ICH E6 (R3) GCP Guideline
Overview of Step 3 draft

Innovation Office & Clinical Trials Branch
Health Products Regulation Group
Health Sciences Authority

OUTLINE

- Background
- Overview of ICH E6 (R3)
  - ICH E6 (3) Principles
  - ICH E6 (R3) Annex 1
- Public consultation
- References

BACKGROUND OF ICH E6 GOOD CLINICAL PRACTICE (GCP) GUIDELINES

ICH E6 (R1) 1996

- *Harmonised guidelines for clinical trials to support registration of medicinal products.*

ICH E6 (R2) 2016

- *Integrated addendum to encourage implementation of innovative and efficient approaches to GCP, while continuing to ensure human subject protection.*

ICH E6 (R3) (Draft)

- *Modernisation of ICH E8 guidelines on General Considerations on Clinical Trials; and*
- *Subsequent renovation of ICH E6 guideline on Good Clinical Practice.*

https://admin.ich.org/sites/default/files/inline-files/ICH_Reflection_paper_GCP_Renovation_Jan_2017_Final.pdf

GAP ANALYSIS
BEFORE DRAFTING ICH E6 (R3)

Stakeholder Comment Analysis

- Academic Responses
  - **Open letter to EMA & ICH**
  - **Published articles**
- Responses to **Clinical Trials Transformation Initiative (CTTI) survey**, and interviews on "Informing the Renovations to the ICH E6" Project
- Inputs from **regional public engagement**

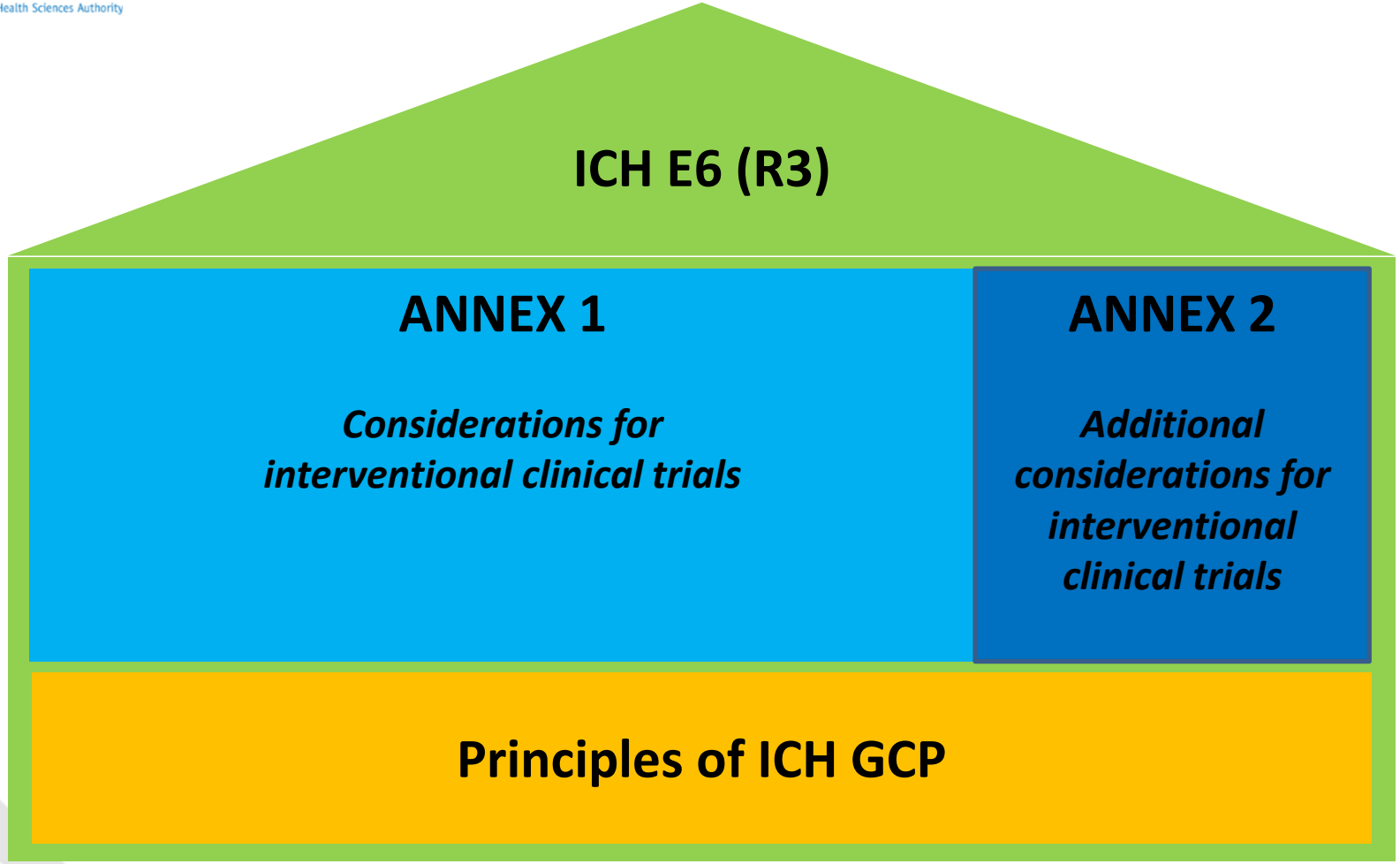
Relevant ICH guideline Analysis

- **ICH efficacy guidelines**

GAP ANALYSIS
BEFORE DRAFTING ICH E6 (R3)

- **Feedback received from gap analysis:**
  - Although E6 is intended for clinical trials to support registration/approval of medicinal products, it is also **widely applied to other types of clinical trials of medicinal products.**
  - **Concerns** that the current guidance has a **"one-size-fits-all" approach** to clinical trials.
  - **Concerns** about ability of clinical trials to **meet all GCP requirements in different situations (e.g., during public health emergencies).**
  - **Concerns** that **GCP requirements** were being **applied where it is not applicable.**

OVERVIEW OF ICH E6 (R3)



NB: Annex 2 will contain additional considerations for clinical trials with decentralised elements, pragmatic elements and Real World Data.

UNIQUE FEATURES ABOUT ICH E6 (R3) DEVELOPMENT PROCESS

Engagement with academic stakeholders

Enhanced transparency

- Draft principles published in Apr 2021
- Public web conference conducted in May 2021

Training materials will be developed to clarify or provide supplementary explanation to the application of GCP guidelines

NEW FEATURES ABOUT ICH E6 (R3) STRUCTURE AND CONTENT

New Structure

- Principles
- Annexes

Facilitates Innovation

- Innovative clinical trial designs, e.g., decentralised elements, pragmatic elements, Digital Health Technologies, electronic consent, remote consent
- Public health emergencies / pandemics

Fit for purpose

- Proportionality and risk-based approaches, with a focus on Critical to Quality Factors

Encourages transparency

- Clinical trial registration
- Result reporting

REVISED STRUCTURE OF ICH E6 (R3)

E6 (R3) draft guideline

E6 (R3) draft guideline subject to public consultation consists of parts I, II, III (composed of 4 sections), glossary, and appendices.

Open for public consultation now

I. INTRODUCTION

II. PRINCIPLES OF ICH GCP

III. ANNEX I

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

GLOSSARY

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

OVERVIEW OF ICH E6 (R3)

Substantial changes

- **Principles of GCP**
- **Annex 1**
  - Investigator
  - Sponsor
  - Data Governance – Investigator and Sponsor **[NEW]**
- **Glossary**
- **Appendices**
  - Essential Records for the Conduct of a Clinical Trial

Other changes

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

ICH E6 (R3) PRINCIPLES

- **OVERALL SUMMARY OF CHANGES**

ICH E6 (R3) PRINCIPLE	TOPIC	ICH E6 (R2) REF
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 1

- **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.**
  - ***Safety of participants should be reviewed periodically*** *as new safety information becomes available.*
  - *Scientific goal and purpose should be carefully considered so as* ***not to unnecessarily exclude particular participant populations.***
  - ***Participant selection process*** *should be* ***representative of the anticipated population that would use the medicinal product in future.***
  - *A* ***qualified physician / qualified dentist / other qualified healthcare professionals*** *(in accordance with local regulatory requirements) should have the overall responsibility for the* ***trial-related medical care given to, and medical decisions made on behalf of, participants****.*

ICH E6 (R3) PRINCIPLE 2

- **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.**
  - ***Legal representative should give consent for potential participants who are unable to give informed consent.***
  - *The process and information provided should enable potential participants to **evaluate the benefits and risks of participating in the trial** and to make an **informed decision on whether or not to participate in the trial**.*
  - *The information provided during the informed consent process should be **clear and concise** so as to be **understandable** by potential participants / legal representative.*
  - *The informed consent process should take into consideration **relevant aspects of the trial**, such as:*
    - *Characteristics of the participants;*
    - *Trial design;*
    - *Anticipated benefit and risk of medical intervention(s);*
    - *Setting and context in which the trial will be conducted (e.g., trials in emergency situations); and*
    - *Potential use of technology to inform participants (or their legal representatives) and obtain informed consent.*

ICH E6 (R3) PRINCIPLE 3

- **Clinical trials should be subject to an independent review by an institutional review board/independent ethics committee (IRB/IEC).**
  - ***Periodic review of the trial by the IRB/IEC*** *should also be conducted in accordance with applicable regulatory requirements.*

ICH E6 (R3) PRINCIPLE 4

- **Clinical trials should be scientifically sound for their intended purpose and based on robust and current scientific knowledge and approaches.**
  - ***Periodic review of scientific knowledge and approaches*** *should be performed to determine whether modifications to the trial are needed.*

ICH E6 (R3) PRINCIPLE 5

- **Clinical trials should be designed and conducted by qualified individuals.**
  - ***Individuals with different expertise and training may be needed across all phases of a clinical trial,*** *such as physicians, scientists, ethicists, technology experts, trial coordinators, monitors, auditors and statisticians.*

ICH E6 (R3) PRINCIPLE 6

- **Quality should be built into the scientific and operational design and conduct of clinical trials.**
  - *Quality of a clinical trial is considered in this guideline as* ***fit for purpose****.*
  - *The* ***quality and amount of the information*** *generated during a clinical trial should support* ***good decision making****.*
  - ***Factors critical to the quality*** *of the trial should be identified. These factors are attributes of a trial that are fundamental to the* ***protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results.***
  - ***Quality by design*** *involves focusing on the design of all components of the trial in order to maximise the likelihood of trial success (i.e., that the* ***trial will answer the research question****).*

ICH E6 (R3) PRINCIPLE 7 - NEW

- **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.**
  - ***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*
    - *Risks to reliability of trial results*
  - *The focus should be on the* ***risks to participants beyond those associated with standard medical care****.*
  - *The* ***risks relating to investigational products that have a marketing authorisation*** *when used in the clinical trial context* ***may differ from the routine care of patients*** *and should be taken into consideration.*
  - ***Risks to critical to quality factors*** *should be* ***managed and adjusted throughout the clinical trial.***

ICH E6 (R3) PRINCIPLE 8

- **Clinical trials should be described in a clear, concise and operationally feasible protocol.**
  - *A **well-designed trial protocol** is fundamental to the **protection of participants and for the generation of reliable results.***
  - *The **scientific objectives of any trial** should be **clear** and **explicitly stated** in the protocol.*

ICH E6 (R3) PRINCIPLE 9

- **Clinical trials should generate reliable results.**
  - *Systems and processes that aid in data capture, management and analysis should be **fit for purpose, capture the data required by the protocol, and proportionate to the risks.***
  - ***Trial processes** should be **operationally feasible**, **avoid unnecessary complexity**, **procedures and data collection**, and **support the key trial objectives**.*
  - *Appropriate **management of data integrity, traceability and protection of information** allows **accurate reporting, interpretation, availability and verification of trial information**.*
  - *The **transparency of clinical trials** in drug development includes **registration on publicly accessible** and **recognised databases** and the **public posting of clinical trial results**.*

ICH E6 (R3) PRINCIPLE 10 - NEW

- **Roles and responsibilities in clinical trials should be clear and documented appropriately.**
  - *The **sponsor may transfer** or the **investigator may delegate** some or all their tasks, duties or functions (hereafter referred to as activities), 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**, including quality and integrity of the trial data, **resides with the sponsor or investigator, respectively.***
  - *The **sponsor or investigator should maintain appropriate oversight or supervision** of the aforementioned activities, respectively.*

ICH E6 (R3) PRINCIPLE 11

- **Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be stored, shipped, handled and disposed of in accordance with the product specifications and the trial protocol.**
  - *Measures should be in place to ensure that the **investigational product provided to trial participants retains its quality**.*
  - *Investigational products should be **used in accordance with the protocol and relevant trial documents.***
  - ***Manufacturing, handling and labelling of investigational products** should be undertaken in a manner that **aligns with treatment assignment** and **maintains blinding**, where applicable.*
  - ***Investigational product labelling** should follow applicable regulatory requirements.*
  - *Adequate measures to ensure that the investigational product is **handled and shipped appropriately** should be implemented.*

ICH E6 (R3) ANNEX 1

IRB / IEC

- **OVERALL SUMMARY OF CHANGES**

ICH E6 (R3) Section	ICH E6 (R2) Ref.
1.1 – Responsibilities	3.1 • Section 3.1.6 on non-therapeutic trials removed
1.2 – Composition, Function and Operations	3.2
1.3 – Procedures	3.3
1.4 – Records	3.4
1.5 – Submission and Communication • In R3, added global language about reporting to IRB/IEC and regulatory authorities	N/A

ICH E6 (R3) ANNEX 1

IRB / IEC

- **Responsibilities**
  - **IRB/IEC should review the following additional information, where applicable:**
    - Assent form
    - Informed consent process
    - Current scientific information, such as basic product information brochure (e.g. SmPC, package leaflet or labelling), including their updates
    - Any other information to be provided to the trial participant(s), including a description of the media through which such information will be provided
  - If **minors** are to be included in a trial, the IRB/IEC should review **the assent information** considering the **age, maturity and psychological state of the minor**, as well as **applicable regulatory requirements**.
  - **Reasonable reimbursement** of participants **for travel and lodging should not be typically coercive.**
  - **Continuing review** should be based on **degree of risk to trial participants**.

ICH E6 (R3) ANNEX 1

IRB / IEC

- **Composition, Functions and Operations**
  - **IRB Composition**
    a) at least one member whose primary area of interest is **not in medical sciences.**
  - **Provision of information**
    - **Investigator site staff and/or sponsor**.
- **Documented Procedures and Communication**
  - May be maintained / performed **electronically**.
- **Records**
  - **Retained** in accordance with **applicable regulatory requirements** (NB: 3 years from trial completion has been removed)

ICH E6 (R3) ANNEX 1

INVESTIGATOR

- **OVERALL SUMMARY OF CHANGES**

ICH E6 (R3) Section	ICH E6 (R2) Ref.
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

ICH E6 (R3) ANNEX 1

INVESTIGATOR

- **OVERALL SUMMARY OF CHANGES**

ICH E6 (R3) Section	ICH E6 (R2) Ref.
2.8 – Informed Consent to 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 – Clinical Trial / Study Reports	4.13

ICH E6 (R3) ANNEX 1

INVESTIGATOR

- **Investigator**

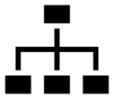
  A person responsible for the conduct of the clinical trial, including the trial participants for whom that person has responsibility during the conduct of the trial. If a trial is conducted by a team of individuals, the investigator is the responsible leader of the team and may be called the principal 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) at or from where trial-related activities are conducted under the investigator's/institution's supervision.

ICH E6 (R3) ANNEX 1

INVESTIGATOR



- **Delegation**
  - In situations where trial activities are performed in accordance with **routine clinical care, delegation documentation may not be required**.

- **Training**
  - Training should correspond to what is necessary to enable persons / parties to **fulfil their delegated trial activities that go beyond their usual training and experience.**

- **Engagement of service providers**
  - Investigator may be **supported by the sponsor** to identify a suitable service provider, but **retains the final decision and ultimate responsibility.**
  - **Agreements** made by investigator / institution and service providers for trial-related activities should be **documented**.

ICH E6 (R3) ANNEX 1

INVESTIGATOR

- **Protocol Compliance**
  - Investigator should **review deviations communicated by the sponsor**.
  - **Important deviations**, which impact participant safety / data credibility, should be **explained** and **CAPA implemented**.

- **Medical Care**
  - **Other 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**
  - The investigator may **delegate activities for safety reporting** to **qualified investigator site staff**, but **retains the overall responsibility for safety of the trial participants** under their responsibility and compliance with the reporting requirements.

ICH E6 (R3) ANNEX 1

INVESTIGATOR

- **Informed consent**
  - **Mode of documenting informed consent**
    - Paper / Electronic formats
  - **Varied approaches for informed consent**
    - Text, images, videos and other interactive methods may be used
  - **Mode of signing informed consent**
    - Physical / electronic signatures
  - **Remote consent**
    - May be considered, where appropriate.
  - **New information**
    - **Considerations for re-consent**, including **stage of the clinical trial, current status of trial participant** (i.e., new / ongoing trial participants).
    - **Revised informed consent materials** require **IRB approval in advance of use**.

ICH E6 (R3) ANNEX 1

INVESTIGATOR

- **Informed consent (cont'd)**
  - **Impartial witness requirements**
    - May be present **remotely** / in person.
    - Should **contemporaneously sign and personally date** the informed consent document.
  - **Elements of an informed consent form**
    - The process by which the **participant's data will be handled**, including in the event of the **withdrawal of participation** in accordance with regulatory requirements.
    - Trial may be **registered on publicly accessible and recognised databases**.
    - **Trial results and information on trial participant's actual treatment**, if appropriate, will be **made available to the trial participants** should they desire it.

ICH E6 (R3) ANNEX 1

INVESTIGATOR

- **Informed consent (cont'd)**
  - **Clinical trials in minors**
    - **Assent** should be obtained from minors, **depending on their age, maturity and psychological state.**
    - **Re-consent** should be considered during the course of the clinical trial, if the **minor reaches the age of legal consent**.
  - **Exceptional circumstances (e.g. public health emergencies)**
    - **Alternative measures and technologies** in accordance with local IRB/IEC and applicable regulatory requirements may be considered.

ICH E6 (R3) ANNEX 1

INVESTIGATOR

- **End of participation in a clinical trial**
  - **Follow-up measures** required for IP discontinuation / study withdrawal / end of clinical trial.
  - Avoid **unnecessary loss of critical data**.
  - **Value and importance of continuing trial participation** should be explained to trial participant to minimise trial participant withdrawal.
  - Consider **informing participant about trial results** and **treatment assignment** when this information is available from the sponsor after unblinding, with due respect to trial participant's preference to be informed.

- **Investigational Product (IP) management**
  - **Sponsor may facilitate** IP accountability.
  - **Alternative approaches** for IP documentation may be adopted for **locally registered IP.**

ICH E6 (R3) ANNEX 1

INVESTIGATOR

- **Records**
  - **Data integrity** should be ensured irrespective of media used.
  - **Unnecessary transcription steps** between source data and data acquisition tool should be **avoided**.
  - **Timely access and review of data**, including central lab data, centrally read imaging data, ePRO data, other institution's records that may **impact trial participant eligibility, treatment or safety**.
  - Data reported at **milestones** should be **endorsed**.
  - Data reported to sponsor should be identified with an **unambiguous code** that can be **traceable**.
  - Appropriate measures to safeguard **privacy and confidentiality**.
  - **Systems deployed by investigator / institution** that maintain and retain **trial information** should ensure that trial data are protected from:
    - **Unauthorised access, disclosure, dissemination / alteration, and from inappropriate destruction / accidental loss**.

ICH E6 (R3) ANNEX 1

INVESTIGATOR

- **Records (cont'd)**
  - **Requirements for computerised systems:**
    - **Secure** and **attributable access**
    - **Equipment for data acquisition provided to trial participants**
      - Traceability maintained
      - Training of trial participants
    - **Incidents** in the use and operation of computerised systems, which may have a **significant and/or persistent impact on trial data,** should be **reported to the sponsor and IRB** (where applicable).
    - If the **PI leaves / closes a site** during/after the end of the clinical trial, the **sponsor should be notified** of the individual responsible for retention of the site's essential records.

ICH E6 (R3) ANNEX 1

SPONSOR

- **OVERALL SUMMARY OF CHANGES**

ICH E6 (R3) Section	ICH E6 (R2) Ref.
3.1 – Trial Design	5.0, 5.4
3.2 – Resources	NA
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	NA

ICH E6 (R3) ANNEX 1

SPONSOR

- **OVERALL SUMMARY OF CHANGES**

ICH E6 (R3) Section	ICH E6 (R2) Ref.
3.10 – Quality Management	5.0
3.11 – Quality Assurance and Quality Control	5.1, 5.18, 5.19
3.12 – Non-compliance	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

ICH E6 (R3) ANNEX 1

SPONSOR

- **Trial Design**
  - Incorporate **safety and efficacy data** from **non-clinical studies / clinical trials / real world data**
  - Incorporate **Quality by Design (QbD)** by identifying **Critical to Quality (CTQ) factors**, and managing the **risks** to CTQ factors.
  - **Inputs from stakeholders** (e.g. healthcare professionals, patients) should be considered .
  - Protocols, data acquisition tools and other operational documents should be **fit for purpose.**

- **Agreements**
  - Made with **service providers and other parties** (e.g. IDMC, adjudication committee), and updated.
  - **Provide information to investigator** on **any service provider** identified by the sponsor to **undertake activities under the investigator's responsibility**.

ICH E6 (R3) ANNEX 1

SPONSOR

- **Service Providers**
  - **Secure agreement** for compliance, essential record retention, and monitoring / audits / inspections.
  - **Suitability** of service provider should be assessed.
  - **Copy of study protocol and other documents** should be provided, where necessary, to perform their activities.
  - **Quality management** should be implemented.
  - Sponsor should be notified on any **incidents that may impact on the safety of trial participants / trial data**.
  - **Access** to relevant information (e.g. SOPs, performance metrics) for selection and oversight of service providers.
  - **Oversight** of important trial-related activities transferred to service providers and further sub-contracted.
  - Trial-related activities should be conducted in **compliance with GCP**.

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SPONSOR

- **Involvement of multiple sponsors**
  - Respective responsibilities of the sponsors should be documented in an **agreement.**
  - Where the documented agreement **does not specify to which sponsor a given responsibility is attributed**, that **responsibility lies with all sponsors**.

- **Sponsor Oversight**
  - **Quality of trial design, trial conduct, processes undertaken, data generated to ensure reliable trial results, participant safety and appropriate decision making** should be ensured.
  - Trial processes should be conducted in **compliance with protocol, related documents, regulations and ethical standards**.
  - Criteria for determining **important protocol deviations** (i.e. impacting rights, safety and well-being of trial participants and reliability of trial results) should be determined.
  - **Trial-related decisions** should be **assessed** for their impact and **risks** related to such decisions should be managed.

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SPONSOR

- **Sponsor Oversight (cont'd)**
  - Range and extent of oversight measures should be **fit for purpose** and tailored to the **complexity of and risks associated with the trial**.
  - **Quality assurance and quality control** processes should be implemented in oversight of investigators and service providers.
  - **Issues** should be **escalated and followed up** in a timely manner.
  - **Endpoint assessment / adjudication committee** may be appointed to review important endpoints, where blinded data is reviewed to minimise bias.
  - **Committees** established for purposes that could impact trial participant safety or reliability of trial results:
    - Relevant expertise
    - Conflict of interest managed
    - SOPs maintained
    - Decisions documented

ICH E6 (R3) ANNEX 1

SPONSOR

- **Quality Assurance**
  - Implementing strategies to **identify potential / actual causes of serious non-compliances** to enable their CAPA.

- **Audits**
  - When performed, audits should be conducted in a manner that is **proportionate to the risks** associated with conduct of the trial.
  - Purpose is to evaluate whether the **processes put in place to manage** and **conduct the trial** are **effective** and **compliant**.

- **Quality control**
  - Comprises **monitoring** and **data management** processes.
  - Quality control of sites (**other than investigator sites**, e.g. centralised imaging reading facilities) may be undertaken, including on-site / centralised activities, and reported using a **risk-based approach**.

ICH E6 (R3) ANNEX 1

SPONSOR

- **Monitoring**
  - **Remote monitoring** and **monitoring in decentralised settings** included.
  - Monitors should be **independent** of the clinical trial being monitored.
  - **Source data review** and **data analytics** included as monitoring activities.
  - Additional requirement for **Monitoring Plan**:
    - Monitoring of **key data and processes outside the investigator site** (e.g. central reading facilities / central laboratories) should be addressed.
  - **Monitoring activities expanded.**
    - **Communication with parties conducting the trial**
      - *Highlighting **important deviations** and focus of remediation.*
      - *Implementing **proportionate actions** in relation to deviations, errors or omissions.*

ICH E6 (R3) ANNEX 1

SPONSOR

- **Monitoring (cont'd)**
  - **Monitoring activities expanded.**
    - **Monitoring of clinical trial data**
      - ***Adjusting sample size*** *based on previous monitoring results or other indications of insufficient data quality.*
      - ***Verifying critical data****.*
      - *Identifying* ***missing data, inconsistent data, data outliers, unexpected lack of variability*** *and* ***protocol deviations****.*
      - *Examining* ***data trends****.*
  - **Monitoring Reports**
    - *Requirements should be described in* ***sponsor SOPs****.*
    - *Resolution of* ***pending actions*** *not resolved in previous reports should be included.*
    - ***Centralised monitoring reports*** *should be provided to sponsor in a timely manner for review and follow-up.*
    - *Findings requiring* ***escalation for action and resolution*** *should be described.*

ICH E6 (R3) ANNEX 1

SPONSOR

- **Non-compliances**
  - **Adequacy of CAPA** for non-compliances that significantly impact / have the potential to significantly impact trial participant rights, safety or well-being or reliability of trial results should be confirmed.
  - Issues that could **significantly impact trial participant rights, safety or well-being or reliability of trial results** should be notified to the **IRB and RA.**

- **Safety Assessment and Reporting**
  - **Sponsor review of safety information**
    - Sponsor should **aggregate and periodically review** relevant safety information, which may result in updates to study documents.
    - Sponsor should review the available **emerging safety information** to assess whether there is any new data that may affect the trial participant's willingness to continue the trial, impact trial conduct, alter the approval / favourable opinion of IRB/IEC and RA in a timely manner.

ICH E6 (R3) ANNEX 1

SPONSOR

- **Safety Assessment and Reporting (cont'd)**
  - **Safety reporting**
    - Expectedness of an adverse event should be assessed in relation to available product information (e.g. **Reference Safety Information** contained in the IB or **alternative documents**).
    - **Reporting of SUSARs to investigators / institutions and IRBs/IECs** should be undertaken in a manner that **reflects the urgency or the action required** and consider the **evolving knowledge of the safety profile of the product**.
    - **Alternative arrangements for safety reporting to RA, IRBs/IECs** and **investigators** and for **reporting by investigators to the sponsor** should be **prospectively agreed upon** with the RA and the IRBs/IECs, and **described in the clinical trial protocol** (e.g. SAEs considered as efficacy / safety endpoints, which would not be subject to unblinding and expedited reporting).

ICH E6 (R3) ANNEX 1

SPONSOR

- **Safety Assessment and Reporting (cont'd)**
  - **Management of an immediate hazard**
    - **Prompt action** should be taken to address immediate hazards to participants.
    - **Causes** of the hazard should be determined to take appropriate **remedial actions.**
    - **Clinical trial protocol may need to be amended** to address the immediate hazard, and submitted to IRB/IEC and RA.

- **Insurance / Indemnification / Compensation to Participants and Investigators**
  - **Sponsor's policies and procedures** should address the **costs of treatment** of trial participants in the event of **trial-related injuries**.

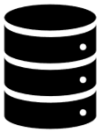
ICH E6 (R3) ANNEX 1

SPONSOR

- **Investigational Products (IP)**
  - **Information on the IP**
    - For **authorised medicinal products**, the sponsor should identify the **basic product information** to be used in the trial.
  - **Manufacturing, Packaging, Labelling and Coding IPs**
    - For **blinded trials**:
      - Mechanism to protect study blind if treatment assignment is unblinded for the purpose of safety reporting to IRB/IEC or RA.
    - **Direct IP supply from sponsor to participants** included.
    - **Retention samples** are **not required to be kept for marketed products.**

ICH E6 (R3) ANNEX 1

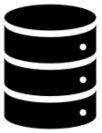
SPONSOR



- **Data and Records**
  - **Data Handling:**
    - Focus QA and QC activities and data review on **critical data**, including **relevant metadata**.
    - **Pre-specify the data** to be collected and the **method of collection**.
    - **Data Acquisition Tools** should be **fit for purpose**, **validated** and ready to use prior to implementation.
    - **Documented processes** to ensure data integrity for the full data life cycle.
    - Provide **guidance to investigators / institutions, service providers and participants** on expectations for data capture, data changes, data retention and data disposal.
    - Ensure that the **investigator has access the required data**, including data from **external sources** (e.g. central lab data / central imaging data / electronic patient reported outcomes data) to enable the investigator to make **decisions on eligibility, treatment, continued participation and medical care**.

ICH E6 (R3) ANNEX 1

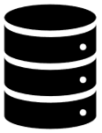
SPONSOR



- **Data and Records**
  - **Data Handling (cont'd)**
    - Seek **investigator endorsement** at predetermined **milestones.**
    - Document the **data management steps** to be undertaken prior to **data analysis**.
    - Document and justify **deviations from planned statistical analysis** or **changes made to data analysis set** after the clinical trial has been unblinded.
    - Document **what happens to the data** when **participant withdraws / discontinues** from the clinical trial.
    - Documented processes for reporting **incidents**, including security breaches, that have **significant impact on trial data**.

ICH E6 (R3) ANNEX 1

SPONSOR



- **Data and Records**
  - **Data Handling (cont'd)**
    - When using **computerised systems,**
      - Maintain a **record of the computerised systems** used for the clinical trial.
      - Maintain **documented procedures**.
      - **User management** and **access rights**
      - For **computerised systems deployed by the investigator / institution** (e.g. Electronic Medical Records), the following should be **assessed during site selection** and **documented**:
        - » Whether they are **fit for purpose**; and
        - » Whether **known issues could be appropriately mitigated**.
      - Process for service providers and investigators to notify the sponsor of **system defects or incidents** that could constitute a serious non-compliance.

ICH E6 (R3) ANNEX 1

SPONSOR

- **Data and Records**
  - **Statistical Programming and Data Analysis**
    - Should be read in conjunction with ICH E9 guideline on Statistical Principles for Clinical Trials.
    - Appropriate and documented **quality control** of statistical programming and data analysis.
    - Ensure **traceability of data transformations** and **deviations** during **data processing and analysis**.
    - **Allocation to / exclusion of each participant** from any analysis is pre-defined.
    - Procedures for **unblinding**.

- **Reports**
  - **For Clinical Trial / Study Reports:**
    - **Investigators** should be provided with a **summary of the trial results**.
    - Provision of **final treatment assignment (for blinded trials) and brief summary of trial outcome to participants** should be considered.

ICH E6 (R3) ANNEX 1

DATA GOVERNANCE

- **OVERALL SUMMARY OF CHANGES**

ICH E6 (R3) Section	ICH E6 (R2) Ref.
4.1 – Safeguard Blinding in Data Governance	NA – Major Revamp
4.2 – Data Life Cycle Elements	
4.3 – Computerised Systems	
4.4 – Security of Computerised Systems	
4.5 – Validation of Computerised Systems	
4.6 – System Failure	
4.7 – Technical Support	
4.8 – User Management	

ICH E6 (R3) ANNEX 1

DATA GOVERNANCE

- **New section in ICH E6 (R3) GCP guideline (Section 4).**
- **Revisions have also been made to Investigator and Sponsor sections:**
  - Investigator section: 2.11, 2.12
  - Sponsor section: 3.16
- **New glossary terms:**
  - **Data Acquisition Tool**
    - 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 an electronic transfer of data from one system to another (e.g., extraction of data from an electronic health record or laboratory system).
    - E.g., CRFs, interactive response technologies (IRTs), patient-reported outcomes (PROs), clinical outcome assessments (COAs) and wearable devices, irrespective of the media used.
  - **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 reconstruct the trial conduct.

ICH E6 (R3) ANNEX 1

DATA GOVERNANCE

- Sponsor should apply **quality control** to the relevant stages of data handling to ensure **data are of sufficient quality to generate reliable results.**

- Manage **computerised systems** to ensure they are **fit for purpose** and in a manner that is **proportional** for their importance to **safety and result reliability.**

- Comprehensive approach to data systems (e.g., IT security, data protection, data validation, metadata, data acquisition tools).
  - The quality and amount of the information generated in a clinical trial should be sufficient to address trial objectives, provide confidence in the trial's results, and support good decision making. The systems and processes that help ensure this quality should be designed and implemented in a way that is proportionate to the risks to participants and the reliability of trial results.

ICH E6 (R3) ANNEX 1

GLOSSARY

New Glossary Terms

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

Revised Glossary Terms

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

ICH E6 (R3) APPENDIX A

INVESTIGATOR'S BROCHURE

- **OVERALL SUMMARY OF CHANGES**

ICH E6 (R3) Section	ICH E6 (R2) Ref.
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

ICH E6 (R3) APPENDIX B

CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENTS

- **OVERALL SUMMARY OF CHANGES**

ICH E6 (R3) Section	ICH E6 (R2) Ref.
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 – Withdrawal of consent / discontinuation of participation	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

- **OVERALL SUMMARY OF CHANGES**

ICH E6 (R3) Section	ICH E6 (R2) Ref.
B.11 – Direct Access to Source Records	6.10
B.12 – Quality Control and Quality Assurance	6.11 • Inclusion of critical to quality factors, monitoring approach and handling of non-compliances.
B.13 – Ethics	6.12
B.14 – Data Handling and Record Keeping	6.4, 6.13 • Inclusion of data collection and retention.
B.15 – Financing and Insurance	6.14
B.16 – Publication Policy	6.15

NB: Section 6.16 on supplements relating to Final CSR removed.

ICH E6 (R3) APPENDIX C

ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

- **OVERALL SUMMARY OF CHANGES**

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

ICH E6 (R3) APPENDIX C

ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

ICH E6 (R3) Section	Summary of key changes
C.1 - Introduction	Nature and extent of essential records depend on trial design, conduct, application of proportionate approaches, and importance and relevance of the record to the clinical trial.
C.2 – Management of Essential Records	• Essential records should **be complete, readable and accessible**. • **Service providers** should maintain records. • **Copies to replace irreversible original records** should be **certified as true copies**.

ICH E6 (R3) APPENDIX C

ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

ICH E6 (R3) Section	Summary of key changes

C.3 – Essentiality of Trial Records	• Sponsor and Investigator will determine which records are essential.
	  • Table 1 – Essential Records for All Trials
	  • Table 2 – Potential Essential Records

Next steps for ICH E6 (R3)

Principles and Annex 1

30 Sep 2023

- Closing date for ICH E6 (R3) public consultation.

Nov 2023

- Review of public comments from all regions.

Aug / Sep 2024

- Step 3 sign-off technical document.

Sep / Oct 2024

- Adoption of technical document.

Public Consultation on draft ICH E6 (R3) GCP guideline by 30 Sep 2023

Please scan the QR code or go to https://www.hsa.gov.sg/therapeutic-products/international-collaboration/ich to submit your feedback on the draft ICH E6 (R3) GCP guideline **by 30 Sep 2023**.

Your feedback is important and contributes towards the finalisation of the ICH guidelines.

Please provide your comments using the template provided by ICH and email to HPRG_feedback@hsa.gov.sg with the subject title: **ICH <Guideline Code> Feedback**.

Draft ICH Guidelines	Status for consultation	Deadline for comments
Guideline Code: E6(R3) Good Clinical Practices (GCP)	Open	30 September 2023

REFERENCES

- Draft ICH E6 (R3) guideline (Step 3) – 19 May 2023
- ICH E6 (R3) (Step 2) presentation – 22 May 2023
- ICH E6 (R3) Explanatory Video – Jun 2023
- EMA Multi-stakeholder workshop on ICH E6 (R3) – 13 and 14 Jul 2023
- ICH E6 (R3) Public Web Conference Report – 18 and 19 May 2021
- ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6 – Jan 2017
- ICH E6 (R2) guideline – 9 Nov 2016