

ICH E6(R3) – The Implementation

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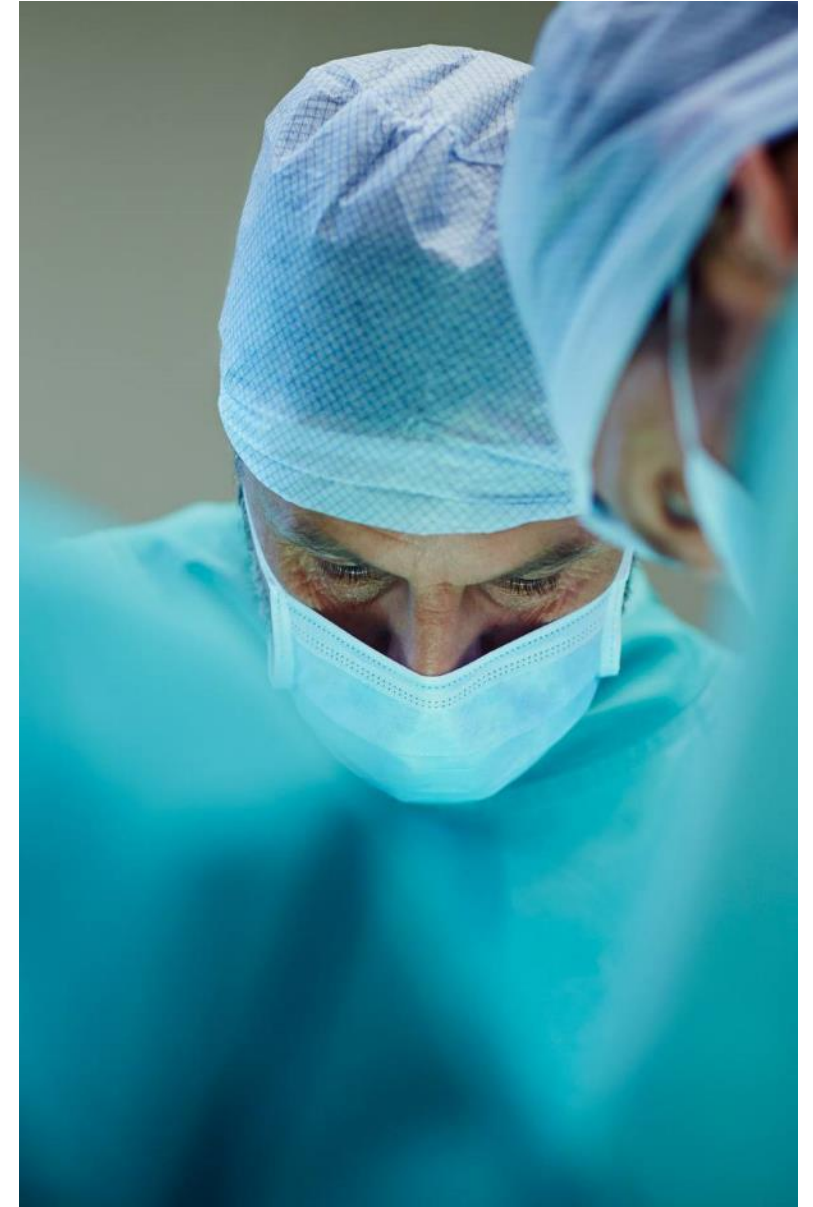


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Agenda

- **Background to the revision, the process and the structure**
- **The investigator**
- **The sponsor**
- **The protocol**
- **Essential Records**
- **Annex 2**
- **Take home messages**



Good Clinical Practice – ICH E6 (R3)

Step 4

Step 4 document – to be implemented

23 January 2025

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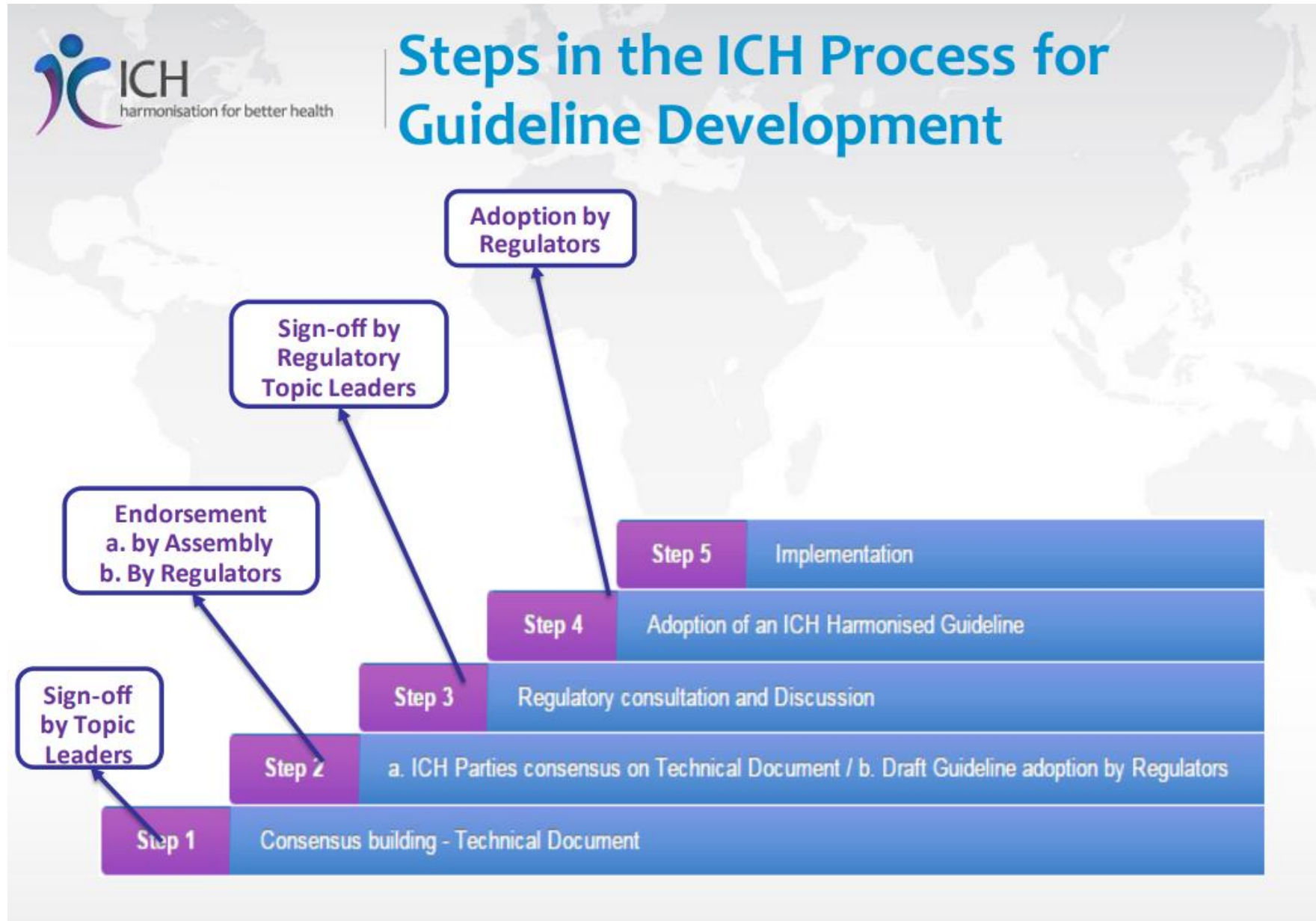
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THE ICH E6(R3) GUIDELINE DEVELOPMENT PROCESS.

Where did we start from and what are the expectations now?

THE ICH PROCESS



Background

- **This guideline reached Step 2 19 May 2023 and was issued by the ICH Regulatory Members for public consultation.**
- **ICH E6(R3) Expert Working Group reviewed public consultation comments and revised the document as appropriate.**
- **This final document has been signed off as a *Step 4* document (6 January 2025) to be implemented by the ICH Regulatory Members.**
- **This document was developed based on a Concept Paper (approved 18 November 2019) and a Business Plan (approved 18 November 2019).**

ICH-E6(R3): Background to this Revision



Home About ICH Work Products Meetings Training Newsroom

ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6 / News / Newsroom / Home

12 January 2017

ICH is inviting public review and comment on a reflection paper on Good Clinical Practice (GCP) “Renovation”, which contains the ICH proposal for further modernization of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the proposed renovation includes the current E8 General Considerations for Clinical Trials and further revision to the E6 Guideline for Good Clinical Practice, which is already undergoing modernization with the recent production of ICH E6(R2).

The reflection paper is available for download via the following link:

- [Reflection paper on GCP Renovation](#)

The goal of the potential renovation is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of study types and data sources that are being employed to support regulatory and other health policy decisions, as appropriate. The underlying principles of human subject protection and data quality would remain. ICH’s decision to invite stakeholder comment on the

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.

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.

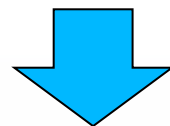
Summary of Stakeholder Engagement to Support the Development of ICH E6(R3), 21 April 2020
https://database.ich.org/sites/default/files/E6-R3_PublicEngagemenSummary_2020_0421.pdf

Increased Transparency

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

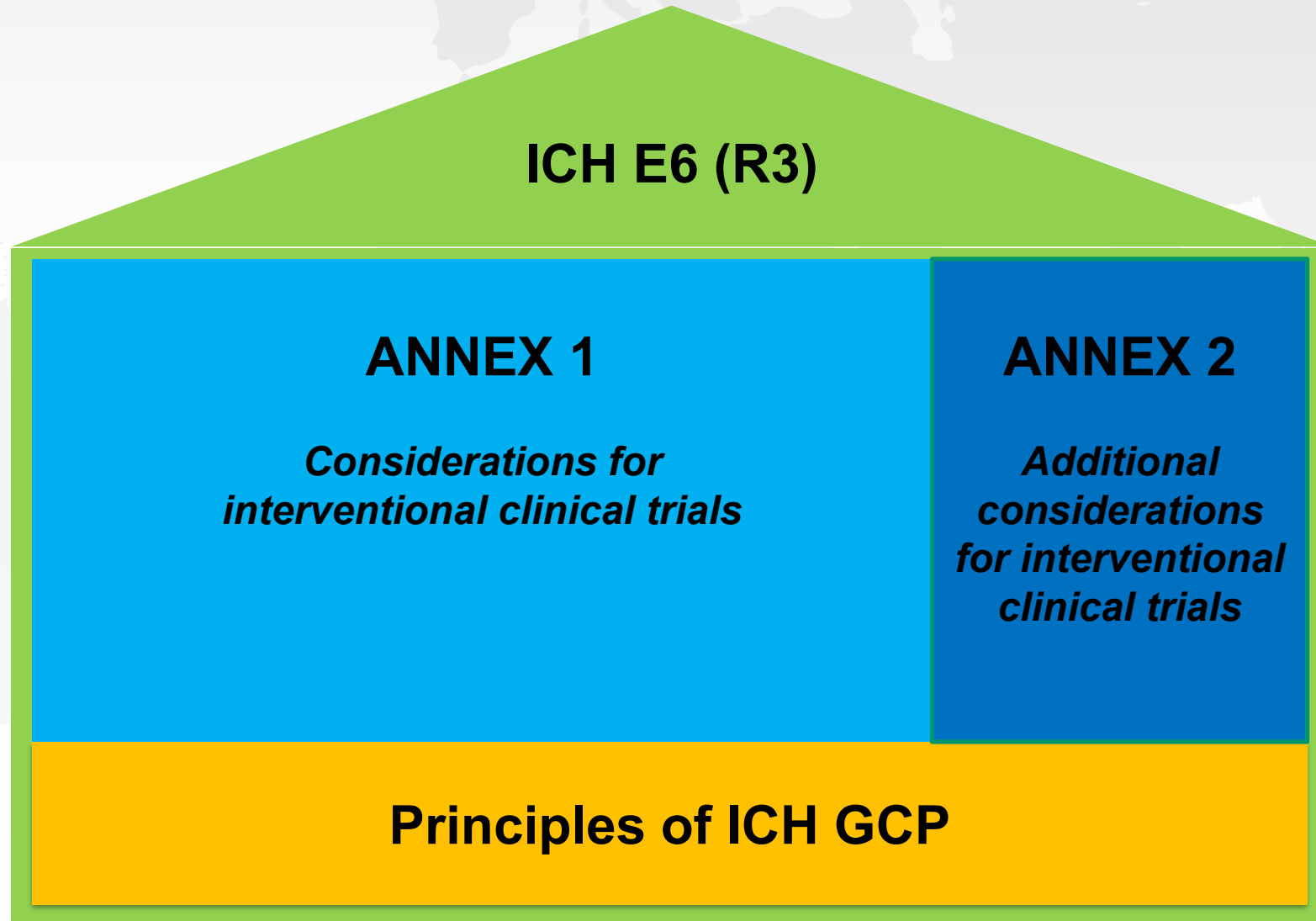
Public Consultation - May to Nov 2023

- Over 7000 Comments received and reviewed.



Final Principles and Annex 1 document adopted - January 2025

OVERVIEW OF ICH E6 (R3)



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*

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.

Summary of Changes

Substantial Changes

- Principles of GCP
- Annex 1
 - Investigator
 - Sponsor
 - Data Governance – Investigator and Sponsor (New)
- Appendix C
 - Essential Records for the Conduct of a Clinical Trial
- Glossary

Other Changes

- Annex 1
 - Institutional Review Board/Independent Ethics Committee (IRB/IEC)
- Appendices A & B
 - Investigator's Brochure
 - Clinical Trial Protocol and Protocol Amendments



THE INVESTIGATOR

What are the changes?

GLOSSARY DEFINITIONS: INVESTIGATOR AND INVESTIGATOR SITE

Investigator

A person responsible for the conduct of the clinical trial, including the trial participants for whom that person has responsibility during the conduct of the trial. If a trial is conducted by a team of individuals, the investigator is the responsible leader of the team and may be called the principal investigator. Where an investigator/institution is referenced in this guideline, it describes expectations that may be applicable to the investigator and/or the institution in some regions. Where required by the applicable regulatory requirements, the “investigator” should be read as “investigator and/or the institution.”

Investigator Site

The location(s) where trial-related activities are conducted and/or coordinated under the investigator’s/institution’s oversight.

ICH E6 (R3) Annex 1

Investigator

ICH E6 (R3) Section	ICH E6 (R2) Section
2.1 – Qualifications and Training	4.1
2.2 – Resources	4.2
2.3 – Responsibilities	4.1, 4.2
2.4 – Communication with IRB/IEC	4.4, 4.10
2.5 – Compliance with Protocol	4.1
2.6 – Premature Termination or Suspension of a Trial	4.12
2.7 – Participant Medical Care and Safety Reporting	4.3, 4.11
2.8 – Informed Consent of Trial Participants	4.8
2.9 – End of participation in a clinical trial	4.3
2.10 – Investigational Product Management	4.6
2.11 – Randomisation Procedures and Unblinding	4.7
2.12 – Records	4.9
2.13 – Reports	4.13

Investigator - Informed Consent

- **Approaches to obtaining 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.

- **New information**

- Considerations for re-consent, including stage of the clinical trial, whether the new information is relevant only to new / existing participants.
- Revised informed consent materials require IRB/IEC approval in advance of use.

- **Enrolment of minors**

- Where a minor is to be included as a participant, age-appropriate assent information should be provided and discussed with the minor as part of the consent process.
- A process for consent should be considered if during the trial, the minor reaches the age of legal consent, in accordance with applicable regulatory requirements.

Investigator (2)

- **Qualifications and training**

- Clarified expectations on evidence for qualifications: allow flexibility about documentation.
- Clarified overall training requirements for trial staff: trial-related training to persons assisting in the clinical trial should correspond to what is necessary to enable them to fulfil their delegated trial-related activities that go beyond their usual training and experience.

- **Medical Care**

- Clarified that other appropriately qualified health professionals may be involved in medical care of trial participants in line with their normal activities and in accordance with local regulatory requirements.

- **Safety Reporting**

- Included language about the reporting of unfavourable medical events occurring in participants before IP administration (e.g., during screening) to the sponsor, if required by the protocol.

Investigator (3)

- **Responsibilities**

- Clarified the expectations between the sponsor and investigator regarding service providers.
- Confirmed that the investigator retains the ultimate responsibility for the persons or parties undertaking the activities delegated.
- Clarified that 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.
- Clarified the requirements for delegation documentation.

- **Considerations for participants who did not reach the routine end of the trial**

- Clarified that appropriate follow up per protocol and/or other protocol-related documents is required.
- Included language about the potential for instructions to avoid loss of already collected data, in accordance with regulatory requirements.

Investigator (4)

- **Computerised systems**
 - Clarified the investigator's responsibility for computerised systems.
- **Data and source records**
 - Clarified expectations regarding identification and maintenance of source records and timely data access and review.
- **Investigational product (IP) management**
 - Clarified that the sponsor may facilitate aspects of IP management.
 - Clarified that the level of investigator oversight will depend on a number of factors including:
 - Characteristics of the IP;
 - Route and complexity of administration;
 - Level of existing knowledge about the IP's safety; and
 - Marketing status of the IP.
 - Clarified that for authorised medicinal products, alternative approaches to IP documentation may be considered, in accordance with applicable regulatory requirements.
 - Included language that the investigators should be prepared and capable from the start of the trial to perform unblinding without undue delay and hindrance in the case of an emergency, to protect participant safety.



THE SPONSOR

What are the changes?

ICH E6 (R3) Annex 1 Sponsor

ICH E6 (R3) Section	ICH E6 (R2) Section
3.1 – Trial Design	5.0, 5.4
3.2 – Resources	N/A
3.3 – Allocation of activities	5.7
3.4 – Qualification and Training	5.3, 5.4
3.5 – Financing	5.9
3.6 – Agreements	5.1, 5.2, 5.6, 5.9, 5.23
3.7 – Investigator Selection	5.6
3.8 – Communication with IRB/IEC and Regulatory Authority(ies)	5.10, 5.11
3.9 – Sponsor Oversight	N/A

ICH E6 (R3) Annex 1

Sponsor

ICH E6 (R3) Section	ICH E6 (R2) Section
3.10 – Quality Management	5.0
3.11 – Quality Assurance and Quality Control	5.1, 5.18, 5.19
3.12 – Noncompliance	5.20
3.13 – Safety Assessment and Reporting	5.16, 5.17
3.14 – Insurance/Indemnification/Compensation to participants and investigators	5.8
3.15 – Investigational Product(s)	5.12, 5.13, 5.14
3.16 – Data and Records	5.5, 5.15
3.17 – Reports	5.21, 5.22

Sponsor

- **Trial Design**

Included language that the sponsor should:

- Ensure that safety and efficacy data from non-clinical studies/clinical trials/real world sources are sufficient to support human exposure.
- Implement QbD, including prospective identification of critical to quality factors and management of important risks.
- Consider seeking inputs from interested parties (e.g., healthcare professionals, patients).
- Ensure that protocols, data acquisition tools and other operational documents are fit for purpose, clear, concise and consistent.
- Avoid unnecessary burden on participants and investigators.

- **Agreements**

- Clarified that agreements with service providers and other parties (e.g., IDMC, adjudication committee) should be in place prior to initiating the activities.
- Clarified that agreements should be updated to reflect significant changes in the activities transferred.

Sponsor (2)

- **Sponsor Oversight**

- Clarified that the sponsor should ensure that the range and extent of oversight measures are fit for purpose and tailored to the complexity of and risks associated with the trial.
- Clarified that quality assurance and quality control processes should be implemented in oversight of investigators and service providers.
- Included language about the oversight of facilities outside of investigator sites, e.g., central image reading facilities, as part of overall QC strategy.

- **Quality Management**

- Further clarified the requirements for the assessment and management of critical to quality factors impacting participant safety or result reliability.
- Encouraged proportionality and clarified acceptable ranges beyond which deviations could represent systemic issues.

Sponsor (3)

- **Monitoring**

- Clarified that monitoring is one of the principal quality control activities.
- Clarified expectations for centralised monitoring and visits to investigator sites (performed on-site or remotely).
- Clarified that the monitoring strategy should consider factors such as the trial purpose, design, blinding, safety profile, and endpoints in line with the risk proportionate approach for that investigational product in that participant population.

- **Investigational Product**

- Clarified that for product that has a marketing authorisation, alternative approaches may be considered e.g.:
 - The basic product information may be used in place of the investigator's brochure.
 - Alternative approach to investigational product accountability records may be applicable, in accordance with local regulatory requirements.

Sponsor (4)

- **Computerised Systems and Data Management**
 - Clarified the importance of certain processes, such as randomisation and blinding, and provided reasonable perspective on when unblinding may occur.
 - Clarified that the requirements for computerised systems should be fit for purpose and risk-based.
 - Clarified requirements of the sponsor's data management processes throughout the full data life cycle.
 - Included requirements related to finalisation of data sets, statistical programming and data analysis.



THE PROTOCOL

What are the changes?

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).



ESSENTIAL RECORDS

What are the changes?

THE OLD ESSENTIAL DOCUMENTS TABLES

- Prescriptive
- Used as a checklist
- One size fits all, when all trials are unique
- Used as an archive

8.2. Before the clinical phase of the trial commences

During this planning stage the following documents should be generated and should be on file before the trial formally start

	Title of Document	Purpose	Located in Files of	
			Investigator / Institution	Sponsor
8.2.1	INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	INFORMATION GIVEN TO TRIAL SUBJECT - INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	X	X
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X

PURPOSE OF NEW ESSENTIAL RECORDS SECTION

New glossary term:

- Essential records are the documents and data (and relevant metadata), in any format, associated with a clinical trial that facilitate the ongoing management of the trial and collectively allow ICH E6(R3) Guideline the evaluation of the methods used, the factors affecting a trial and the actions taken during the trial conduct to determine the reliability of the trial results produced and the verification that the trial was conducted in accordance with GCP and applicable regulatory requirements (see Appendix C).

Purpose:

- Essential Records rather than essential documents.
- To encourage thinking.
- Encourage oversight continuously, not an archive.
- Allows evaluation of the conduct of the clinical trial.

ICH E6 (R3) APPENDIX C

ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

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

INTRODUCTION TO THE ESSENTIAL RECORDS

Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

C.1 Introduction

- C.1.1 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.
- C.1.2 Determining which records are essential will be based on consideration of the guidance in this appendix.

ESSENTIALITY OF RECORDS

C.3 Essentiality of Trial Records

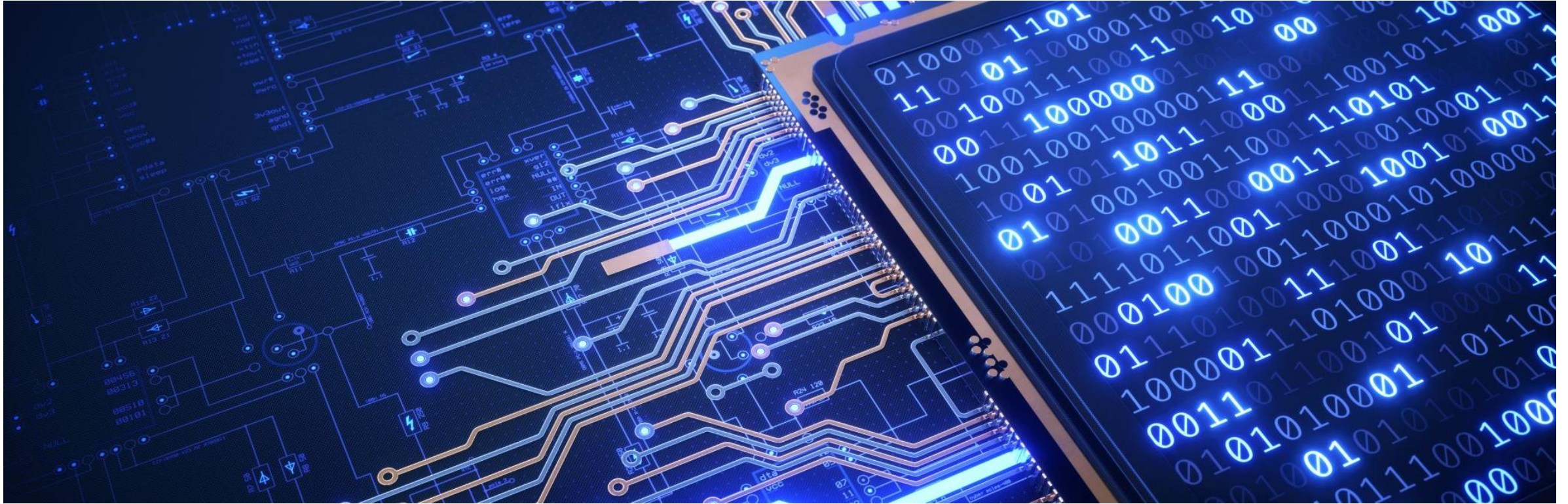
C.3.1 The assessment of whether a record is essential and has to be retained should take into account the criteria below. Such assessment, whilst important, is not required to be documented. A structured content list for storage repository(ies) may be used to prospectively identify essential records. An essential record:

In short how do the records tell the story of what happened to the participants and their data, how the protocol was followed and the deposition of the investigational product during the clinical trial

WHAT DOES THIS MEAN FOR SPONSORS AND INVESTIGATORS?

- Notice no tables – same in the final version.
- To encourage thinking – previously used as a check box
- Where does this fit in relation to CDISC TMF reference model?
 - Still need to file records
 - Need some sort of structure
 - Still needs to be accessible to inspectors for the purposes of the evaluation of the clinical trial conduct.
- I believe you will end up with more questions as to what is an essential document?

Scout and Guide Moto: BE PREPARED!



ANNEX 2

A taster

Good Clinical Practice – ICH E6(R3) Annex 2

Step 2

Step 2 document – to be released for comments

22 November 2024

Good Clinical Practice – ICH E6(R3)

Annex 2

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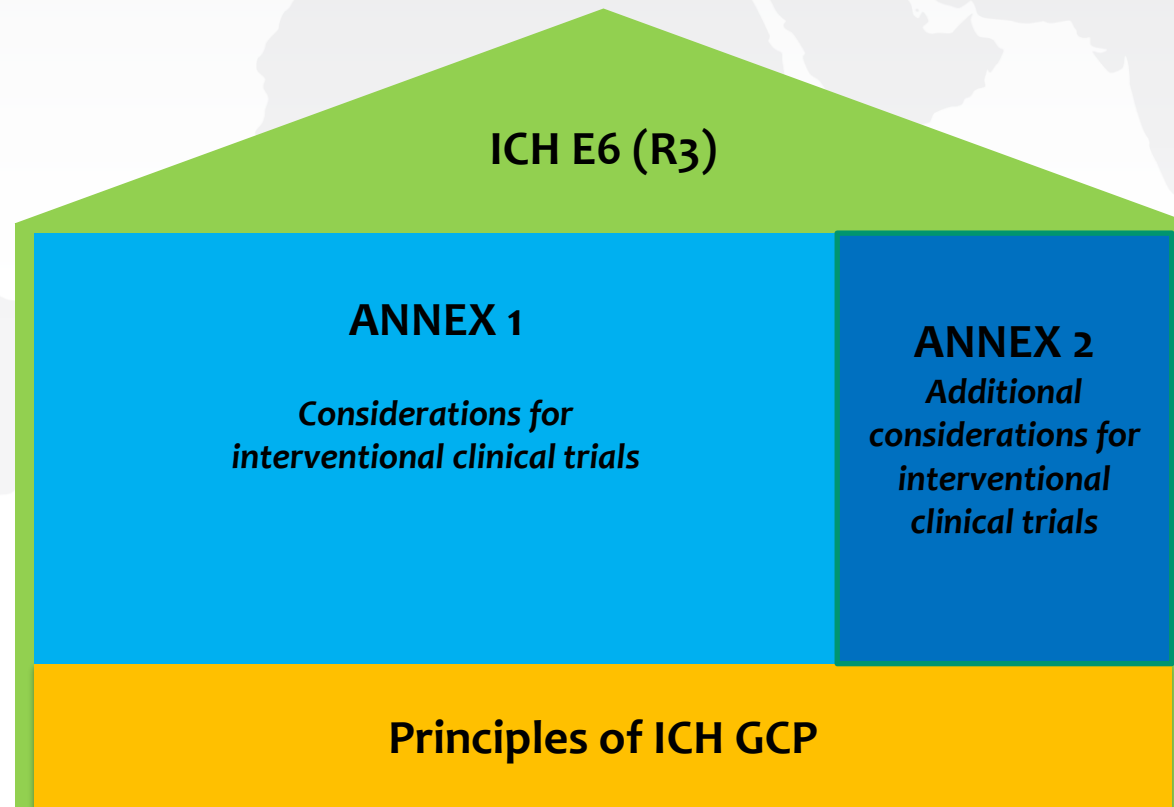
Background: Good Clinical Practice – ICH E6(R3) Annex 2

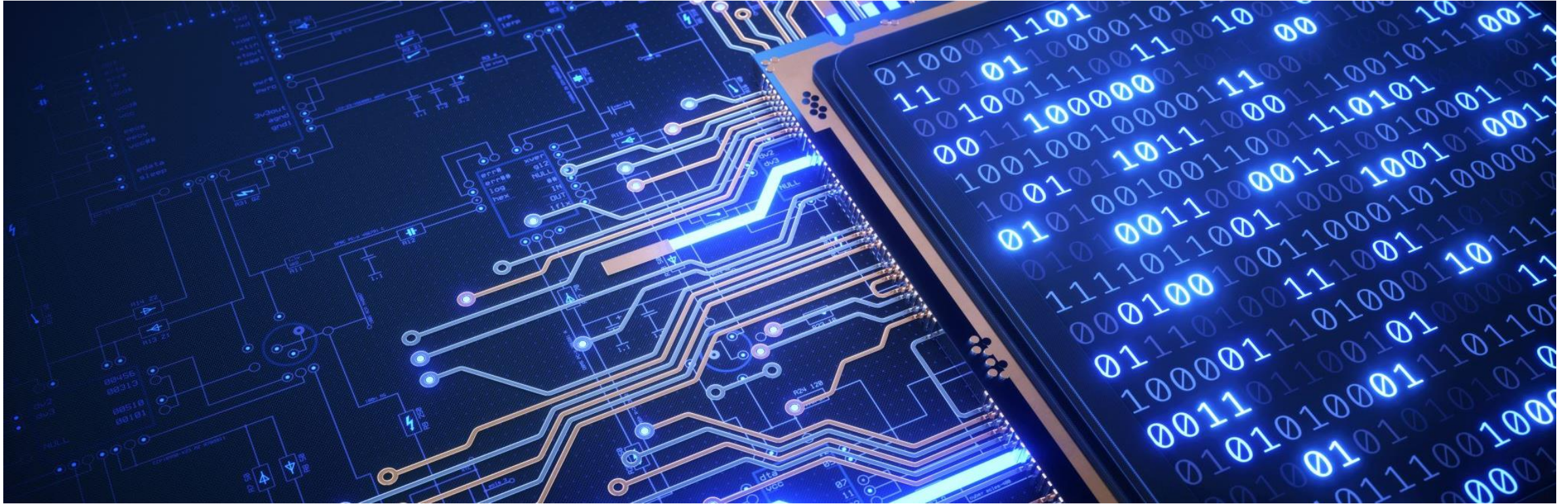
- Has been signed off as a *Step 2* document (06 November 2024) to be issued by the ICH Regulatory Members for public consultation
- Was developed based on a Concept Paper (approved 28 April 2023) and a Business Plan (approved 18 November 2019)
- Is anticipated to be finalised as a *Step 3 Sign-off/Step 4* document to be implemented in the local regional regulatory system: Mid-2025

Background: Good Clinical Practice – ICH E6(R3) Annex 2

- **Annex 2 is not intended to be comprehensive of all clinical trial design elements or data sources**
- **Should be read in conjunction with the ICH E6(R3) Principles and Annex 1 document**
- **Addresses the GCP considerations that arise from the increased use of a wider range of design elements and data sources. It has its foundations in the key concepts of quality-by-design, fitness for purpose and risk proportionality**
- **Annex 2 does not endorse specific design elements or data sources**

OVERVIEW OF ICH E6(R3)





TAKE HOME MESSAGES

What to remember?

TAKE HOME MESSAGES:

- Watch Regulator websites for the implementation of E6(R3)
- Don't read ICH E6(R3) in isolation – consider other E guidelines

Design

- Patient and HCP engagement
- Fit for purpose
- Write a good protocol.
- Consider critical to quality factors.

Conduct

- Responsibilities at investigator and sponsor level.
- Control of investigational product

Analysis

- Data of appropriate quality
- Changes in statistical analysis documented

Reporting

- Transparency of trial results
- Participant results
- Clinical trial report
- Archiving of the essential records.

Proportionality and risk-based approach throughout.

Thank you

Any questions?

