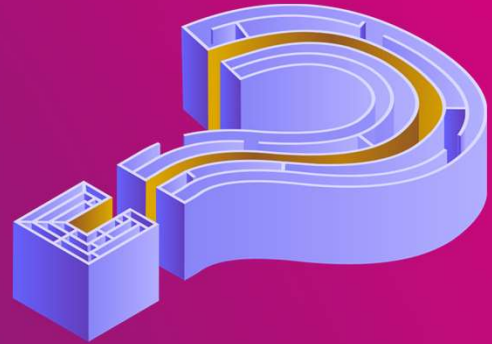


Joint Research
Management Office
Governance Section

GCP E6 R3

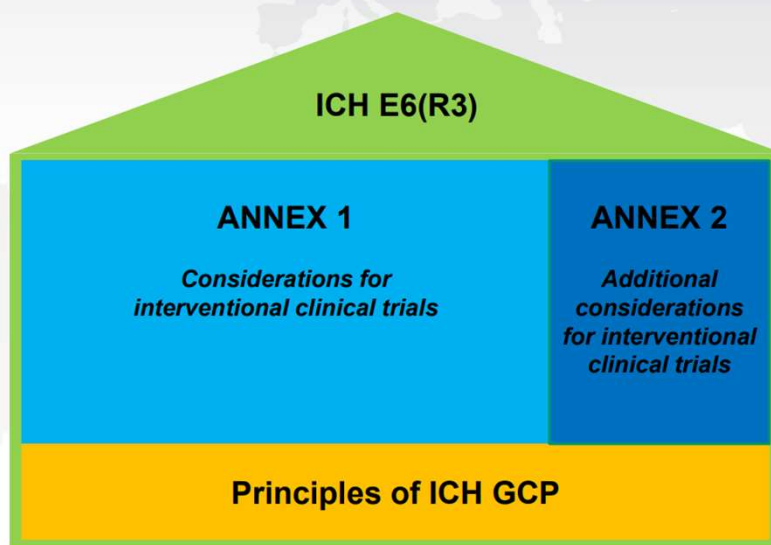


1

Structure



OVERVIEW OF ICH E6(R3)



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What's new

Mostly re-structuring, some more detail. Core concepts remain unchanged.

- Modernisation
- Data section
- Greater emphasis on proportionality
- Focus on changes that affect our researchers

Also touch on changes due to updates to Clinical Trial regulations (from spring 2026)

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Structure



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

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What's new

	R2	R3
Structure	8 sections (glossary, principles, IRBs, investigator responsibilities, sponsor responsibilities, contents of a protocol, contents of an IB, list of essential documents)	6 main sections (introduction, principles, IRBs, investigator responsibilities, sponsor responsibilities, data) plus three appendices (contents of an IB, contents of a protocol, list of essential documents)
Principles	13, each about 3 lines of text	11, with detailed subsections
Nomenclature	"subjects", "patients"	"participants"
PPIE	N/A	Advocates for patients, advocacy groups, etc to provide input into trials

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What's new

	R2	R3
Assent	Not recognised	Referred to
Proportionality	Less emphasis (2 references)	Greater emphasis (22 references)
Consent	4.8.8: <i>"written informed consent form should be signed and personally dated by the subject"</i>	Consent must be "documented"
Technology	Mentions maintaining records <i>"irrespective of the type of media used"</i>	1.2.2 (d): IRBs should be provided with <i>"a description of the media through which [consent] information will be provided"</i>

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What's new

	R2	R3
Electronics and consent	Does not discuss electronic means of consent	2.8.1 (c): <i>"Varied approaches (e.g., text, images, videos and other interactive methods) may be used..."</i>
Remote consent	Does not discuss remote consent	2.8.1 (d): <i>"Obtaining consent remotely may be considered where appropriate."</i> 2.8.1 (e): <i>"...the investigator should assure themselves of the identity of the participant..."</i>
Unblinding	No requirement to notify participants of treatment	2.9.3: <i>"...the investigator should inform the participant about the trial results and treatment received when this information is available from the sponsor after unblinding..."</i>

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What's new

	R2	R3
Electronic access	Requires processes in place	2.12.10 (a) and (b) make it explicit that appropriate people have access, and access is changed/revoked when appropriate
Delegation	Requires delegation is recorded	2.3.2: <i>"...Trial-related training to persons assisting in the trial should correspond to what is necessary to enable them to fulfil their delegated trial activities <u>that go beyond their usual training and experience.</u>"</i> 2.3.3: <i>"...In situations where the activities are performed as part of clinical practice, delegation documentation may not be required."</i>

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What's new

	R2	R3
Follow up if suspended	Not referred to	2.6.1 If study suspended or terminated, <i>"...inform the trial participants ... ensure appropriate therapy and follow-up..."</i>
Unblinding	Timeliness not addressed	2.11 In emergency, <i>"...should be prepared ... to perform unblinding without undue delay"</i>
Data quality risks	Broad reference to risk	6.2 <i>"Factors <u>critical to the quality of the trial</u> should be <u>identified prospectively</u>."</i>
Acceptable ranges for risk control	Not referred to	3.10.1.3 <i>"...sponsor should set pre-specified acceptable ranges (e.g, quality tolerance limits..."</i> If exceeded, <i>"...determine if there is a possible systemic issue..."</i>

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What's new

	R2	R3
Vendors	Requires agreements with vendors	3.6.4: <i>"...activities that are not specifically transferred to and assumed by a service provider are retained by the sponsor."</i>
Deviations	Document deviations and implement CAPAs	3.9.3: <i>"The sponsor should determine necessary <u>trial-specific</u> criteria for classifying protocol deviations as important."</i>
Continuous risk assessment	Implement processes to minimise risk	3.9.4: <i>"Decisions related to the trial should be appropriately assessed ... Risks related to such decisions should be suitably managed..."</i>

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What's new

	R2	R3
PV	Did not mandate review of AEs prior to IMP	3.13.1: "...includes the review of [AEs] occurring ... during screening..." if required by protocol
Data flow diagram	Did not refer to data flow diagrams	3.16.1 (c): "Where necessary, ... a data flow diagram, should be contained in ... a data management plan"
CRFs ready to use pre-trial	No explicit requirement for CRFs to be ready pre-trial	3.16.1 (d): CRFs "should be validated and ready for use prior to their required use in the trial"

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What's new

	R2	R3
PI endorsement of their data	No mention of predetermined milestones	3.16.1 (o): "...sponsor should seek investigator endorsement of their reported data at predetermined important milestones."
Computer systems	Less detail	3.16.1 (x) lists what details are required for computerised systems deployed by the sponsor (i-v), PI/site (vi-viii), or both (ix)
Results to participants	Not referred to	3.17.2 (c) (iii): "Where a summary of trial results is provided to participants, this should have language that is ... understandable to a layperson and non-promotional."

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What's new

	R2	R3
Metadata	Not referred to	4.2.2 discusses "...implementing, evaluating, accessing, managing and reviewing relevant metadata associated with data..."
Audit trail review	Not referred to	4.2.3: "Procedures for review of ... audit trails and other relevant metadata should be in place. It should be a planned activity..."
Audit trails for user access & permissions	Not referred to	4.2.2 (a) (i) states computer systems should log "user account creation, changes to user roles and permissions and user access"
Reviewing access permissions	Not referred to	4.3.8 (b): "Access permissions should be revoked when they are no longer needed. A process should be in place to ensure that user access and assigned roles and permissions are periodically reviewed"

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What's new

	R2	R3
System validation procedures	Validate risk proportionately	4.3.4 (f): "validation procedures (until decommissioning) should cover ... system design, system requirement, functionality testing, configuration, release, setup, installation and change control."
Technical support	Not referred to	4.3.7 (a): Help desks should assist with issues and do trend analysis, where appropriate
Time and date format	Not referred to	4.2.2 (d) uses UTC as an example (states that "automatic capture of date and time [must be] unambiguous")

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What's new

	R2	R3
Essential documents	A list of minimum essential documents	Much more detail regarding expectations for handling of records, including TMF and ISF vs sponsor and site, accessibility, traceability
Essentiality of documents	Not stated	C.3.1: <i>"The assessment of whether a record is essential ... should take into account the criteria below. Such assessment ... is not required to be documented."</i>

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What's new

	R2	R3
Identification of records & their creation / maintenance	Not explicitly stated	C.2.1: <i>"Records should be identifiable and version controlled ... and should include authors, reviewers and approvers ... along with date and signature..."</i>
SOP in case of security breaches to data	Discusses protecting confidential data	C.3.1 (bb): <i>"Defines processes/practices in place in the event of a security breach in order to protect participants' rights, safety and well-being and the integrity of the data."</i>

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Appendix A – contents of an IB

ICH E6(R3) Guideline

APPENDICES

Appendix A. INVESTIGATOR'S BROCHURE

A.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s)¹ that are relevant to the study of the product(s) in human participants. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for and their compliance with many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures.

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Appendix B – contents of a protocol

ICH E6(R3) Guideline

Appendix B. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

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 the reliability of data. Protocol development processes should incorporate input from relevant interested parties, where appropriate. 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. Such adaptability should not adversely affect participant safety or the scientific validity of the trial. For additional information, refer to ICH E8(R1) General Considerations for Clinical Studies, ICH E9 Statistical Principles for Clinical Trials and ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials.

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Appendix C – Essential documents

ICH E6(R3) Guideline

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.

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Glossary



ICH E6(R3) Annex 1 Glossary

New Glossary Terms

- Assent
- Computerised Systems Validation
- Data Acquisition Tool
- Data Integrity
- Metadata
- Reference Safety Information
- Service Provider
- Signature

Revised Glossary Terms

- Adverse Events and Adverse Reaction-related definitions
- Essential Records
- IRB/IEC
- Investigator
- Investigator Site
- Source Records
- Sponsor
- Trial Participant
- And Others...

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Glossary

- “An important medical event that may not be immediately life-threatening or result in death or hospitalisation, ... that may require intervention to prevent serious outcomes ... should generally be considered as serious.”
- Audit trails: “In computerised systems, the audit trail should be secure, computer-generated and time stamped.”

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Glossary

- Certified copies must “...have the same information as the original, including relevant metadata.”
- “In computerised systems, the audit trail should be secure, computer-generated and time stamped.”
- “**Coordinating Investigator:** An investigator assigned the responsibility for the coordination of investigators at different investigator sites participating in a multicentre trial.”

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Glossary

- “**Data Acquisition Tool (DAT)**” (broader than CRFs; can collect data or metadata, and include PROs. Can include wearables)
- Defines metadata: “*The contextual information required to understand a given data element...*”

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1st principle

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirement(s). Clinical trials should be designed and conducted in ways that ensure the rights, safety and well-being of participants.

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1st principle subsections

- Participant's interests prevail over those of science & society
- Review participant safety in a timely manner, inform them of changes
- Risk-benefit analysis in advance; proceed only if benefits outweigh risks
- Inclusivity of participant populations, reflect the broader population
- Drs / dentists responsible for medical care ("appropriately qualified healthcare professionals" can be used)
- Protect confidential information

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2nd principle

Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants (or their legally acceptable representatives, where applicable) are well-informed

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2nd principle subsections

- Documented freely given consent (or assent) from participant or representative
- The aim is to enable potential participants to make an informed choice
- Consent process should consider relevant aspects (patient characteristics, trial design, risks/benefits, setting of study, use of technology in consent)
- In emergency settings, get consent from participant or representative ASAP according to regulations and ethics approval

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3rd principle

Clinical trials should be subject to an independent review by an IRB/IEC.

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3rd principle subsections

- Conduct study according to approved protocol
- Ethics committees should review studies periodically according to regulations

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4th principle

Clinical trials should be scientifically sound for their intended purpose and based on adequate and current scientific knowledge and approaches.

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4th principle subsections

- Pre-clinical and clinical information on IMPs should support study
- Knowledge about condition, biological mechanisms, population, should support study
- Periodic review for updates needed to consider modifying study

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5th principle

Clinical trials should be designed and conducted by qualified individuals.

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5th principle subsection

- People with different expertise may be needed (including drs, nurses, pharmacists, scientists, ethicists, tech experts, coordinators, monitors, auditors, biostatisticians). Must be qualified by education, training, experience.

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6th principle

Quality should be built into the scientific and operational design and conduct of clinical trials.

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6th principle subsections

- Quality = fitness for purpose
- Focus on essential aspects to protect participants and data
- Implement ways to detect non-coms and implement CAPAs

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7th principle

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.

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7th principle subsections

- Processes proportionate to risks to participants and data
- Focus on risks associated with participation, e.g. if IMPs have different risks in patient population
- Manage risks proactively, implement CAPAs
- Don't do more than necessary (e.g. collection of unnecessary data, performing unnecessary scans)

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8th principle

Clinical trials should be described in a clear, concise, scientifically sound and operationally feasible protocol.

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8th principle subsections

- Well-designed protocol fundamental to protection of participants and data
- Scientific objectives must be clear
- Protocol and associated documents must be clear, concise, and feasible

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9th principle

Clinical trials should generate reliable results.

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9th principle subsections (1 of 2)

- Data captured must be sufficient to believe results
- Processes for data capture & management should be fit for purpose and capture necessary data, and implemented proportionate to risks
- Computer systems must be fit for purpose

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9th principle subsections (2 of 2)

- Maintain record integrity and traceability, protect personal information
- Maintain essential records, make available to monitors/ auditors/ inspectors
- Record studies in publicly accessible databases, post results

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10th principle

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

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10th principle subsections

- Sponsor can delegate, but retains responsibility
- Agreements should clearly define roles and responsibilities. Sponsors / investigators remain responsible for delegated duties
- Sponsor must maintain oversight

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11th principle

Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be managed in accordance with the product specifications and the trial protocol.

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11th principle subsections

- Manufacture IMP according to GMP
- Ensure IMP retains its quality
- Use IMP according to protocol
- Handle IMP according to & maintaining blinding
- Label according to regulations
- Implement processes for handling, shipping, storing, dispensing, returning, and destroying IMP

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CTIMP regulation changes (overview – spring 2026)

- DSUR line listing removed (appropriate discussion instead)
 - How are you monitoring safety?
- Terminology
 - Amendment → modification
 - Site → location
 - Grounds for Non-Acceptance → Request for Further Info
- MHRA acceptance lapses after 24 months if no recruitment
- Registered health professionals accepted as investigators
- No more SUSARs to REC (only MHRA) for CTIMPs
- USM notification 3 → 7 days (but phone call within 24 hours)

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Modifications (overview – spring 2026)

1) Substantial Modification

- i. **Route A:** Substantial impact on participants or data (reviewed by MHRA)
- ii. **Route B:** no safety concerns (automatic MHRA approval, needs REC approval)
 1. Condition A
 2. Condition B
 3. Condition C

2) Modification of an Important Detail: Notify

3) Minor Modification: Non-notifiable

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CTIMP regulation changes (substantial modifications)

- **Route A:** Substantial impact on participants or data (submit to MHRA)
- **Route B:** no safety concerns (automatic approval)
 - **Condition A:** Not first in human, same modification approved in USA, EU, or EEA (and nothing UK specific)
 - **Condition B (protocol changes):** Changes to primary endpoint/objective, end of trial criteria, patient interactions related to IMP, concomitant medication use, UK specific requirements, statistically significant trial design changes
 - **Condition C (IB changes):** New data no impacting safety, RSI increase frequency of ARs (no new terms), change not impacting safety profile, SmPC change related to undesirable effects

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CTIMP regulation changes (non-substantial modifications)

- Notify MHRA of **non-substantial** modifications only when next substantial modification submitted

All modifications must be approved by JRMO first

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Summary

Expectations the same

- Emphasis on proportionality
- More guidance regarding data
- Continuous assessment of risk
- Practical changes regarding modifications

Detailed training regarding CTIMP regulations before spring 2026 – watch this space

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