggest to start addressing these challenges and what are the main aspects to consider in this first phase?

Principles

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Principles, main changes

Most of the old virtues of principle 2.1-2.13 in R2 have been transferred to R3 and elaborated to connect them to text in annex 1, thus further tying the principles to the annexes

There are two new principles (principle 7 on risk proportionality and principle 10 on responsibilities)

ICH E6 (R3) Principle

ICH E6 (R3) PRINCIPLE	TOPIC	ICH E6 (R2) PRINCIPLE
1	Ethical Principles	2.1, 2.2, 2.3, 2.7, 2.11
2	Informed Consent	2.9
3	IRB/IEC Review	2.6
4	Science	2.4, 2.5
5	Qualified Individuals	2.8
6	Quality	2.13
7	Risk Proportionality	N/A
8	Protocol	2.5
9	Reliable Results	2.10
10	Roles and Responsibilities	N/A
11	Investigational Products	2.12

ICH E6(R3) Principle 7

Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected and that avoids unnecessary burden on participants and investigators.

Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected.

- Risks to rights, safety and well-being of participants; and
- Risks to the reliability of trial results.

The focus should be on the risks associated with trial participation.

Risks to critical to quality factors should be managed proactively and adjusted when new or unanticipated issues arise once the trial has begun.

Trial processes should be operationally feasible and avoid unnecessary complexity, procedures and data collection.

ICH E6(R3) Principle 10

Roles and responsibilities in clinical trials should be clear and documented appropriately.

The sponsor may transfer or the investigator may delegate their tasks, duties or functions, but they retain overall responsibility for their respective activities.

Agreements should clearly define the roles, activities and responsibilities for the clinical trial and be documented appropriately. Where activities have been transferred or delegated to service providers, the responsibility for the conduct of the trial resides with the sponsor or investigator, respectively.

The sponsor or investigator should maintain appropriate oversight of the aforementioned activities.

Glossary, selected changes

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Selected new or significantly revised glossary terms

Adverse Events and Adverse Reaction-Related Definitions
Agreement
Assent
Audit trail *(will be covered in the data governance part of the presentation)*
Data acquisition tool *(will be covered in the data governance part of the presentation)*
Data integrity *(will be covered in the data governance part of the presentation)*
Informed consent
Investigator site
Metadata *(will be covered in the data governance part of the presentation)*
Reference safety information
Service provider
Signature
Sponsor

AE - ADR – SAE - SUSAR

The glossary terms have been put under a header of ”Adverse Events and Adverse Reaction-Related Definitions” to facilitate the reading

Adverse Drug Reaction (ADR):

- In the pre-approval clinical experience with a new investigational product or its new usages (particularly as the therapeutic dose(s) may not be established): unfavourable and unintended responses, such as a sign (e.g., laboratory results), symptom or disease related to any dose of a medicinal product where a causal relationship between a medicinal product and an adverse event is a reasonable possibility. The level of certainty about the relatedness of the adverse drug reaction to an investigational product will vary. If the ADR is suspected to be medicinal product-related with a high level of certainty, it should be included in the reference safety information (RSI) and/or the Investigator’s Brochure (IB)
- The previous wording was: “is at least reasonable possibility, i.e. the relationship cannot be ruled out”

AE - ADR – SAE - SUSAR

Important medical event

An important medical event that may not be immediately life-threatening or result in death or hospitalisation, that may jeopardise the participant or that may require intervention to prevent serious outcomes (see ICH E2A and E19) should generally be considered as serious

Agreement

Agreement

A document or set of documents describing the details of any arrangements on delegation or transfer, distribution and/or sharing of activities and, if appropriate, on financial matters between two or more parties. This could be in the form of a contract. The protocol may serve as the basis of an agreement

Assent and informed consent

Assent
Affirmative agreement of a minor to participate in clinical trial. The absence of expression of agreement or disagreement should not be interpreted as assent

Informed Consent
A process by which a participant or their legally acceptable representative voluntarily confirms their willingness to participate in a trial after having been informed and been provided with the opportunity to discuss all aspects of the trial that are relevant to the participant's decision to participate. Varied approaches to the provision of information and the discussion about the trial can be used. This may include, for example, providing text in different formats, images and videos and using telephone or video conferencing with investigator site staff. Informed consent is documented by means of a written (paper or electronic), signed and dated informed consent form. Obtaining consent remotely may be considered when appropriate

Service provider

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

Sponsor

Sponsor
An individual, company, institution or organisation that takes responsibility for the initiation, management and arrangement of the financing of a clinical trial

A clinical trial may have one or several sponsors where permitted under regulatory requirements

All sponsors have the responsibilities of a sponsor set out in this guideline. In accordance with applicable regulatory requirements, sponsors may decide in a documented agreement setting out their respective responsibilities. Where the documented agreement does not specify to which sponsor a given responsibility is attributed, that responsibility lies with all sponsors

Questions or comments?

Annex 1, IRB/IEC

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IRB/IEC

- Included global language about reporting to IRB/IEC and regulatory authorities.
- Updated to reflect digitisation and variable approaches to obtaining consent.
- Clarified the potential for participants to be compensated for costs incurred to participate in the trial.
- Clarified that the IRB/IEC should review the assent information, considering the age, maturity and psychological state of the minor, as well as applicable regulatory requirements.

Annex 1, Informed concent

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Questions for your consideration

What are your criteria for when a reconsent is requested?

– For all participants

– For new participants

– At all? Is it sometimes enough to just inform participants and document this in medical records?

Do you always mark changes clearly in the new versions of the consent to make life easier for the participants and sites?

Annex 1, Informed consent

- Varied approaches to the provision of information and the discussion about the trial can be used. This may include, for example, providing text in different formats, images and videos and other interactive methods
- The information should be as clear and concise as possible, use simple language and avoid unnecessary volume and complexity
- Informed consent is documented by means of a written (paper or electronic), signed and dated informed consent form
- Obtaining consent remotely may be considered when appropriate
- When using computerised systems for informed consent processes, also refer to the EU e-guideline section A 5.3 in terms of: inclusivity, facilitating participants' understanding, establishing identity, access and confidentiality (among others) and note that in the e-guideline we divide into a) providing information b) the possibility to ask question, and c) the actual obtaining of consent

Annex 1, Re-consent

2.8.2 The participant or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue trial participation. The communication of this information and confirmation of the willingness to continue trial participation should be documented

New information that could impact a participant's willingness to continue participation should be assessed to determine if re-consent is needed (e.g., depending on the stage of the trial, consideration should be given to whether the new information is relevant only to new participants or to existing participants). If re-consent is needed (e.g., information on emerging safety concerns), new information should be clearly identified in the revised informed consent materials. Revised informed consent materials should receive the IRB/IEC's approval/favourable opinion in advance of use

Annex 1, End of participation

2.9.1 When a participant decides to stop treatment with the investigational product or withdraw from a trial; is discontinued from the trial; or reaches the routine end of the trial, the investigator should follow the protocol and/or other protocol-related documents

For participants who did not reach the routine end of the trial, this may include instructions to avoid loss of already collected data, in accordance with applicable regulatory requirements, to ensure that trial results are reliable. In general, loss of already collected data may bias results and may lead to, for example, inaccurate conclusions regarding the safety profile of the investigational product

In the EU, it is very clear from the Clinical Trial Regulation that: “without prejudice to Directive 95/46/EC, the withdrawal of informed consent should not affect the results of activities already carried out, such as the storage and use of data obtained on the basis of informed consent before withdrawal”

Annex 1, End of participation

2.9.2 Although a participant is not obliged to provide a reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. The investigator should consider if a discussion with the participant or the participant's legally acceptable representative is appropriate. This discussion should focus on the reasons for withdrawal to determine if there are ways to address the concerns such that the participant could reconsider their withdrawal without unduly influencing the participant's decision. The investigator or delegated investigator site staff should consider explaining to the participant the value of continuing their participation to minimise trial participants withdrawal. In this process, the investigator should ensure that it does not interfere with the participant's decision to refuse or withdraw participation at any time.

2.9.3 Where relevant, the investigator should inform the participant about the trial results and treatment received when this information is available from the sponsor after unblinding, with due respect to the participant's preference to be informed.

Questions or comments?

Annex 1, Qualification and training

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Annex 1, Qualification and training

- The investigator(s) should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial (2.1.1) and should provide evidence of such qualifications and should be familiar with the appropriate use of the investigational product(s) as described in the protocol, in the current Investigator's Brochure, in the product information and/or in other information sources provided by the sponsor (2.1.2).
- The investigator should also have sufficient time, an adequate number of available and qualified staff, and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely (2.2.2).
- Regarding other persons or parties to whom the investigator has delegated trial-related activities, the investigator should ensure that they are appropriately qualified and are adequately informed about relevant aspects of the protocol, the investigational product(s) and their assigned trial activities (including activities conducted by staff provided by other parties in accordance with local regulatory requirements). Trial-related training to persons assisting in the trial should correspond to what is necessary to enable them to fulfil their delegated trial activities that go beyond their usual training and experience (2.3.2).

Annex 1, Qualification and training

- The sponsor should utilise appropriately qualified individuals (and service providers) for the activities to which they are assigned (e.g., biostatisticians, clinical pharmacologists, physicians, data scientists/data managers, auditors and monitors) throughout the trial process (3.4, 3.11.2.1.(b), 3.11.4.2 (a), 3.16.1 (x) (ii), 4.3.2 and C.3.1.(l and m)).

- When using service providers, the sponsor is responsible for assessing the suitability of and selecting the service provider to ensure that they can adequately undertake the activities transferred to them (3.6.7).

- This includes assessing the suitability of the training of the service provider's staff.

DKMA Q&A: Training in GCP

- In determining the need for retraining in general, it should be considered if performing clinical trials is a standard for that person or party (e.g. often the case in oncology and hematology departments) or the person or party only occasionally is involved in clinical trials, in which case training in relation to the individual trial is more appropriate.

- Retraining should specifically be considered whenever there are significant updates to the guidelines, such as the publication of a new revision like E6 R3.

- More specifically to E6 R3, the Danish Medicines Agency is expecting that principal investigators are familiarised with/trained in E6 R3 as they are one of the two legally responsible parties of a trial (together with the sponsor).

- For the persons or parties to whom the investigator has delegated trial-related activities, the need for retraining will depend on their tasks.

DKMA Q&A: Training in GCP

- If a person performs tasks in areas where the guideline has not changed, retraining is not required; however, it is likely that for the major part of clinical trial staff they will need some degree of retraining, due to the substantial amount of changes in the guideline.
- It should be considered that some protocols and manuals already describe the tasks of delegated persons and parties to a degree that training and retraining may be reduced, depending on their tasks.
- With regards to the amount, frequency and method of training, the Danish Medicines Agency does not have a specific expected standard (e.g. yearly, every other year etc.).
- The responsible parties (the principal investigator and the sponsor) should ensure that training and qualifications are adequate for the tasks. As trials vary, this is consequently not a one size fits all approach.
- As the sponsor is responsible for selecting the investigator(s)/institution(s) (3.7.1), the sponsor has co-responsibility to ensure that each investigator is qualified by education, training and experience.

DKMA Q&A: Gap analysis and inspections

- ICH E6 R3 will enter into force 23 July 2025. In the period until then, the responsible parties (sponsors and investigators) should prepare themselves for the future implementation by performing a gap analysis or via other means identify new or revised training requirements for new or ongoing trials.

- The GCP inspectors may evaluate this gap analysis during GCP inspections and assess whether the training requirements of ICH E6 R3 are adequately implemented and documented.

Questions received

- Do all types of vendors need to have training on ICH E6 R3?

- Will the training the inspectors are being given be made available as this will help auditors ensure they are interpreting things the same way and QA departments better understand expectations and prepare accordingly?

- The flexibility of R3 is important and is very welcome ("justified/where required/where necessary" is referenced 30 times in R3). How will consistency of interpretation by EU GCP inspectors on what is "justifiable" or "required" be assured?

- What does it mean in practice that the delegation doesn’t need to be documented for normal practice? for example nurses drawing blood as per standard do not need to be on the delegations log? The same for ECG etc… as long it is standard and not directly impacting the endpoints of the study?

Questions for your consideration

– What are your current requirements for GCP-training for different roles (investigator sites/service providers/sponsor)?

– What are your considerations related to your own procedures going forward?

Questions or comments?

Annex 1, safety

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Safety of the participants

Principle 1.2

The safety of the participants should be reviewed in a timely manner as new safety information becomes available, which could have an impact on participant safety, their willingness to continue in the trial or the conduct of the trial

Safety of the participants

2.7.1 Medical Care of Trial Participants

- (a) A qualified physician or, where appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) who is an investigator or a sub-investigator for the trial should have the responsibility for trialrelated medical care and decisions
- (b) Other appropriately qualified healthcare professionals may be involved in the medical care of trial participants, in line with their normal activities and in accordance with local regulatory requirements
- (c) During and following participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware
- …

Safety reporting (investigator to sponsor)

(a) Adverse events and/or abnormal test results required for safety evaluations (as outlined in the protocol) should be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol. Unfavourable medical events occurring in participants before investigational product administration (e.g., during screening) should be considered and reported to the sponsor if required by the protocol

(b) All serious adverse events (SAEs) should be reported immediately (after the investigator reasonably becomes aware of the event) to the sponsor. The investigator should also include an assessment of causality. In accordance with applicable regulatory requirements, the protocol may identify SAEs not requiring immediate reporting; for example, deaths or other events that are endpoints. Subsequent information should be submitted as a follow-up report, as necessary

(c) …

(d) …

Safety reporting (sponsor)

3.13.2

a) The sponsor should submit …safety updates and periodic reports…

b) The sponsor should…expedite the reporting…of all suspected, unexpected and serious adverse reactions (i.e., SUSARs).

c) Safety reporting to regulatory authorities should be undertaken by assessing the expectedness of the reaction in relation to the applicable product information (e.g., the reference safety information (RSI) contained within the Investigator's Brochure or alternative documents) in accordance with applicable regulatory requirements…

d) The reporting of SUSARs to investigator(s)/institutions(s) and to the IRB(s)/IEC(s) should be undertaken in a manner that reflects the urgency of action required and should take into consideration the evolving knowledge of the safety profile of the product and should be performed in accordance with applicable regulatory requirements. In some regions, periodic reporting of line listings with an overall safety assessment may be appropriate.

Safety reporting (sponsor)

(e) Urgent safety issues requiring immediate attention or action should be reported to the IRB/IEC and/or regulatory authority(ies) and investigators without undue delay and in accordance with applicable regulatory requirements.

(f) Alternative arrangements for safety reporting to regulatory authorities, IRBs/IECs and investigators and for reporting by investigators to the sponsor should be prospectively agreed upon with the regulatory authority(ies) and, if applicable, the IRB/IEC, and described in the clinical trial protocol (e.g., SAEs considered efficacy or safety endpoints, which would not be subject to unblinding and expedited reporting; see ICH E2A). See ICH E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials.

Question for your consideration

– As a sponsor: What kind of urgent safety information do you send to participating investigators during the trial (SAEs/SARs/SUSARs?) – and in which format (individual CIOMS forms or line listings (monthly/quarterly/6-monthly)?

Questions or comments?

Annex 1 Investigational medicinal product (IMP)

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IMP handling

2.10.1 Responsibility for investigational product(s) management, including accountability, handling, dispensing, administration and return, rests with the investigator/institution.
The sponsor may facilitate aspects of investigational product management (e.g., by providing forms and technical solutions, such as computerised systems, and arranging distribution of investigational product to trial participants)

2.10.2 When the investigator/institution delegates some or all of their activities for investigational product(s) management to a pharmacist or another individual in accordance with local regulatory requirements, the delegated individual should be under the oversight of the investigator/institution

2.10.3 Where the investigator has delegated activities related to investigational product management or aspects of these activities have been facilitated by the sponsor, the level of investigator oversight will depend on a number of factors, including the characteristics of the investigational product, route and complexity of administration, level of existing knowledge about the investigational product's safety and marketing status

IMP handling

2.10.4 The investigator/institution and/or a pharmacist or other appropriate individual should maintain records of the product's delivery, the inventory, the use by each participant (including documenting that the participants were provided the doses specified by the protocol) and the return to the sponsor and destruction or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable) and the unique code numbers assigned to the investigational product(s) and trial participants. For authorised medicinal products, alternative approaches to the aforementioned may be considered, in accordance with local regulatory requirements

2.10.5 The investigational product(s) should be stored as specified…

2.10.6 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol

2.10.7 …the investigator… should explain the correct use… and should check…that each participant is following the instructions properly

IMP handling

2.10.8 The investigational product may be shipped to the participant's location or supplied to/dispensed at a location closer to the participant (e.g., at a local pharmacy or a local healthcare centre). The investigational product may be administered at the participant's location by investigator site staff, the participant themselves, a caregiver or a healthcare professional

2.10.9 Investigational product management should be arranged and conducted in accordance with applicable regulatory requirements, and safeguards should be in place to ensure product integrity, product use per protocol and participant safety

IMP handling

3.15.3.a:
The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s). Where appropriate, the sponsor may supply the investigational product(s) to the trial participants in accordance with applicable regulatory requirements…. Various approaches for shipping and dispensing may be undertaken, for example, by taking into consideration the characteristics of the investigational products, the route and complexity of administration and the level of existing knowledge about the investigational product's safety profile…in accordance with applicable regulatory requirements, and safeguards should be in place…

In 3.15.2 (d), new and revised language has been included about protecting the blinding and that the investigators should be permitted to rapidly perform unblinding without undue delay and hindrance in the case of an emergency, to protect participant safety.

Questions or comments?

Annex 1 Protocol deviations

Annex 1 Protocol deviations

2.5.3 The investigator should document all protocol deviations. In addition to those identified by the investigator themselves, protocol deviations relevant to their trial participants and their conduct of the trial may be communicated to them by the sponsor (see section 3.11.4.5.1(b)). In either case, the investigator should review the deviations, and for those deviations deemed important, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence, where applicable (see section 3.9.3)

3.11.4.5. Monitoring … should generally include
1. Communication with parties conducting the trial…
b) Informing the investigator or other parties and individuals involved in the trial conduct of relevant deviations from the protocol, GCP and the applicable regulatory requirements and, if necessary, taking appropriate action designed to prevent recurrence of the detected deviations. Important deviations should be highlighted and should be the focus of remediation efforts as appropriate

Annex 1 Protocol deviations

3.9.3 The sponsor should determine necessary trial-specific criteria for classifying protocol deviations as important. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the trial data or that may significantly affect a participant's rights, safety or wellbeing

3.10.1.3 Risk Control …Where relevant, the sponsor should set pre-specified acceptable ranges (e.g., quality tolerance limits at the trial level) to support the control of risks to critical to quality factors. These pre-specified ranges reflect limits that when exceeded have the potential to impact participant safety or the reliability of trial results. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed

Plus other language related to appropriate communication and reporting of yet a subset of deviations/non-compliance. The requirements vary between regions e.g. serious breach reporting in the EU

Annex 1 Protocol deviations in ICH E3

STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS

10.2 Protocol Deviations
All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment should be described

In the body of the text, protocol deviations should be appropriately summarised by centre and grouped into different categories, such as:
• those who entered the study even though they did not satisfy the entry criteria
• those who developed withdrawal criteria during the study but were not withdrawn
• those who received the wrong treatment or incorrect dose
• those who received an excluded concomitant treatment
In appendix 16.2.2, individual patients with these protocol deviations should be listed, broken down by centre for multicentre studies

Question received

– Why was the dichotomy of noncompliance and serious breaches not harmonised?

Questions or comments?

Annex 1 (Data Governance), selected changes

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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

Data governance – sub-agenda

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

Investigator responsibilities for data governance

Sponsor responsibilities for data governance

Essential records (selected) related to data governance

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

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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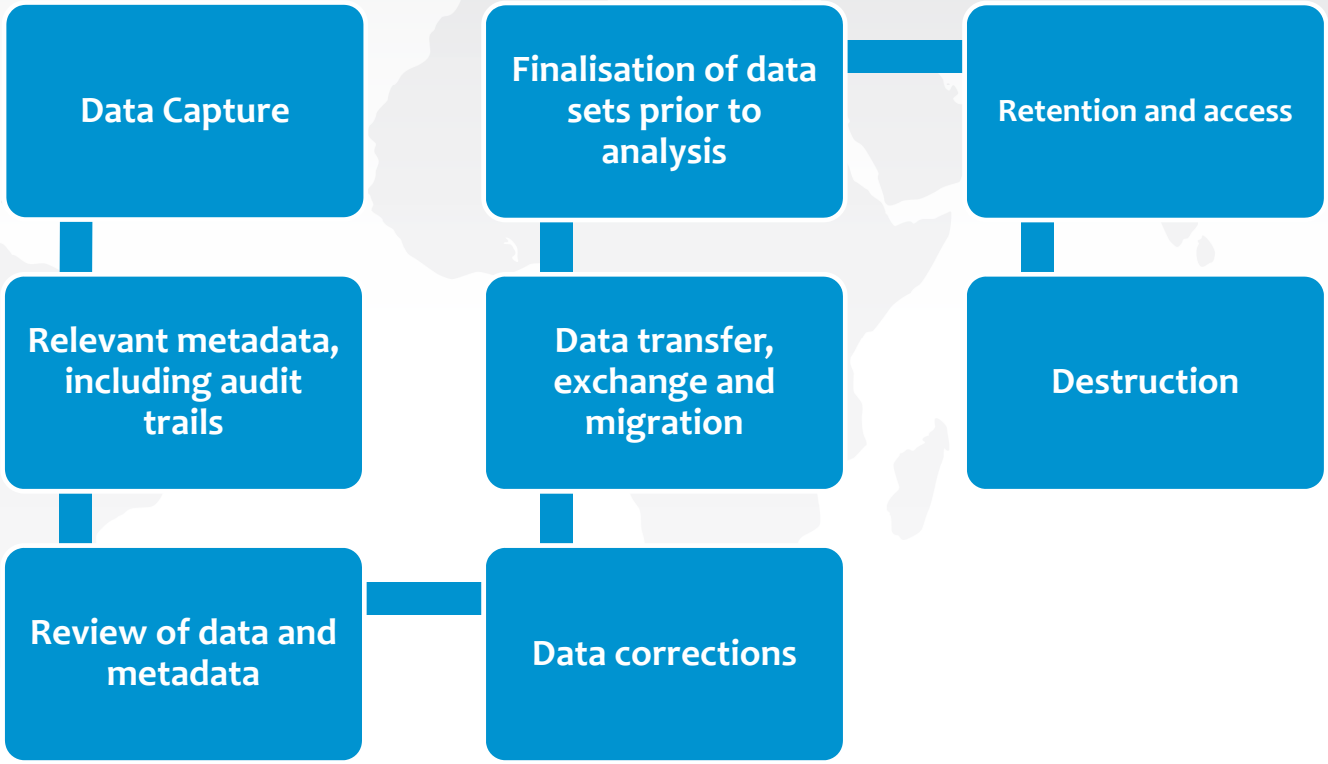
Data Governance

- 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.

Selected topic 1: Responsibility for computerised systems

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Data Governance (3)

- Clarified that computerised systems should be fit for purpose, depending on their specific use in the clinical trial.
- Specified that the approach to the management of computerised systems should be proportionate to their importance to participant safety and the reliability of trial results.
- Clarified that responsibilities for computerised systems should be clear and documented.
- Described the elements of computerised system life cycle to be addressed from design to decommissioning.

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

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)

There is a strong 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

For all systems

(ix) Ensure that there is a process in place for service providers and investigator(s)/ institution(s) to inform the sponsor of incidents that could potentially constitute a serious noncompliance…

ICH E6 R3 New section 4

Computerised systems

Summary of responsibilities:

- The sponsor is responsible for ensuring that for computerised systems which they put in place, the expectations for computerised systems as described in this section are addressed in a risk proportionate manner
- The sponsor should review whether the systems used by the investigator/institution (e.g., electronic health records and other record keeping systems for source data collection) are fit for purpose in the context of the trial
- In the event that the investigator/institution deploys systems specifically for the purposes of conducting clinical trials, the investigator/institution should ensure that the expectations are proportionately addressed and implemented

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?
- Can you speak more to sponsor assessment of systems implemented by the investigator - I can imagine that this will require more collaboration at the beginning of the study… and 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?

Question(s) received

- Direct access to investigators' system is a challenge. What mitigation is acceptable?
- Common mitigation system for not validated eHMR is the printing out medical record sign and date them by the PI; this system is assessed as compliant by the Sponsor. In the new framework set by R3, is this practice still acceptable?
- Should the sponsor provide the eISF validation documentation to the experimental site? These kinds of systems are provided by the sponsor but are managed and overseen by the investigator side

Deviations related to PIs TMF

Cases with examples of sponsor co-responsibility for PI TMFs (ISF)

Case 1: Implementation of a portal holding documentation for PI actions

Case 2: Sponsor pressure on site to implement specific electronic ISF

Case 3: Sponsor delivering complex electronic IRT accountability records as paper

Questions or comments?

Selected topic 2: Data and metadata review

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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

Metadata review, expectations

E-guideline:

Procedures for risk-based trial specific audit trail reviews should be in place

Performance of data review should generally be documented

Data review should focus on critical data

Data review should be proactive and ongoing review is expected unless justified

Manual review as well as review by the use of technologies to facilitate the review of larger datasets should be considered

In addition to audit trail review, metadata review could also include (among others) review of access logs, event logs, queries, etc.

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

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

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

Case example, automated metadata review

Based on slides borrowed with permission from Willie Muehlhausen, presented during the recent meeting in Copenhagen between a sub-group of stakeholders and GCP IWG members

3D Accelerometer Data

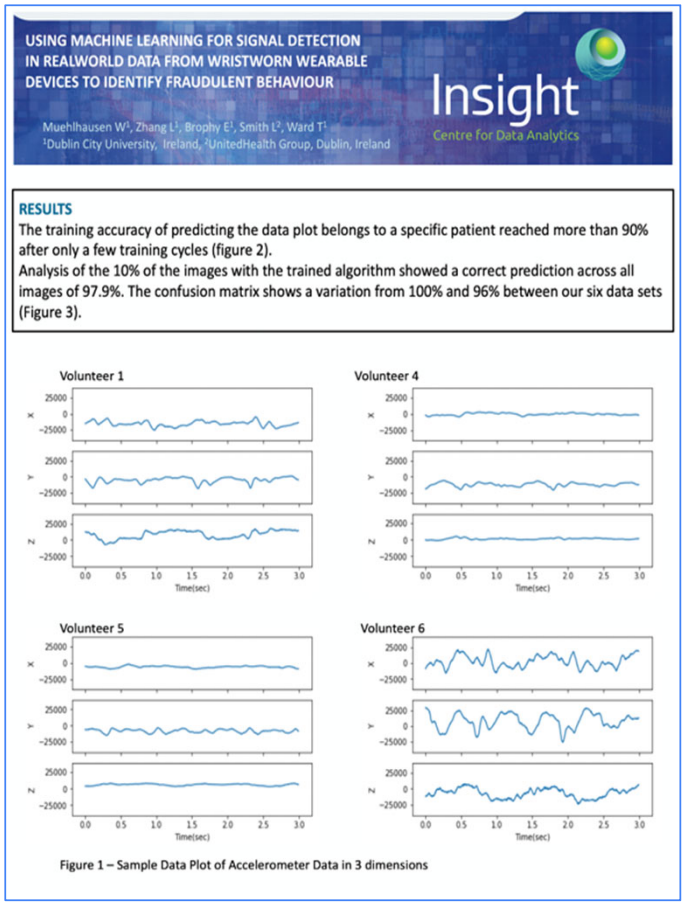
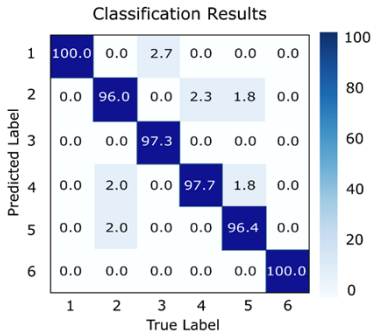
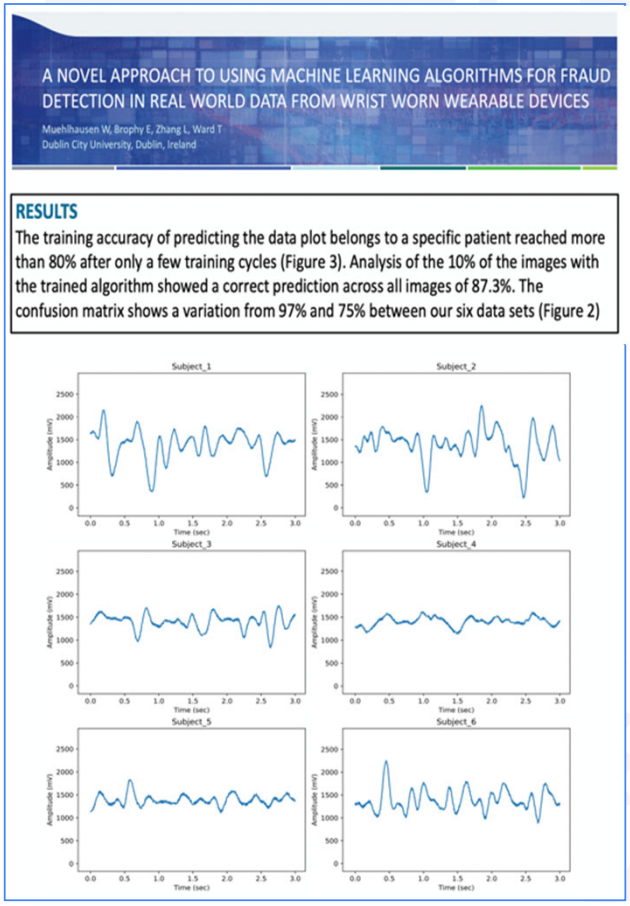
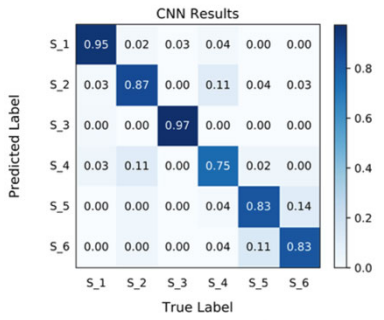


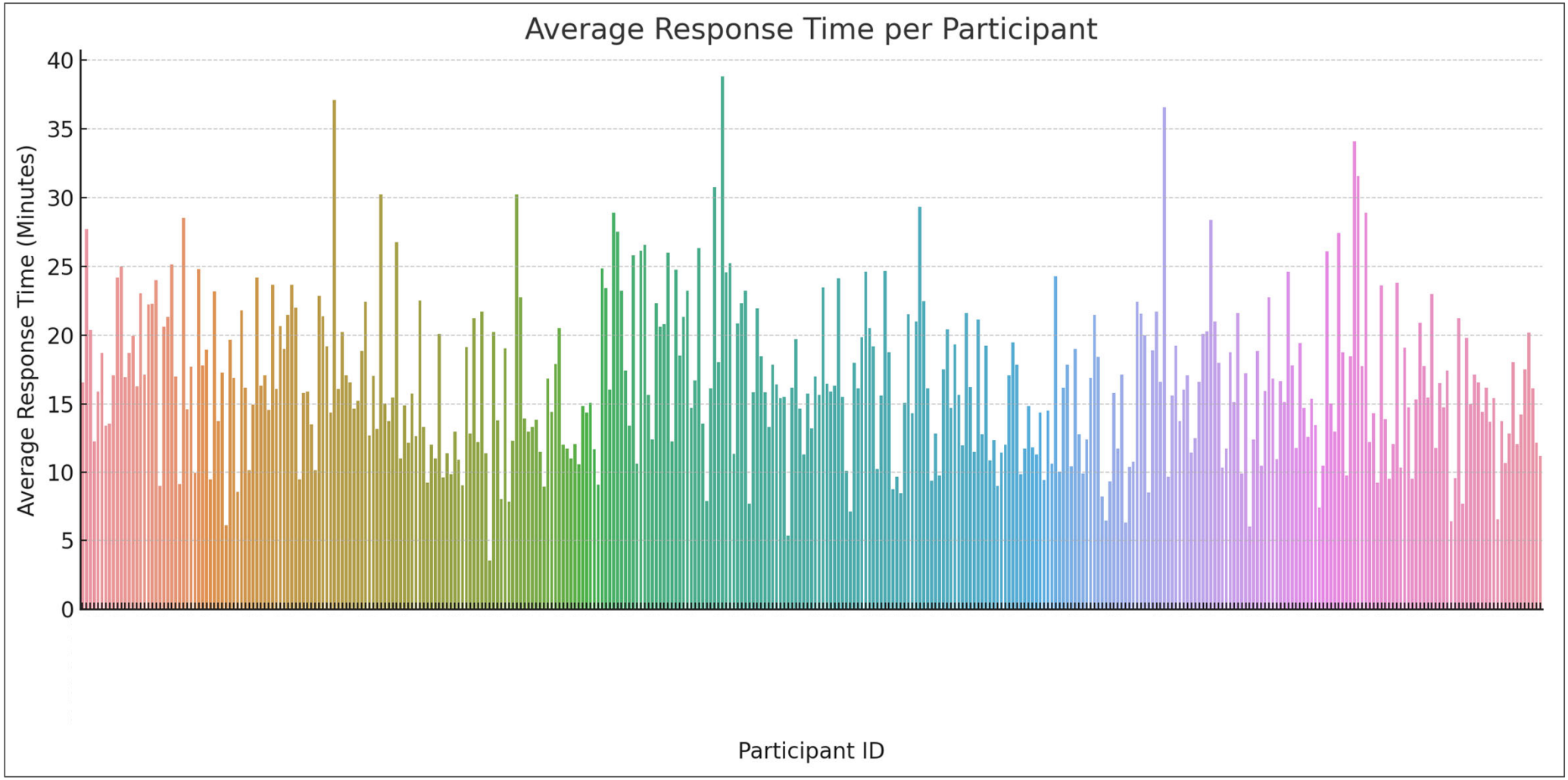
Figure 1 – Sample Data Plot of Accelerometer Data in 3 dimensions

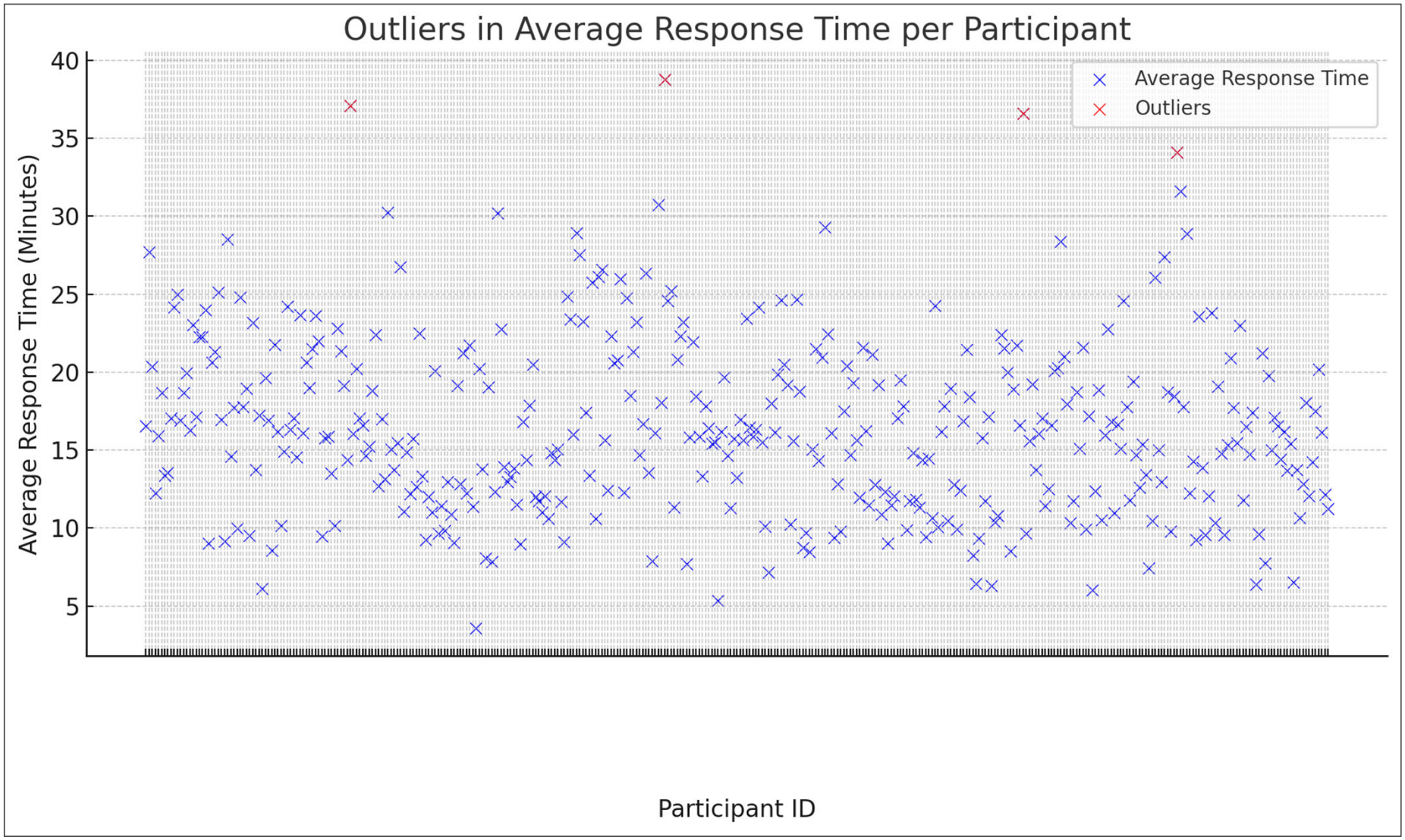


Photoplethysmography (PPG)






Average Response Time per Participant
Average Response Time (Minutes)
0
5
10
15
20
25
30
35
40
Participant ID


Outliers in Average Response Time per Participant
Average Response Time (Minutes)
Participant ID
Average Response Time
Outliers
40
35
30
25
20
15
10
5

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?

Questions or comments?

Selected topic 3: Data endorsement

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

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

The investigators are responsible for data entered into eCRFs and other data collection tools under their supervision (electronic records). Those data should be reviewed and signed-off

The signature of the PI or authorised member of the investigator's staff is considered as the documented confirmation that the data entered in the eCRF and submitted to the sponsor are attributable, legible, original, accurate, and complete and contemporaneous (ICH-GCP 4.9.1)…

The acceptable timing and frequency for the sign-off needs to be defined and justified for each trial by the sponsor and should be determined by the sponsor on a risk-based manner…

Points of consideration are types of data entered, non-routine data, importance of data, data for analysis, length of the trial and the decision made by the sponsor based on the entered data, including the timing of such decisions

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

It is essential that data are confirmed prior to interim analysis and the final analysis and that important data related to e.g. reporting of SAEs, adjudication of important events and endpoint data, DSMB review, are signed off in a timely manner. In addition, a timely review and sign-off of data that are entered directly into the CRF as source is particularly important…

Therefore, it will rarely be sufficient to just implement one signature immediately prior to database lock…

To facilitate timely data review and signing by the PI or her/his designated representative, the design of the EDC system should be laid out to support the signing of the data at the defined timepoints…

Adequate oversight by the PI is a general requirement to ensure clinical trial participant safety and data quality and integrity. Oversight can be demonstrated via various means, one of them being review of reported data

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?

Questions or comments?

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

DKMA published Q&As on these topics

Common deviations related to data-handling, etc. in investigator-initiated trials

For example on:

- Statistical analysis
- Unblinding
- Randomisation
- Audit trail and metadata review

NB! These have not yet been reviewed following publication of E6 R3

Important message from these Q&As

GCP inspections have often found the TMF documentation to be insufficient with respect to the above processes (data finalisation, database lock, database review and decisions, time of unblinding…).

This creates uncertainty about the actual course of events of these specific processes, which are of vital importance to the credibility of the trial results. As a result, they are often classified as critical deviations and may have serious consequences for, for example, publications, applications for marketing authorisations, etc.

During our GCP inspections, we have seen several cases of deviations related to randomisation and/or blinding. Among them were coding errors resulting in stratification errors, unblinding of sponsor staff, lack of documentation of the blinded completion of important assessments (e.g. assessment of endpoints) as well as lack of documentation of communication between the manufacturer and supplier of randomisation lists. Randomisation and blinding processes are essential in a clinical trial, which is why any deviations in this area are often classified as critical.

Questions or comments?

Selected topic 5: Data corrections

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ICH E6 R3 Sponsor (data governance focus)

(i) The sponsor should not make changes to data entered by the investigator or trial participants unless justified, agreed upon in advance by the investigator and documented

(j) The sponsor should allow correction of errors to data, including data entered by participants, where requested by the investigators/participants. Such data corrections should be justified and supported by source records around the time of original entry

Questions/comments received

– How should e-diaries be managed? Is it acceptable that subjects enter and change their answers themselves in a e-diary if they find out that something is wrongly entered? Could you describe how you see the process?

A few other questions related to data governance

- About the above sentences: INV 2.12.1: "...the investigator should ensure the integrity of data under their responsibility" SPONSOR 3.16 "..should ensure the integrity and confidentiality of data generated and managed." Does it means that Inv is responsible for data, and Sponsor for the systems?
- In connection to patients' data privacy and data collection by the sponsor, what is your opinion on sponsors asking patients to use their own mobile devices to complete information on ePRO platforms?
- Comment to e-tools used by study participants- important that access to training , support and people who can speak the same language as study participants

Questions or comments?

Annex 1 (Appendices), selected changes

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ICH E6 (R3) Appendix A
Investigator's Brochure

ICH E6 (R3) Section	ICH E6 (R2) Section
A.1 – Introduction	7.1
A.2 – General Considerations	7.2
A.3 – Contents of the Investigator's Brochure • A.3.6 (b) – In R3, added frequency and nature of AEs should be included to determine expectedness of Serious Adverse Reactions.	7.3

Investigator's Brochure

- Added that a list of adverse reactions identified as the reference safety information, including information on their frequency and nature, should be included.
- Reorganised the order of language for clarification.
- Examples of title page and table of contents removed as same information can be read in the text of the guideline.

ICH E6 (R3) Appendix B

Clinical Trial Protocol and Protocol Amendments

ICH E6 (R3) Section	ICH E6 (R2) Section
B.1 – General Information	6.1
B.2 – Background Information	6.2
B.3 – Trial Objectives and Purpose	6.3
B.4 – Trial Design	6.4
B.5 – Selection of Participants	6.5
B.6 – Discontinuation of Trial Intervention and Participant Withdrawal from Trial	6.5
B.7 – Treatment and Interventions for Participants	6.6
B.8 – Assessment of Efficacy	6.7
B.9 – Assessment of Safety	6.8
B.10 – Statistical considerations	6.9

ICH E6 (R3) Appendix B

Clinical Trial Protocol and Protocol Amendments (2)

ICH E6 (R3) Section	ICH E6 (R2) Section
B.11 – Direct Access to Source Records	6.10
B.12 – Quality Control and Quality Assurance	6.11
B.13 – Ethics	6.12
B.14 – Data Handling and Record Keeping	6.4, 6.13
B.15 – Financing and Insurance	6.14
B.16 – Publication Policy	6.15

NB: E6 (R2) Section 6.16 on supplements relating to Final CSR removed.

Protocol

The guideline was updated to:

- Highlight the importance of the protocol, such as:
  - Building adaptability into the protocol, for example, by including acceptable ranges for specific protocol provisions, can reduce the number of deviations or in some instances the requirement for a protocol amendment.
- Encourage simplicity and clarity.
  - Clinical trials should be described in a clear, concise and operationally feasible protocol. The protocol should be designed in such a way as to minimise unnecessary complexity and to mitigate or eliminate important risks to the rights, safety, and well-being of trial participants and reliability of data.
- Address the implication for withdrawal of consent or discontinuation by the investigator.
- Broaden the statistical section to include statistical inference methodologies (e.g., Bayesian design and estimands).

ICH E6 (R3) Appendix C

Essential Records for the Conduct of a Clinical Trial

ICH E6 (R3) Section	ICH E6 (R2) Section
C.1 – Introduction	8.1
C.2 – Management of Essential Records	N/A – Major Revamp
C.3 – Essentiality of Trial Records	

Essential Records

- Provided guidance on what makes a record essential.
  - Many records are generated before and during the conduct of a clinical trial. The nature and extent of those records generated and maintained are dependent on the trial design, its conduct, application of risk proportionate approaches and the importance and relevance of that record to the trial.
- Provided clarity on the content and maintenance of essential records.
- Developed one table of examples of essential records, e.g., protocols, investigator brochure or basic product information, informed consent forms, necessary approvals/opinions.
- Provided guidance about access by the sponsor and investigator/institution to one another's relevant essential records in order to fulfill their respective responsibilities.

Question received

– With the revised section on Essential Records, what impact do you expect on the current trend to bigger and larger TMF/ISF?

Only the principles and Annex 1 contain requirements

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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Supportive slides on sites' eISFs

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Case 1

The sponsor had deployed a portal to exchange documents with the site. The portal was also used to document site staff acknowledgement of receipt, training, review etc.

Examples are protocol versions, SUSARs etc.

The site had downloaded documentation from the portal to a hard drive at the end of the trial.

Case 1 (continued)

The following major deviation was given during an investigator site inspection:

The external hard drive at the site does not fulfil the expectations to an electronic TMF for the following reasons (among others):

- There was no overall index of the content of the external hard drive even though some of the content was placed in folders mimicking the sponsor's defined TMF (based on DIA reference model) and it was consequently not possible to readily find e.g. documents from the IWRS system and the adjudication system among all the other documents.
- Due to the lack of index it was not possible to get an overview of the content without opening all documents and it was therefore not possible to ascertain whether all relevant documents were filed
- An index was found in the paper part of the ISF where it was stated that parts of the TMF was electronic; however, it was not clear where and from which periods, and some documents were doublets, others apparently missing.

Case 1 (continued)

- The site staff was also unaware of the content and not able to find documents within a reasonable time. As an example, the site staff was not aware that documentation from the IWRS (site accountability records) was on the hard drive It was not defined who should have access to the hard drive and there was no access protection on the device
- Documents can be uploaded and deleted without traceability
- Documents can be changed without traceability if not archived in appropriate formats
- All documents have been downloaded on the same day and the TMF has not been maintained

Reference documents: ICH GCP 4.9.4, 5.6.1, 5.18.4 (b), (k) and (p) plus 8.1. (and national legislation)

Case 1 (continued)

The site had perceived the portal and the downloaded documents as part of their ISF; however, the sponsor has delivered the system to be used as a portal for exchange of documents and not as a substitute for an ISF.

The site should ensure to maintain an appropriate TMF, irrespective of media used. Reference to the EU guideline was given.

The inspectors find that the sponsor is co-responsible for the insufficient ISF as they are responsible for pre-qualifying the site and determining whether the investigator is maintaining the essential documents (deviations given accordingly).

Case 2

The following major deviation was given during an investigator site inspection:

The PI has not ensured that the ISF has been maintained. Below is a list of challenges seen in relation to the archiving:

- *Access control:* The site did not have robust procedures on providing accesses to the ISF. Sponsors were given uncontrolled accesses to write, upload and delete documents.
- *Upload and control of documents:* The site did not have control with which documents were uploaded (and potentially deleted).
- Numerous documents were located in ”library” and were not linked to the ISF folder structure. The users were not familiar with linking between a document and the ISF folders.
- *Document status:* There is a risk that a site works according to the wrong version of the protocol. The CRO has uploaded several protocols signed by the sponsor but not approved yet. In addition, the site had not changed status on obsolete documents.

Case 2 (continued)

- The procedures around maintaining the ISF are unnecessarily burdensome for the site. As an example, the site is receiving several documents in paper formats which they then have to scan and upload to the electronic system in order for them to be available to the sponsor representatives online.
- *Naming conventions:* The documents do not consistently have meaningful names. As an example protocol amendment numbers can only be seen when opening the documents.

Reference document(s): ICH GCP 4.9.4, 5.0, 8.1

Case 2 (continued)

Additional comments to the deviation:

The DKMA does not wish to hinder the use of electronic ISFs; however, essential documents should be maintained and archived in a timely manner by trained staff.

The PI should ensure that when electronic ISFs are used in a clinical trial, a suitable number of persons should be trained in the use of the system. The PI should manage expectations with the sponsor with regards to how essential records are delivered to the site.

The DKMA finds that the sponsor is co-responsible for the deviation as the site was pressured by the sponsor to use a different ISF than the site is used to (paper). It is clear from monitoring reports that the site had XX unfiled documents. The DKMA requested audit trail from the system relevant to uploaded documents. It was seen that XX of YYY documents in the system were uploaded immediately prior to the inspection.

It is the PI's choice (and responsibility) which ISF to use. The sponsor/CRO should not put inappropriate pressure on the PI, which can adversely impact the resources of the site staff.

Case 2 (continued)

In case the sponsor provides the site ISF system or convinces the site to use a certain ISF, the DKMA finds that the sponsor is co-responsible for suitable training of the site.

In addition, the sponsor/monitor is responsible for determining whether the investigator is maintaining the essential documents.

Finally, the site informed the inspectors that the sponsor representatives no longer had access to the ISF; however, this was not correct according to the list of access required from the vendor during the inspection.