LOOKING BACK AT 2023

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Health Products Regulation Group

Health Sciences Authority

OUTLINE

- GCP Inspection Framework
- GCP Inspections conducted in 2023
- Important Points to Note
  - GCP 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.

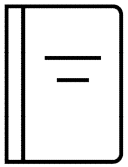
Assess compliance to protocol and applicable regulations, guidelines and standard operating procedures for clinical trials.

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)*

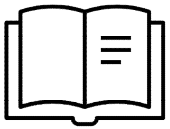
- GCP inspections may either be protocol-specific or systems-based.

GCP Inspection Criteria



Study protocol

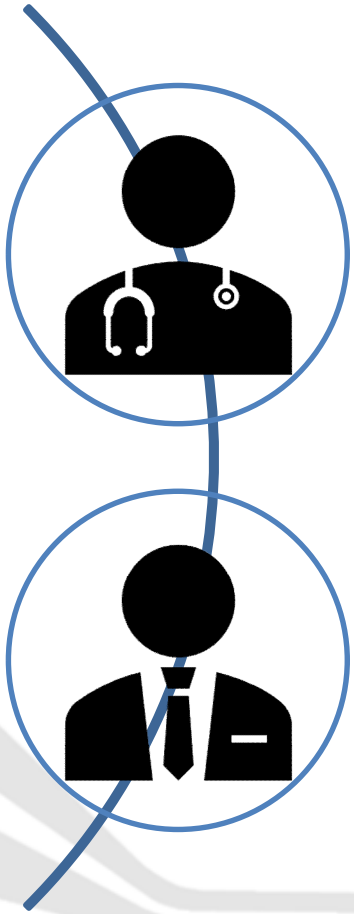
Regulations



ICH E6 GCP Guidelines

Standard Operating Procedures

Inspectee



GCP 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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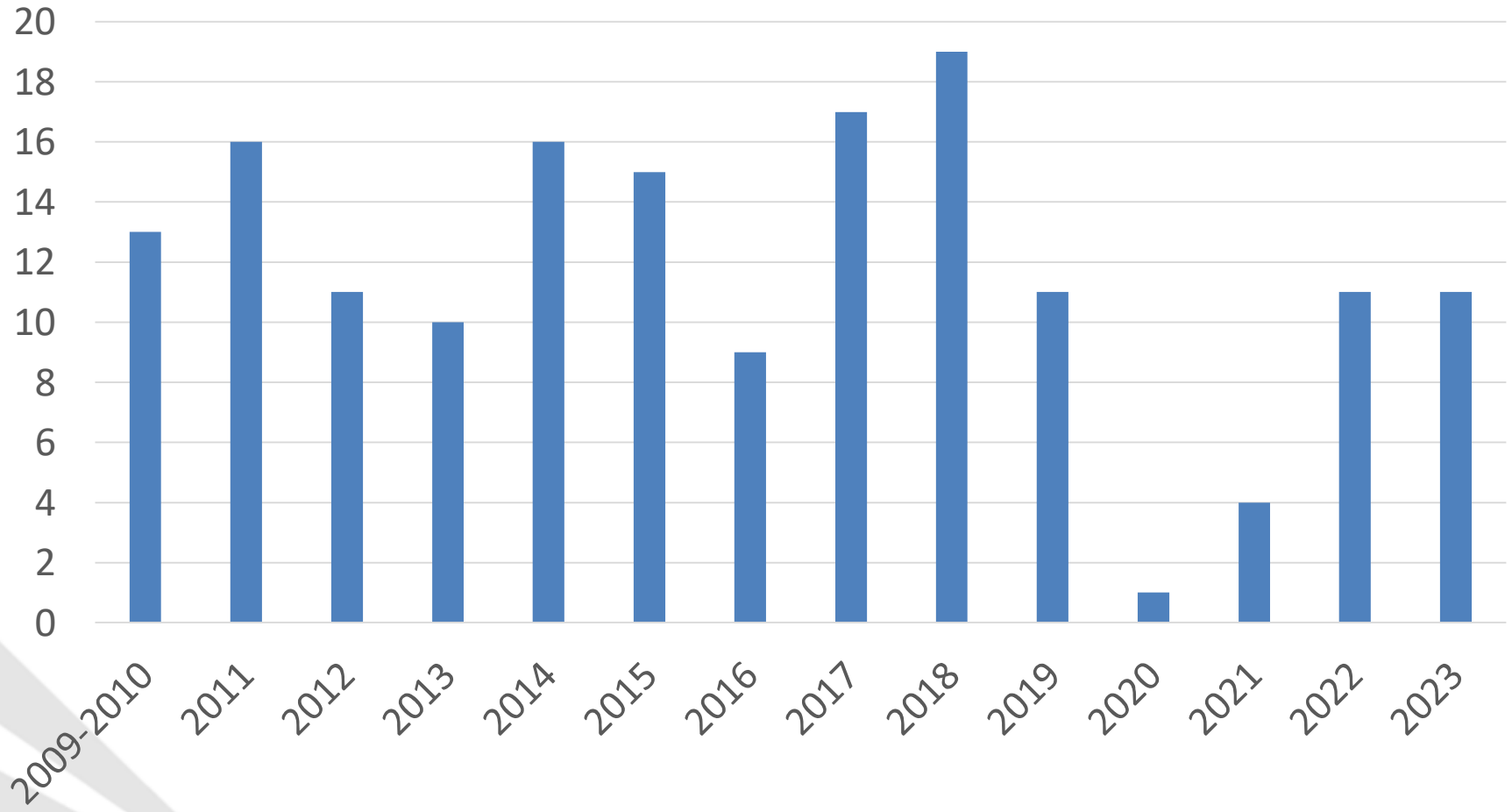
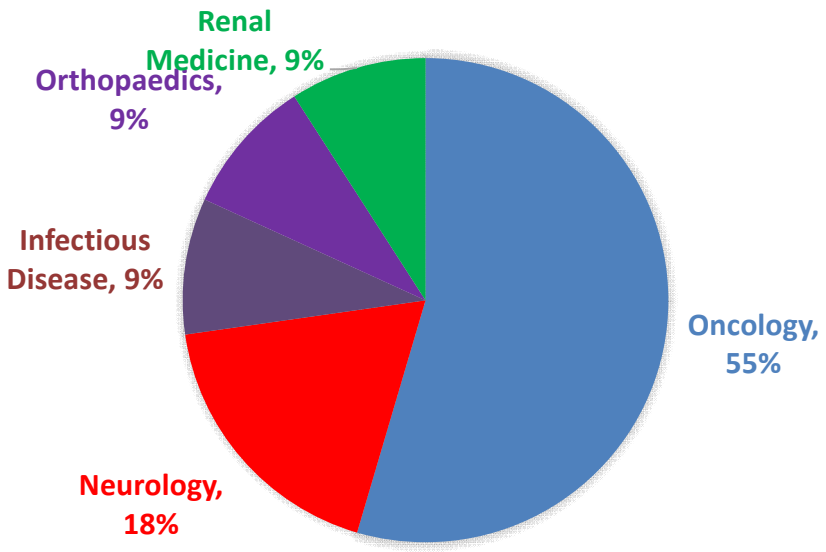
GCP Inspections (2009-2023)

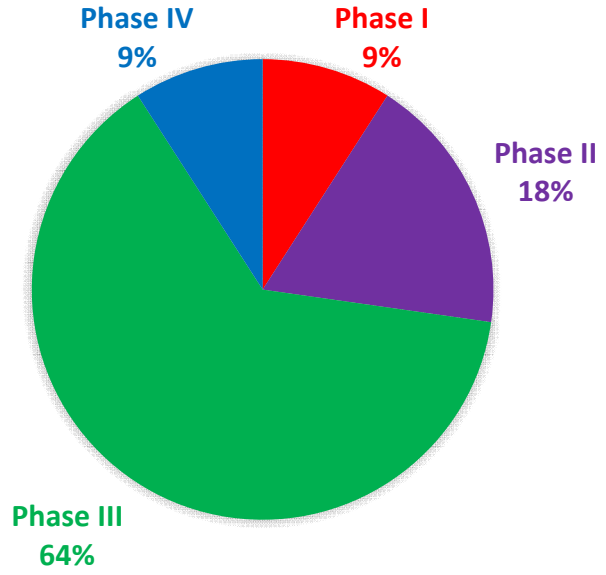


GCP Inspections (2023)

Distribution by Therapeutic Area



Distribution by Phase of Clinical Trial



GCP Inspections (2023)

Study termination / suspension

- **Study termination**
  - No clinical trials were terminated through GCP Inspections.
- **Study suspension**
  - *5 clinical trials:*

Source	GCP Inspections	Serious Breach Notification	Others
No. of clinical trials	3	1	1
Reason for recruitment suspension	• Critical GCP Inspection Findings *(refer to subsequent slides)*	• Unable to comply with product release specifications [Quality of IP, Safety of trial participants]	• Significant GMP deficiencies impacting IP manufacture [Quality of IP].

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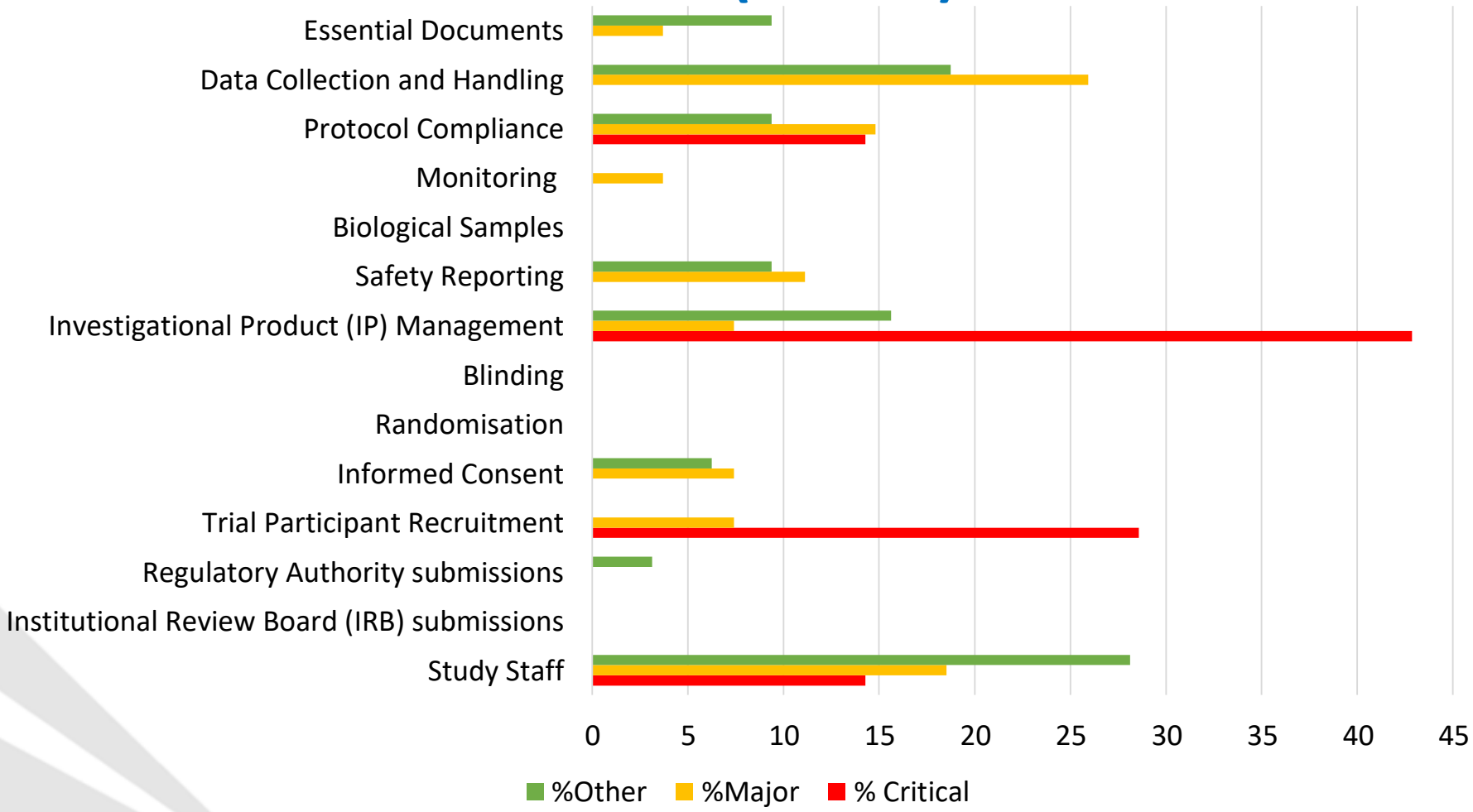
GCP Site Inspections (2023) (N = 11)



Investigational Product (IP) Management

- **Critical GCP Inspection Finding**
  - The IP was not manufactured in compliance with Good Manufacturing Practice (GMP), thereby potentially impacting the quality of the IP and the safety of trial participants.

    1. Inadequate processes for handling environmental monitoring deviations during sterile product manufacturing.

➢ **Important Point to Note:**

❑ Ensure that process is established for handling and reporting of environmental monitoring deviations identified during sterile product manufacturing.

Investigational Product (IP) Management

- **Critical GCP Inspection Finding**

  2. Inadequate processes for control of starting materials for use in manufacture of Investigational Product.

  - **Important Point to Note:**
    - IP Manufacturer should establish a quality system for control of starting materials.

Investigational Product (IP) Management

- **Critical GCP Inspection Finding**

  3. No established process for ensuring timely provision of product release test results by third party laboratories.

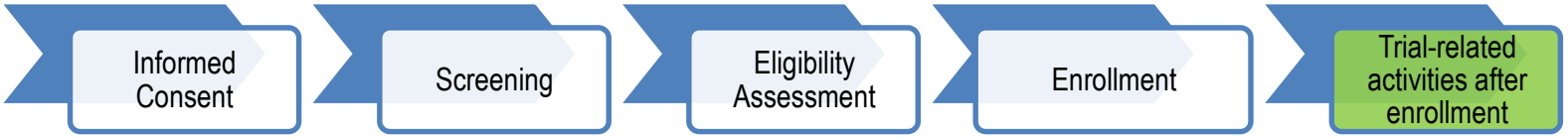
  - **Important Point to Note:**
    - The IP manufacturer should establish a process and timeframe to obtain the product release test results from third party laboratories in a timely manner.

Trial Participant Recruitment

- **Critical GCP Inspection Finding**
  - Trial-related activities for enrolled trial participants had been conducted before trial participants were enrolled into the clinical trial, thereby impacting safety of the trial participants.

➢ **Important Point to Note:**

❑ PI should ensure that eligibility assessment is performed prior to enrolment of trial participants, and trial-related activities after enrolment should be performed thereafter.



Study Staff

- **Critical GCP Inspection Finding**
  - There was inadequate supervision by the PI, thereby impacting safety of the trial participants:
    - New PI was not appointed prior to his/her departure from the trial site.
    - Study staff were not delegated and adequately qualified to perform significant trial-related activities (e.g., informed consent, eligibility assessment, investigational product management, key efficacy and safety assessments etc.).
    - Study staff were not informed about the protocol amendment.

Study Staff

Important Points to Note for Change of PI:

Current PI / Sponsor should identify new PI.

Current PI / Sponsor should determine which essential documents require updating (e.g., Informed Consent Document).

Current PI should seek approval from IRB for change of PI.

Sponsor should seek approval from HSA for change of PI.

Sponsor should make arrangements to revise the Clinical Trial Agreement.

Current PI should hand over investigator responsibilities to new PI.

New PI should delegate the study staff by completing a new delegation log.

Study Staff

- **Important Points to Note for delegation and training of study staff:**

Type of trial-related activity	Significant trial-related activity performed by	Is delegation required?	Is training required?
Not part of routine clinical care	Individual	Yes	Yes
	Entity	Yes – A representative in a supervisory position may be delegated and will be in charge of training and supervising the other staff.	Yes
Part of routine clinical care	Individual	May not be required, but there should be documentation of their involvement in the clinical trial.	No
	Entity		No

Ref.: https://www.hsa.gov.sg/clinical-trials/conducting/principal-investigator

Protocol Compliance

- **Critical GCP Inspection Finding**
  - There were serious non-compliances to the study protocol, thereby impacting the safety of the trial participants and data credibility.

➢ **Important Point to Note:**

- ❑ PI should comply with the study protocol.
- ❑ Sponsors should discourage protocol waivers, as they impact quality and interpretation of trial data.
  - ❑ Sponsors should incorporate Quality By Design (QBD) into the design of the study protocol, i.e.,
    - Prospectively identify and periodically review the Critical to Quality factors that impact safety of trial participants, data integrity and validity of trial results. For e.g., eligibility criteria, randomisation, masking, type of controls, IP handling and administration, study endpoints etc.

Data Collection and Handling

- **Major GCP Inspection Finding**
  - Delays in investigators documenting review of study assessments for eligibility assessment and safety assessments.
  - Lack of attributability and accuracy in source documents.
  - Lack of audit trail in the electronic data collection form, thereby resulting in data integrity not being assured.

➢ **Important Points to Note:**

- ❑ PI should document review of study assessments in a contemporaneous manner.
- ❑ Study staff should ensure that source documents are attributable and accurate.
- ❑ Sponsor and PI should ensure that audit trail is available in the data collection form, regardless of media used.

Safety Reporting

- **Major GCP Inspection Finding**
  - **Discrepancies in review and documentation of Adverse Events (AEs):**
    - **Safety Reporting**
      - Delays in PI determining whether Unexpected Serious Adverse Drug Reactions (USADRs) should be reported to the IRB.
    - **Documentation of AEs**
      - Lack of attributability in the completion of the AE Tracking Logs.

➢ **Important Points to Note:**

- ❑ PI should promptly review USADRs to determine if they should be reported to the IRB.
- ❑ The AE Logs should be attributable.

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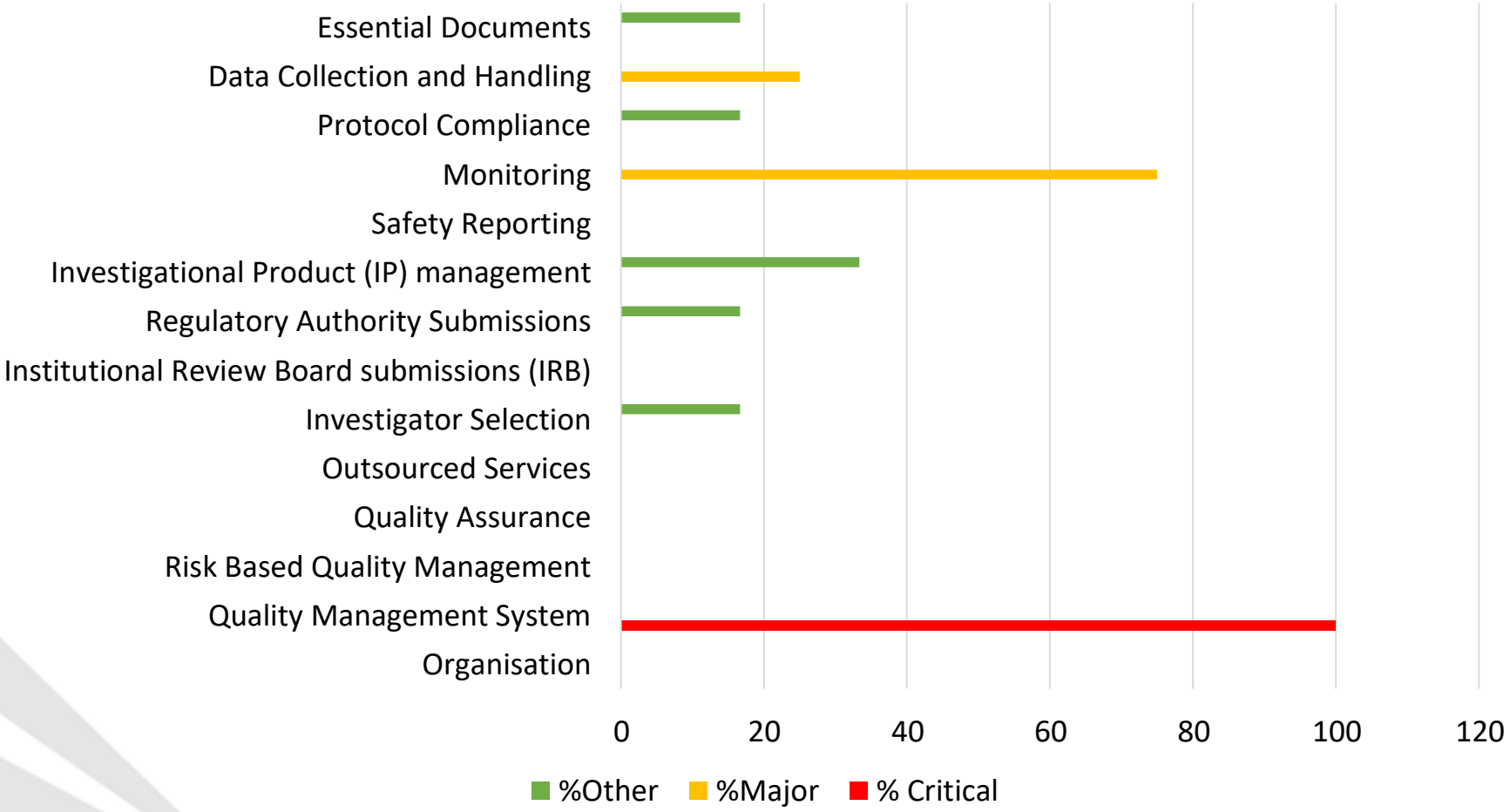
Sponsor Inspections (2023) (N=3)



Quality Management System

- **Critical GCP Inspection Finding**
  - Inadequate Quality Management System to maintain sufficient sponsor oversight of clinical trials.
    - Lack of SOPs and training.
    - Sponsor was not aware of departure of PI.
    - Sponsor did not perform serious breach assessment for non-compliances.

Quality Management System

- **Important Points to Note for Quality Management System:**
  - For investigator-initiated clinical trials (IITs):
    - The institution is the local sponsor.
    - The institution should comply with the sponsor responsibilities specified in the regulations and GCP. The institution may transfer some of the sponsor responsibilities to the PI.
    - The institution should establish a Quality Management System and ensure that staff are trained.
    - The institution should maintain adequate oversight of the IIT.
    - The PI and Sponsor should assess whether a non-compliance is considered a Serious Breach and document the assessment.

Monitoring

- **Major GCP Inspection Finding**
  - Monitor was inadequately qualified to monitor the clinical trial.
  - Inadequate monitoring, thereby resulting in lack of prompt actions by the sponsor to secure compliance.

➢ **Important Points to Note:**

- ❑ Sponsor should ensure that the Monitor is adequately qualified to monitor the clinical trial.
- ❑ Monitor should comply with the Monitoring Plan and escalate important deviations to the Sponsor and PI to secure compliance.

Data Collection and Handling

- **Major GCP Inspection Findings**
  - **Electronic Patient Reported Outcomes (ePRO)**

The sponsor did not adequately manage the risks associated with using ePRO, thereby resulting in lack of prompt action to secure compliance.

- PI did not have access to the ePRO platform.
- Lack of translated ePROs, thereby resulting in the need to use translators despite the protocol requiring the participants to directly complete the ePRO.
- Site staff were unable to access the web-based back-up option, thereby resulting in using paper PRO.
- In situations where paper PRO was used as a back-up option, the Monitor did not verify the accuracy of transcription from paper PRO to ePRO.

Data Collection and Handling

Important Points to Note for ePRO:

SPONSOR

- ❑Ensure that PI has access to the ePRO platform.
- ❑Determine if the inability to complete the ePRO should be identified as a risk in the Risk Management Plan. For e.g.,
  - Unable to read the ePRO
  - Lack of validated translations
  - Inability to access the ePRO and back-up options
- ❑In situations where paper PRO is used as a back-up option,
  - Determine if the Monitoring Plan should be revised to verify the accuracy of transcription from the paper PRO to ePRO.
  - Determine how discrepancies in transcription from the paper PRO and ePRO should be rectified.

PRINCIPAL INVESTIGATOR

- ❑Maintain supervision of ePRO.
- ❑Ensure that data change requests are approved prior to implementation.
- ❑If paper PROs are used, ensure that study staff verify the accuracy of the transcription from paper PRO to ePRO.

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Direct Access to Source Documents

- **GCP requirements**
  - The PI should provide direct access to source documents for the purpose of monitoring, audits and GCP inspections (i.e., local and overseas GCP inspections) to evaluate the clinical trial.
  - The sponsor should secure agreement from all involved parties to ensure direct access to source documents.

- **Current problem**
  - Some healthcare institutions may be unable to provide direct access to trial participants' Electronic Medical Records (EMR), and provide over-the-shoulder access or printed EMR.
  - Impact of lack of direct access:
    - Inability to verify if the rights, safety and well-being of trial participants have been safeguarded;
    - Inability to verify if the trial data is credible; and
    - Undue impact for marketing authorisation application in overseas jurisdictions with the possibility of regulatory authorities not accepting the trial data.

Direct Access to Source Documents

- **Resolution**
  - Investigators should provide direct access to source documents for monitoring, audits and GCP inspections.
  - Sponsors should ensure that the Clinical Trial Agreement adequately addresses the terms for direct access.

ICH E6 (R3)
Good Clinical Practice (GCP) Guideline

Nov 2023
- Completion of public consultation for Principles and Annex 1 on considerations for interventional clinical trials.

Apr – Oct 2024
- Public consultation for Annex 2 on additional considerations for interventional clinical trials (i.e., decentralised elements, pragmatic elements and real world data)

Oct 2024
- Adoption of Principles and Annex 1 by ICH.

March 2025
- Adoption of Annex 2 by ICH.

NB: HSA will keep you informed of the implementation timelines for Singapore.

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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.
- 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 guidelines
  https://www.ich.org/page/efficacy-guidelines
- Regulatory Guidances
  https://www.hsa.gov.sg/clinical-trials/regulatory-guidances

Thank you!

www.hsa.gov.sg

We welcome your queries!

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