LOOKING BACK AT 2024

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OUTLINE

- GCP Inspection Framework
- GCP Inspections conducted in 2024
- Regulatory Actions Taken in 2024
- Important Points to Note
  - Site Inspections
  - Sponsor Inspections
- Regulatory Updates
- Conclusion

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Objectives of GCP Inspections

Safeguard the rights, safety and well-being of trial participants.

Verify the quality and integrity of the clinical trial data submitted to the Regulatory Authority.

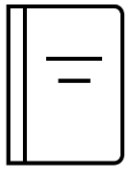
Assess compliance to protocol and applicable regulations, guidelines and standard operating procedures for clinical trials.

Scope of GCP Inspections

- Clinical trials regulated by the Health Sciences Authority
  - Clinical trials that are subject to the requirements of a:
    - *Clinical Trial Authorisation (CTA);*
    - *Clinical Trial Notification (CTN); or*
    - *Clinical Trial Certificate (CTC)*

- GCP inspections may either be protocol-specific or systems-based.

GCP Inspection Criteria



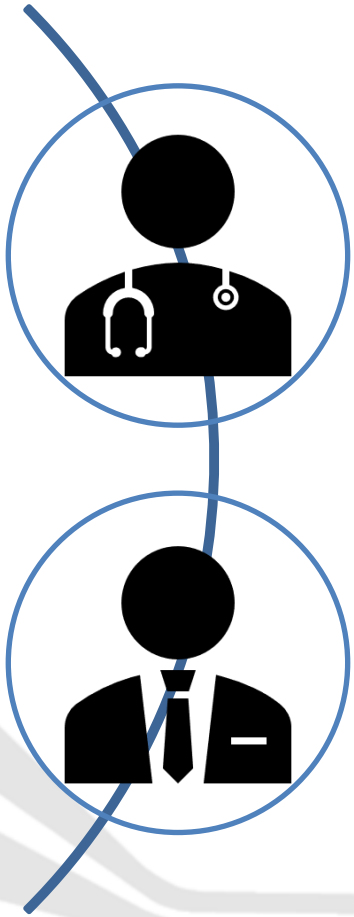
Study protocol

Regulations

ICH E6 GCP Guideline

Standard Operating Procedures

Inspectee



Site Inspection

→Principal Investigator

Sponsor Inspection

→Local Sponsor

Classification of GCP Inspection Findings

CRITICAL

- Conditions, practices or processes that adversely affect the rights, safety or well-being of the trial participants and/or the quality and integrity of data.

MAJOR

- Conditions, practices or processes that might adversely affect the rights, safety or well-being of the trial participants and/or the quality and integrity of data.

OTHER

- Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the trial participants and/or the quality and integrity of data.

COMMENTS

- Suggestions to improve quality or to reduce the potential for a non-compliance from occurring in future.

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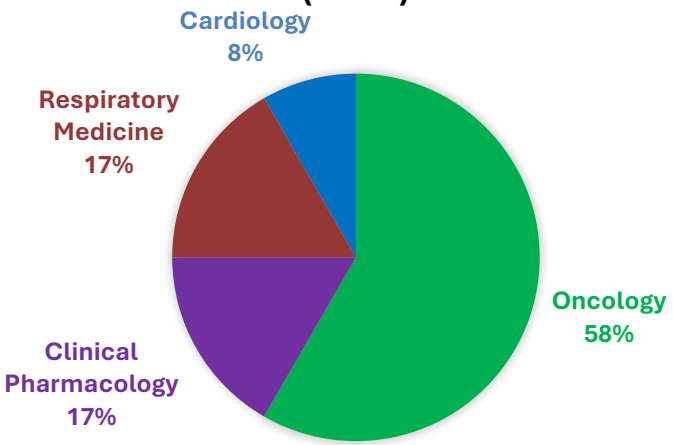
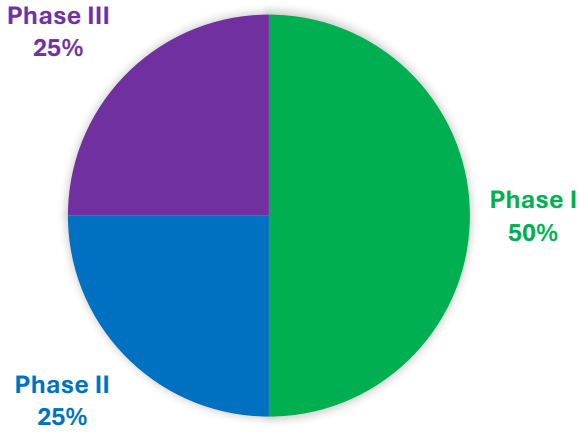
GCP Inspections (2024)

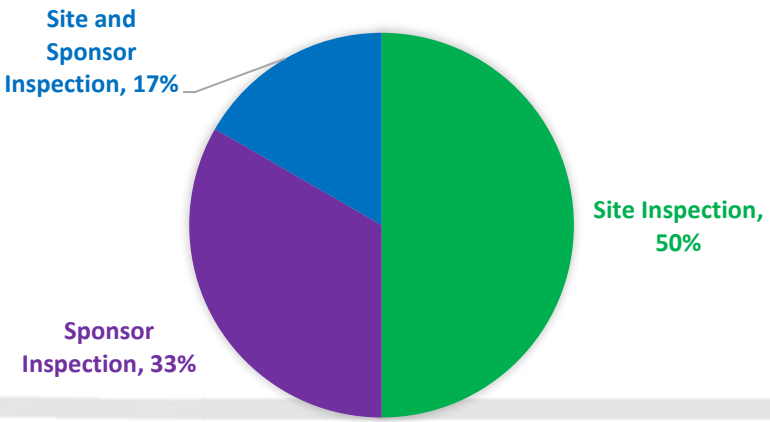
DISTRIBUTION BY THERAPEUTIC AREA (N=12)



DISTRIBUTION BY TRIAL PHASE (N=12)



TYPES OF GCP INSPECTION (N=14)



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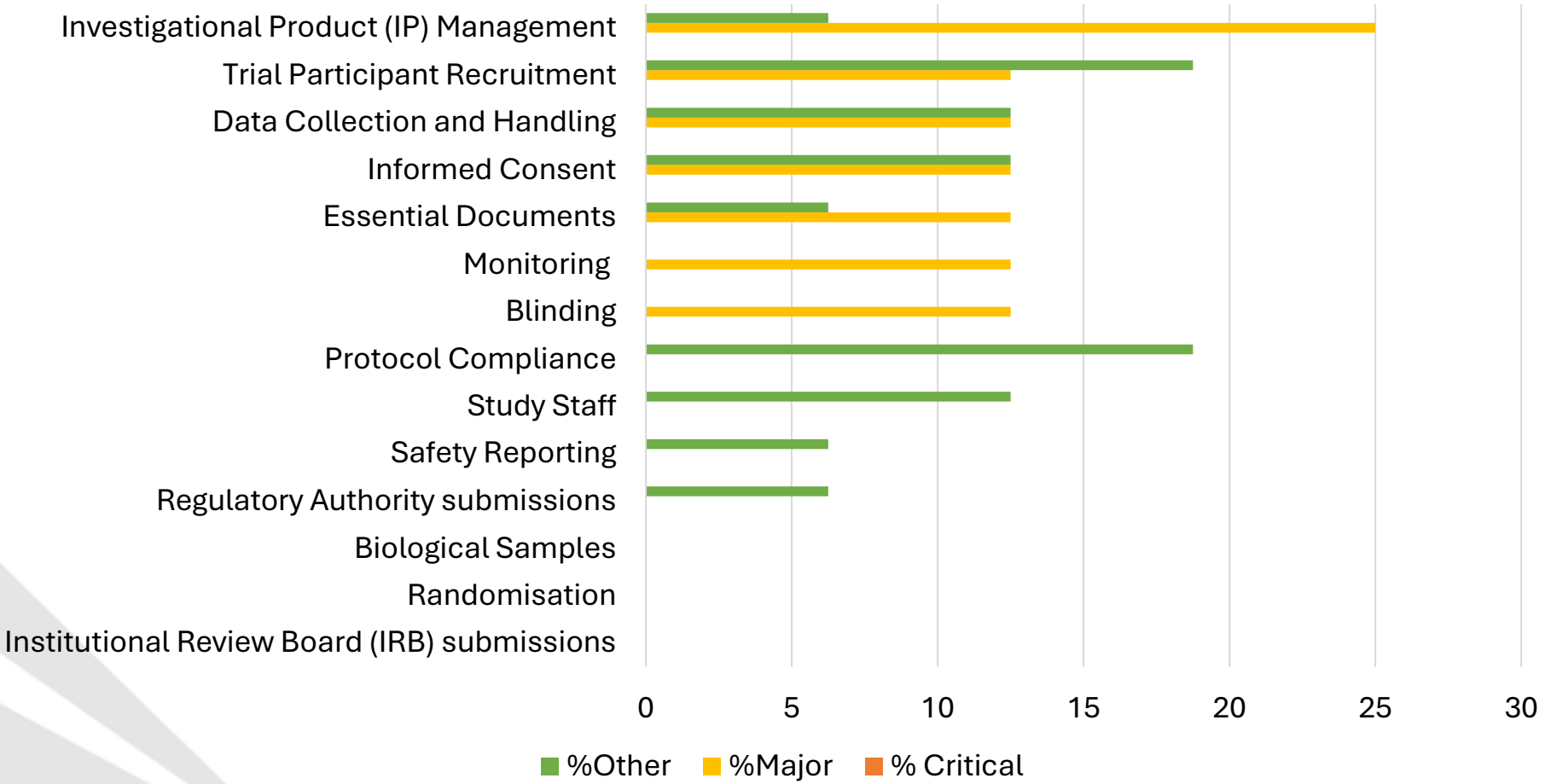
Regulatory Actions Taken in 2024

Type of Regulatory Action	No. of clinical trials	Reason(s)
Trial Termination	0	NA
Trial Suspension	0	NA
Recruitment Suspension	0	NA
Suspension of Investigational Product (IP) Manufacture	1	• Major GMP deficiencies identified, including environmental monitoring failure, which could potentially impact the quality of the IP.

Site Inspections (2024) (N = 8)



Prescribing Investigational Products

- **Major GCP Inspection Finding**
  - The Principal Investigator (PI) did not ensure that IP was prescribed under the instructions of an investigator, who was a medical doctor.
    - ❖ ***Important Points to Note:***
      - ❖ *The PI is overall responsible for trial conduct, including prescribing the IP.*
      - ❖ *A qualified physician / dentist (where applicable), should have the overall responsibility for the trial-related medical care given to and medical decisions made on behalf of participants.*
        - ❖ *The PI may delegate a Sub-Investigator, who is a qualified practitioner, to prescribe the IP.*

Obtaining Informed Consent for Adults Lacking Capacity

- **Major GCP Inspection Finding**
  - The Principal Investigator (PI) did not ensure that an investigator and independent doctor had documented the assessment of capacity of the participants, prior to obtaining informed consent from their respective legal representatives.

❖***Important Points to Note:***

❖*For clinical trials involving adults lacking capacity:*

❖*The investigator and an independent doctor must assess and document the capacity of the participant prior to obtaining informed consent from the participant's legal representative.*

Eligibility Assessment by an Allied Health Professional

- **Major GCP Inspection Finding**
  - The Pharmacist, who had been delegated as a Sub-Investigator, had assessed the eligibility of a trial participant, despite not being qualified to make trial-related medical decisions for eligibility assessment.

❖ ***Important Points to Note:***

❖ *A qualified physician / dentist (where applicable), should have the overall responsibility for the trial-related medical care given to and medical decisions made on behalf of the participants. For e.g.,*

❖ *Informed consent, eligibility assessment, IP dosing, safety assessment etc.*

Safeguarding Blinding through Investigational Product labelling

- **Major GCP Inspection Finding**
  - The IP and placebo were not labelled in a manner that protected the study blind, as the treatment groups (e.g., X or Y) reflected in the randomisation list were specified on the IP label.

❖ ***Important Points to Note:***

❖ *For randomised, double-blind clinical trials:*

❖ *Consider using individual treatment kit numbers for each IP.*

❖ *Avoid labelling the IP using treatment groups (e.g., X and Y), as unblinding one participant will result in unblinding of all participants, thereby significantly compromising the study blind.*

Sponsor Oversight for IITs

- **Major GCP Inspection Finding**
  - There was inadequate sponsor oversight of trial monitoring, as the Monitor did not submit the Monitoring Plan and Monitoring Visit Reports to the sponsor for review.

❖ ***Important Points to Note:***

❖ *For investigator-initiated clinical trials (IITs):*

❖ *The sponsor is the healthcare institution.*

❖ *The sponsor should ensure the following to maintain adequate sponsor oversight of monitoring:*

❖ *Ensure that all IITs are monitored;*

❖ *Keep track of the monitoring status of IITs;*

❖ *Receive a copy of the Monitoring Plan;*

❖ *Review Monitoring Visit Reports; and*

❖ *Document review of Monitoring Visit Reports.*

Electronic Patient Reported Outcomes

- **Major GCP Inspection Finding**
  - There was a lack of quality systems in the completion of the Patient Reported Outcomes (PRO) for the clinical trial.
    - According to the study protocol, the CRCs had to administer the PROs to the participants remotely via a telephone call. However,
      - The CRC did not provide a copy of the PROs to the participants for reference prior to conducting the telephone call,.
      - The CRC did not use validated translations of the PROs for participants who had been unable to read English.
      - The CRC had used the eCRF as a source document to complete the PROs, which was contrary to the eCRF guidelines which specified that the eCRF should not be used as a source document.

Electronic Patient Reported Outcomes

- ***Important Points to Note:***
  - *The study protocol should clearly describe how the PROs should be completed, including handling situations where the participant is unable to complete the PRO). For e.g.,*
    - *Language barriers*
    - *Literacy issues*
    - *Cognitive impairment*
    - *Technological challenges*
    - *Time constraints*
    - *Health issues*

Essential Documents Maintenance

- **Major GCP Inspection Finding**
  - A Source Document Location List was not maintained for the clinical trial.
  - The IP Accountability Form was completed electronically without an audit trail.
  - Several essential documents were destroyed prematurely, as they were no longer current.

❖ ***Important Points to Note:***

❖ *Source Document Location List should be maintained to define the source documents, methods of data capture and their location, and updated throughout the clinical trial.*

❖ *Essential documents should not be maintained electronically without an audit trail.*

❖ *Source Documents should not be destroyed until after the archival period and confirmation by the sponsor.*

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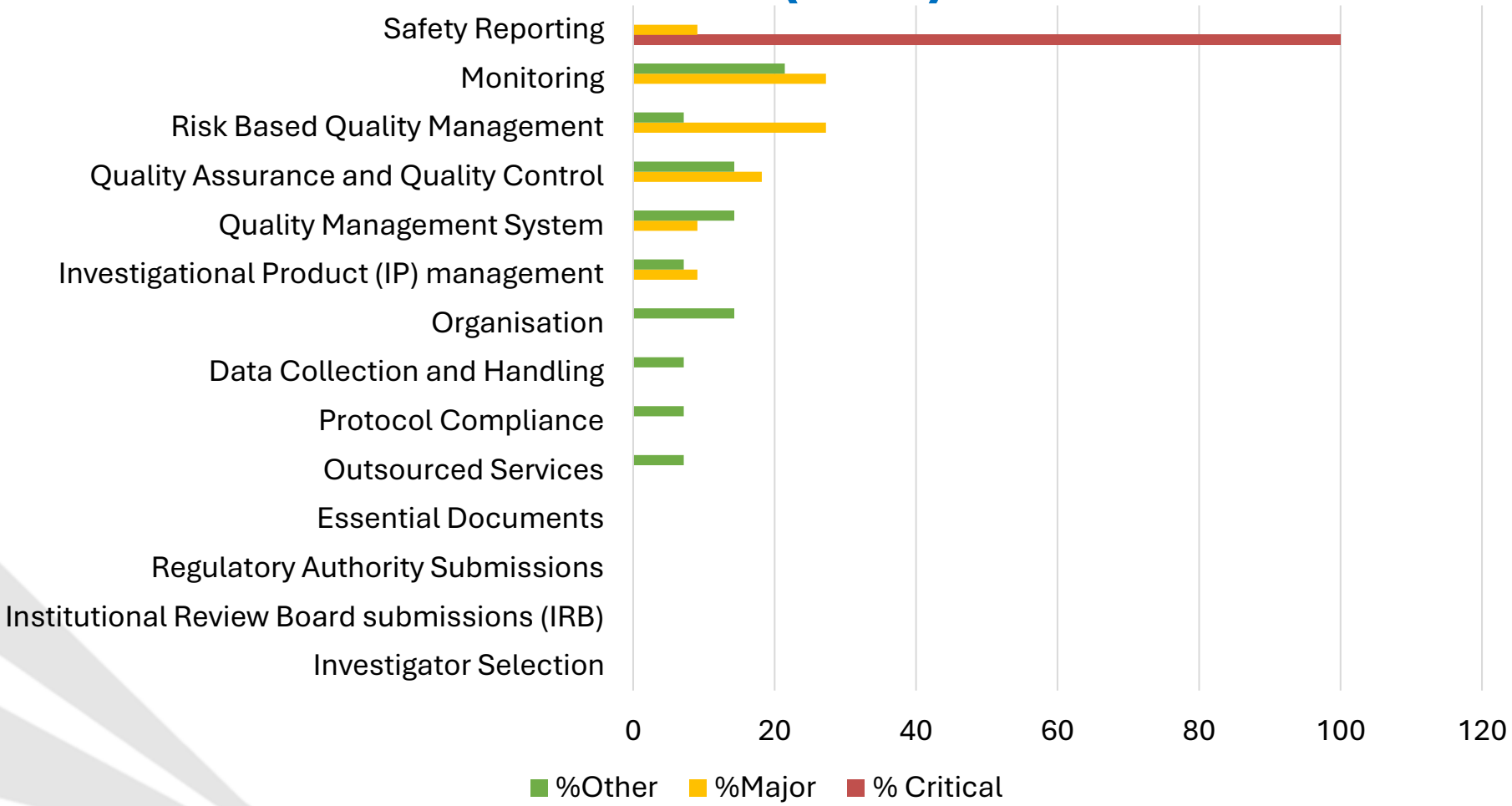
Sponsor Inspections (2024) (N=6)



Safety Assessment & Reporting

- **Critical GCP Inspection Finding**
  - There was a lack of quality systems for safety management and reporting, thus impacting data integrity.
    - **Safety Database**
      - There was a lack of adequate audit trail for the safety database, as it had been maintained in Microsoft Excel.
    - **Unblinding Process for reporting Unexpected Serious Adverse Drug Reactions (USADRs)**
      - The unblinding process to facilitate USADR reporting by the sponsor was not appropriate.
        - Unblinding was only performed if it had been triggered by the PI, thereby resulting in under-reporting of USADRs to HSA.
        - After unblinding was performed to facilitate Expedited Safety Reporting, the treatment assignment was communicated back to the PI, thereby introducing bias in the conduct of the trial by the PI and compromising trial integrity.

Safety Assessment & Reporting

- **Critical GCP Inspection Finding (cont'd)**
  - There was a lack of quality systems for safety management and reporting, thus impacting data credibility and trial integrity.

    - **Safety Reporting**
      - There was a lack of attributability in the drafting and review of Serious Adverse Events (SAEs).

❖ ***Important Points to Note:***

- ❖ *The Safety Database should not be maintained in MS Excel, as it lacks audit trail, thereby significantly impacting data integrity.*
- ❖ *The unblinding process to facilitate Expedited Safety Reporting should be independent of the PI's decision for unblinding.*
- ❖ *There should be attributability in the sponsor's drafting and review of SAEs.*

Safety Assessment

- **Major GCP Inspection Finding**
  - There was no documented procedure for safety assessment and safety reporting by the Lead Sponsor.
  - There was no documentation of the safety assessment performed by the Lead Sponsor.

❖ ***Important Points to Note:***

❖ *For Multi-Sponsor IITs:*

❖ *The Lead Sponsor should ensure that there is a documented procedure for safety assessment and reporting from trial sites to sponsors.*

❖ *The Lead Sponsor should ensure that the safety assessment is documented.*

Sponsor Oversight of IITs

- **Major GCP Inspection Finding:**
  - The sponsor did not maintain adequate sponsor oversight of the monitoring status of IITs.
  - It was not possible to verify if the Monitor had been adequately qualified to monitor the clinical trial due to missing training documentation.

❖ ***Important Points to Note:***

❖ *For IITs:*

❖ *The sponsor should ensure that all IITs are monitored.*

❖ *The sponsor should maintain the training documentation of the Monitors to demonstrate that they are adequately qualified to monitor the clinical trial.*

Risk-based Quality Management for IITs

- **Major GCP Inspection Findings**
  - The risk-based quality management implemented by the sponsor was inadequate for IITs
    - There was no documented process for the risk identification, evaluation and control for IITs regulated by HSA.

❖ ***Important Points to Note:***

❖ *For IITs:*

❖ *The sponsor should establish a documented procedure for risk-based quality management.*

❖ *The sponsor should perform and document the risk assessment prior to trial initiation, and review the risk control measures periodically.*

Maintenance of Documented Procedures for IITs

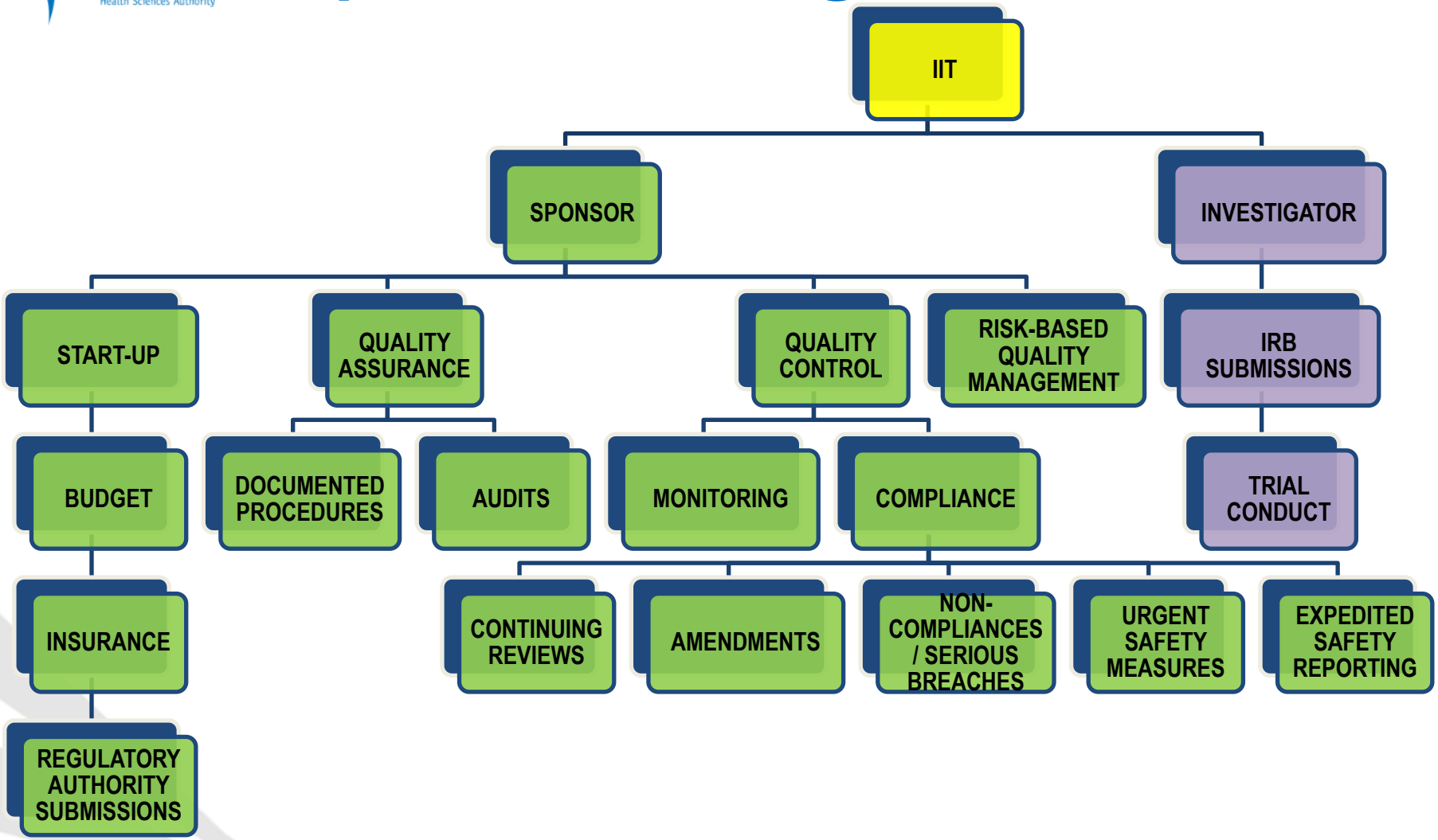
- **Major GCP Inspection Findings:**
  - The sponsor did not implement adequate documented procedures for IITs.

❖ ***Important Points to Note:***

❖ *For IITs:*

❖ *The sponsor is responsible for establishing, implementing and maintaining appropriate quality assurance and quality control processes and documented procedures to ensure that trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and the applicable regulatory requirement(s).*

Sponsor Oversight of IITs



Documented Procedures to be maintained for sponsor of IITs

Study start-up

- Clinical Trial Agreements
- Budgeting
- Risk-based Quality Management
- Initial application to IRB
- Initial application to HSA
- Trial Master Files

Study Conduct

- Continuing Review / Trial Status Reports
- Study / Substantial amendments
- Non-compliance reports
- Serious Breach Notifications
- Urgent Safety Measure notifications
- Expedited Safety Reports
- Safety updates
- Monitoring
- Audits

Study Closure

- Final Clinical Study Reports
- Archival

Allocation of Responsibilities between Sponsor and Investigator for IITs

Sponsor Responsibility	Sponsor	Investigator
Trial Design	❑	❑
Resources	❑	❑
Allocation of activities	❑	❑
Qualification & Training	❑	❑
Financing	❑	❑
Agreements	❑	❑
Investigator Selection	❑	❑
Communication with IRB & RA	❑	❑
Sponsor Oversight	❑	❑
Quality Management	❑	❑

Allocation of Responsibilities between Sponsor and Investigator for IITs

Sponsor Responsibility	Sponsor	Investigator
Quality Assurance & Quality Control	❑	❑
Non-compliance	❑	❑
Safety Assessment and Reporting	❑	❑
Insurance / Indemnification / Compensation to Participants and Investigators	❑	❑
Investigational Product	❑	❑
Data and Records	❑	❑
Reports	❑	❑

Risk-Based Quality Management for IITs

Risk-Based Quality Management for IITs

Risk Identification	Risk Evaluation*	Risk Control
Trial design		
Phase of clinical trial		
Trial population		
PI's experience		
Resources		
Facilities		
Informed consent requirements		
Registration status of IP		
Randomisation		
Blinding		
Data collection and handling		
Trial Monitoring		
TOTAL		**NA**

**Risk Score: Low =1, Medium = 2, High = 3*

Quality Control Measures for IITs

Trial start-up

- Ensure that the study protocol and informed consent material contain all the required elements.
- Monitor IRB and HSA submission and approval timelines

Trial Conduct

- Review Trial Monitoring Plans
- Conduct Trial Monitoring Visits
- Review Trial Monitoring Visit Reports
- Review trial status
- Monitor IRB and HSA submission and approval timelines for amendments.
- Review Non-compliance reports, Serious Breach Notifications and Urgent Safety Measure notifications, including impact assessment, root cause analysis and CAPA Plan.
- Review SAEs

Trial Closure

- Review Final Clinical Study Reports

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ICH E6 (R3) GCP guideline

Background

- Evolution of ICH E6 GCP guideline

Revision 1: 1996

- Described responsibilities and expectations of stakeholders in the conduct of clinical trials.

Revision 2: 2016

- Integrated addendum to encourage implementation of improved and more efficient approaches to GCP.

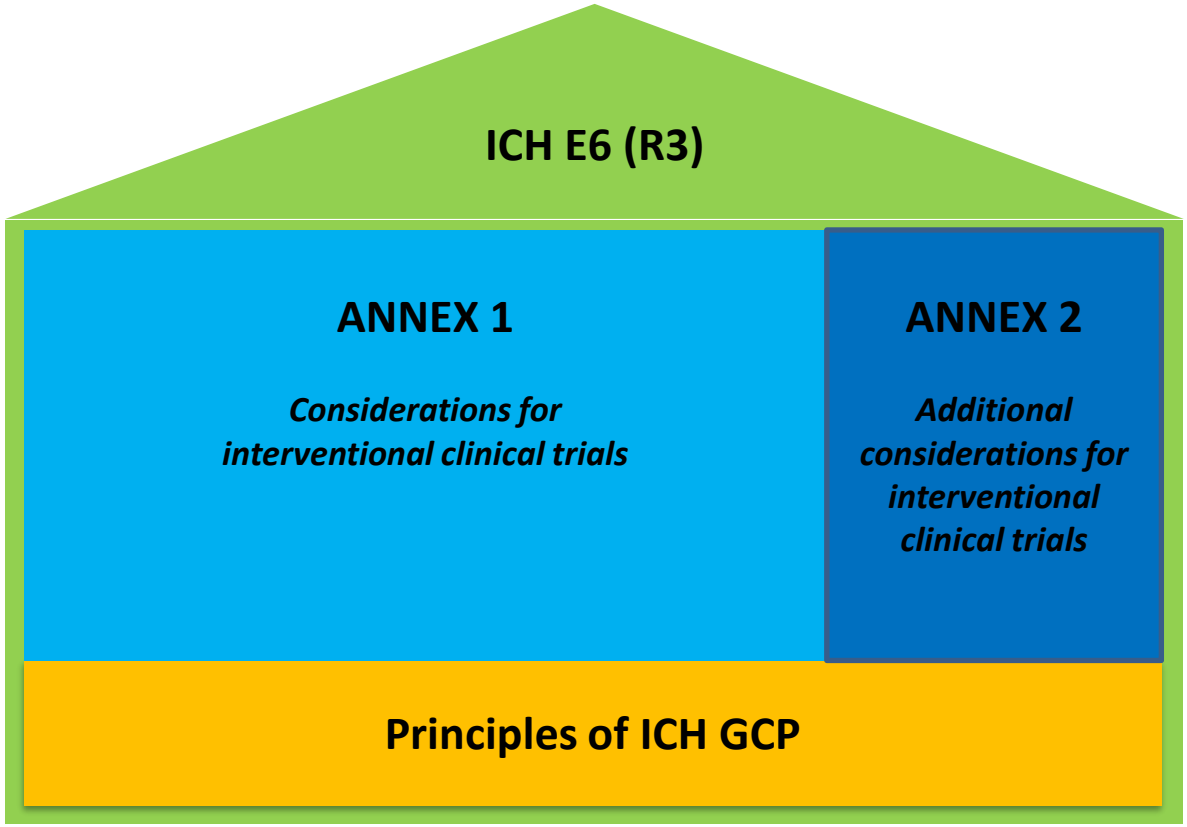
Revision 3: 2025

- Following the ICH Reflection Paper on GCP Renovation in Jan 2017,
  - There was a need to modernise ICH guidelines relating to clinical trial design, planning, management and conduct.
  - The scope of the proposed renovation included revising the ICH E6 and E8 guidelines.

NB:
- *ICH E6: Guideline for Good Clinical Practice*
- *ICH E8: Guideline on General Considerations for Clinical Trials*

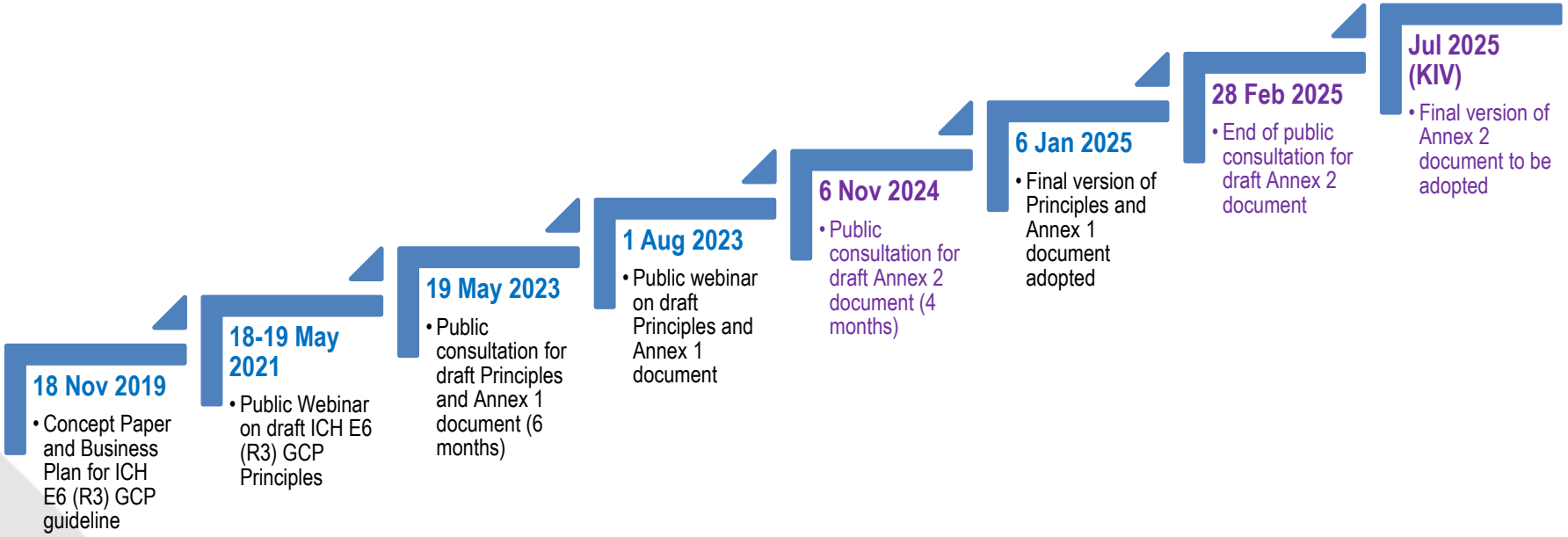
ICH E6 (R3) GCP guideline

Overview



ICH E6 (R3) GCP guideline

Key Timelines



ICH E6 (R3) GCP guideline

Implementation timeline for Singapore

- **1 Jan 2026**
  - ❑ Perform a gap analysis to identify changes required for your Quality Management System and training materials (if applicable).
  - ❑ Adopt a proportionate approach to training to ensure compliance, thereby ensuring trial participant protection and reliability of trial results.
    - ❑ PIs should be familiar with the revised ICH E6 (R3) GCP guideline.
    - ❑ Other investigator site staff should be trained depending on their delegated tasks.
    - ❑ Training should be tailored to enable staff to fulfil tasks that extend beyond their usual training and experience.

Conclusion

- Sponsors and investigators play an important role in maintaining the quality of a clinical trial.
- Implement systems with procedures that assure the quality of every aspect of the clinical trial.
- The revised ICH E6 (R3) GCP guideline will be implemented for Singapore from 1 Jan 2026.
- If it was never documented, it was never done!
- It is always better to prepare, than repair!

References

- Clinical trials and CRM regulations
  https://www.hsa.gov.sg/clinical-trials/overview
- ICH E6 (R2) Good Clinical Practice (GCP) guideline
  https://www.ich.org/page/efficacy-guidelines
- ICH E6 (R3) Good Clinical Practice (GCP) guideline
  https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf
- Regulatory Guidances
  https://www.hsa.gov.sg/clinical-trials/regulatory-guidances

Thank you!

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We welcome your queries!

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