LOOKING BACK AT 2020-2021

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Health Products Regulation Group

Health Sciences Authority

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OUTLINE

- GCP Inspections
- Regulatory updates
- International Collaborations

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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.

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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.

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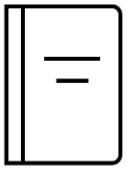
GCP Inspection Criteria



Study protocol

Regulations

ICH E6 GCP Guidelines

Standard Operating Procedures

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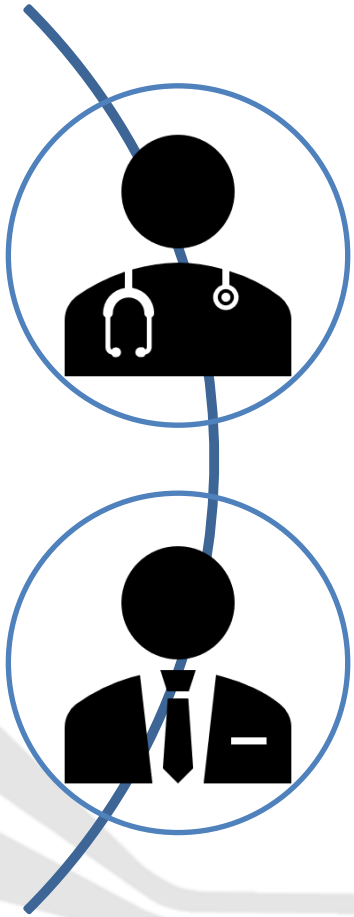
Inspectee



GCP Site Inspection

→Principal Investigator

Sponsor Inspection

→Local Sponsor

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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 prevent a non-compliance from occurring in future.

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Conducting GCP Inspections During a Pandemic

- **2020**
  - 1 GCP Site Inspection conducted in Jan 2020.
  - GCP inspections suspended due to pandemic.
- **2021**
  - 4 remote Sponsor Inspections conducted.

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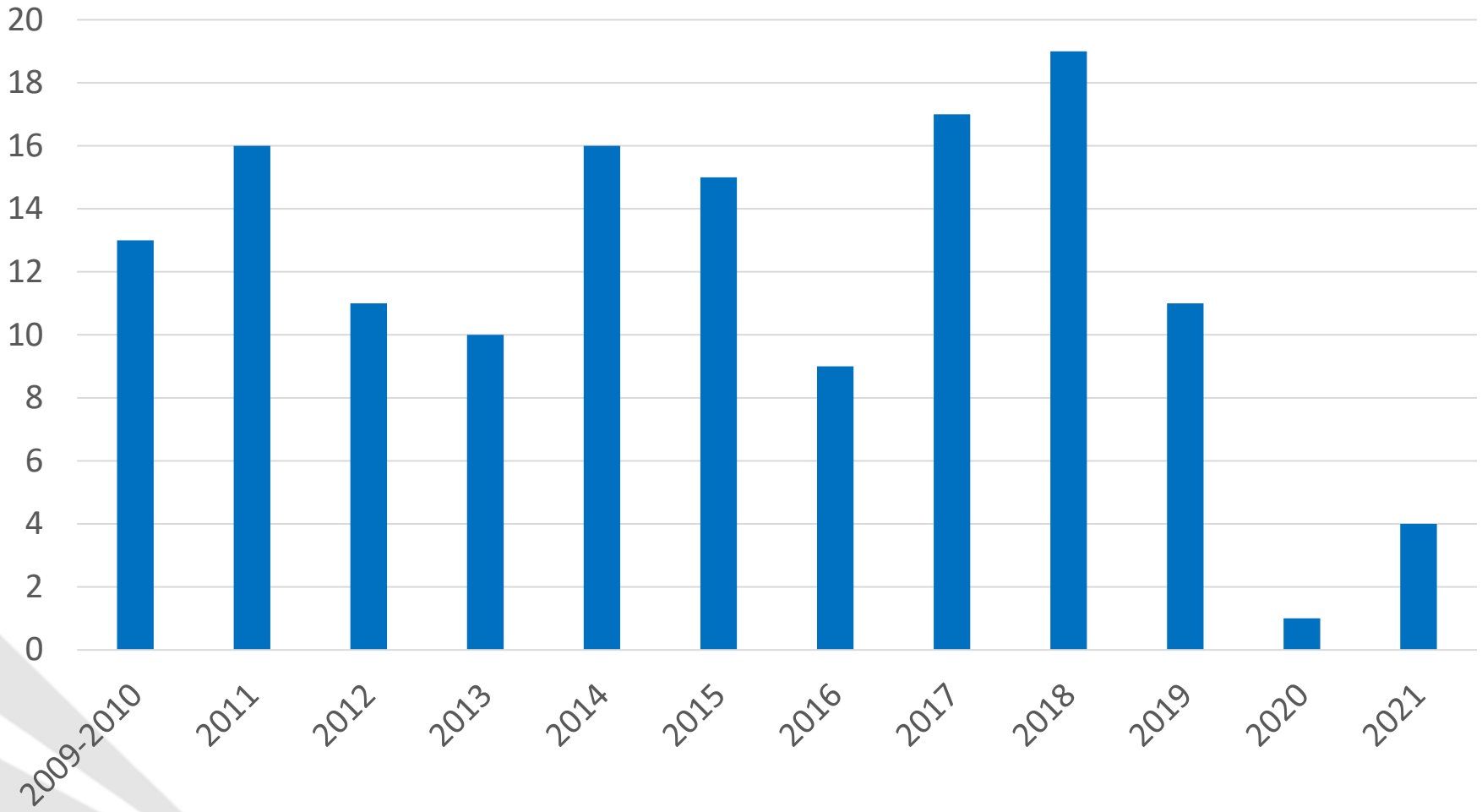
GCP Inspections (2009-2021)



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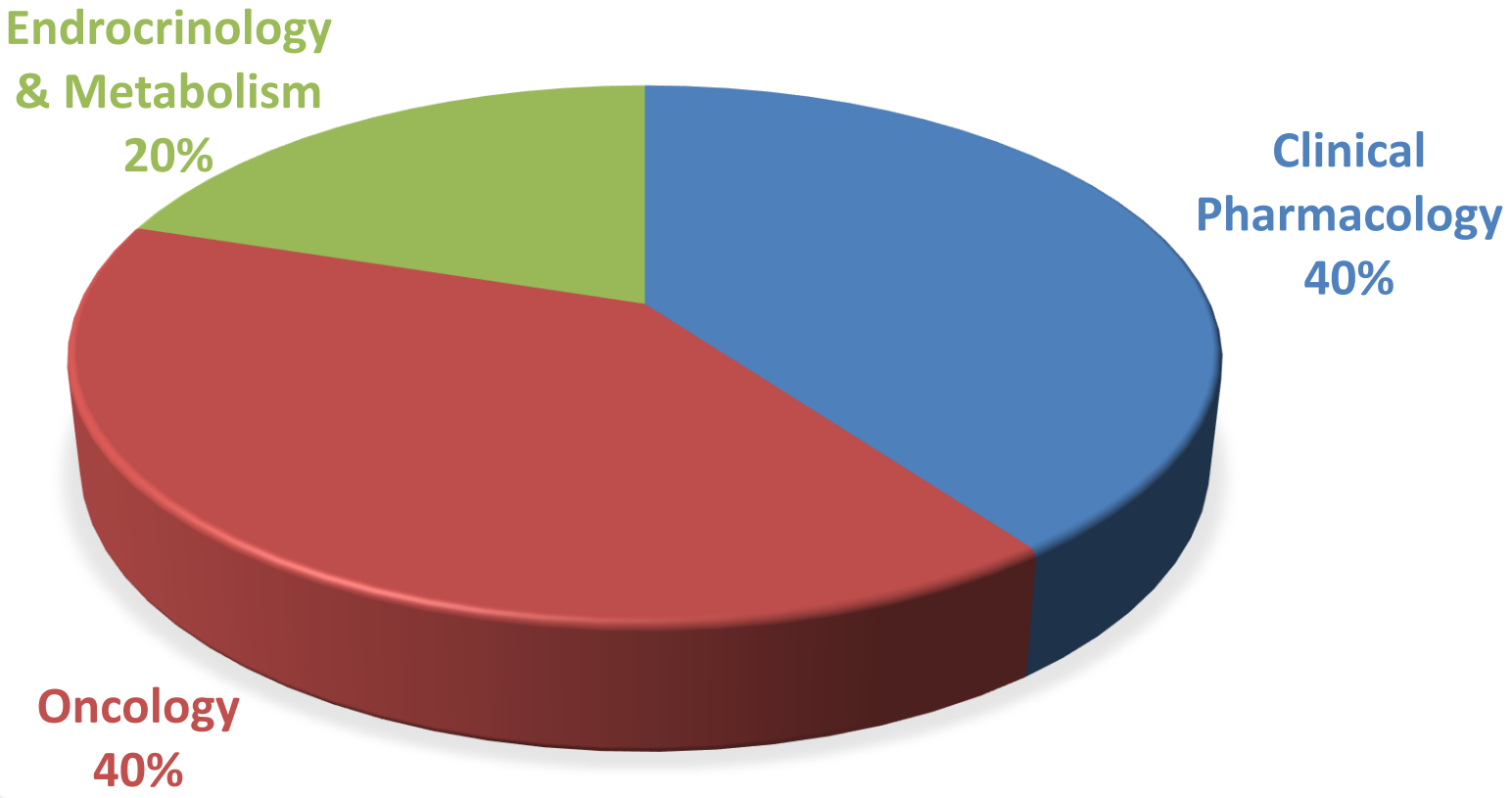
GCP Inspections (2020-2021)

Distribution by Therapeutic Area



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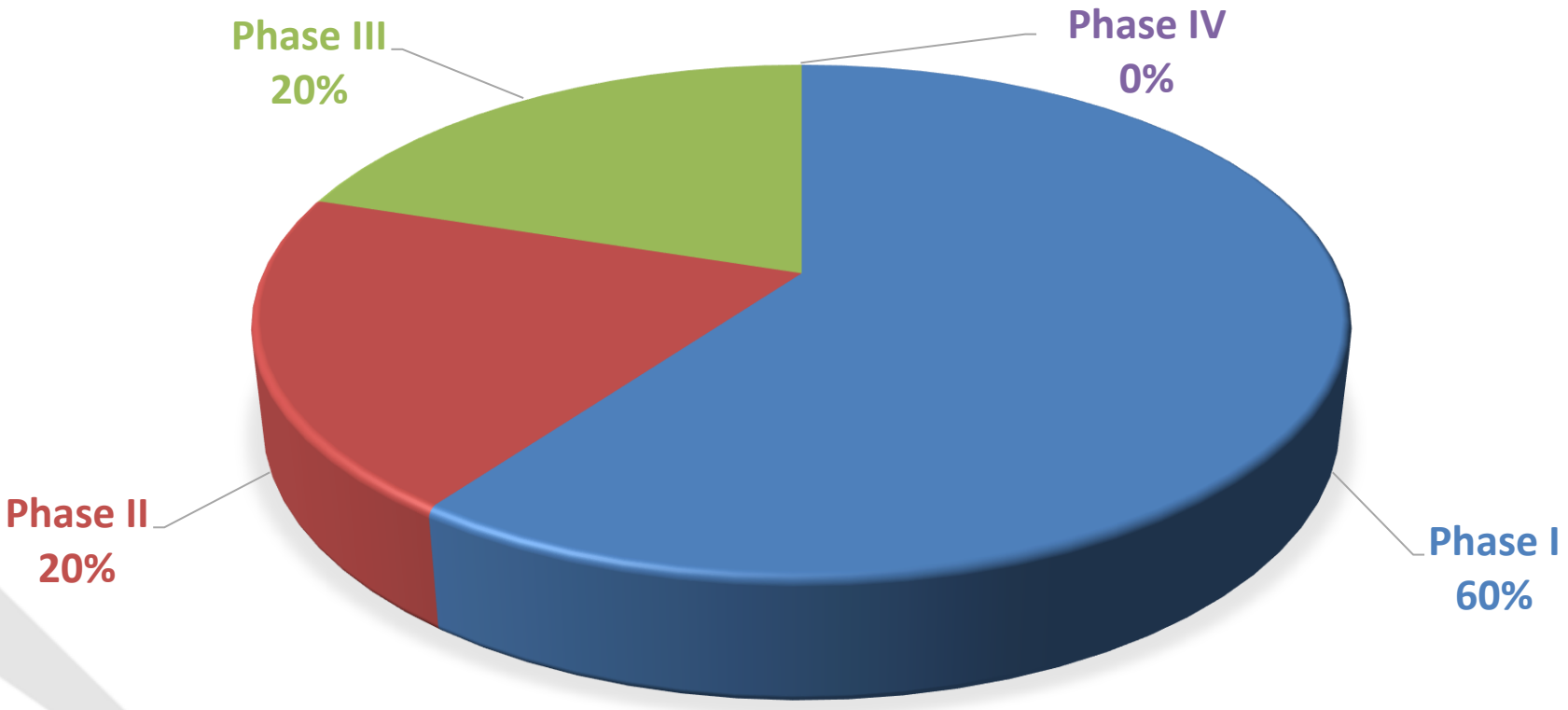
GCP Inspections (2020-2021)

Distribution by Phase of CT



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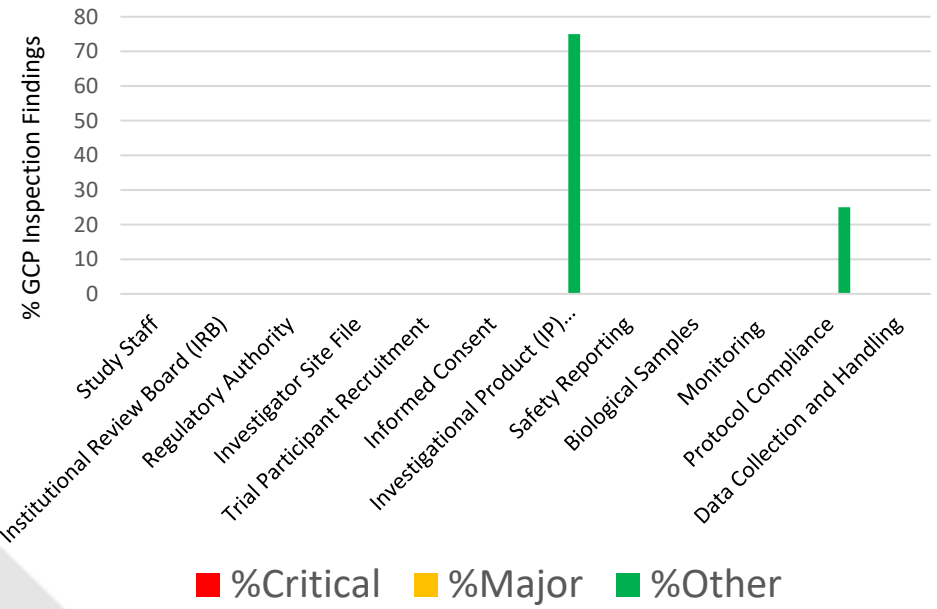
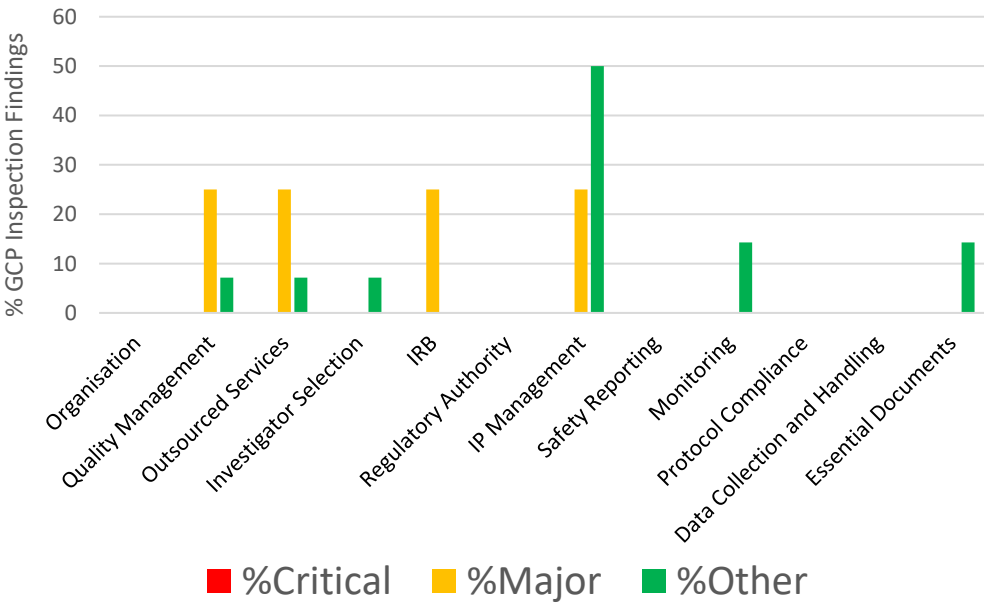
GCP INSPECTION FINDINGS 2020-2021

GCP SITE INSPECTIONS



SPONSOR INSPECTIONS



No clinical trials were suspended or terminated through GCP Inspections.

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IMPORTANT POINTS TO NOTE

Sponsor Inspections

- **Quality Management**
  - Lack of adequate quality risk management
    - ➢ *Quality Risk Management should be performed by sponsor to identify critical data and processes that may impact trial participant protection and data credibility.*
  - Unable to ascertain who had approved study manuals.
    - ➢ *Documentation of approval of study manuals should be maintained.*

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IMPORTANT POINTS TO NOTE

Sponsor Inspections

- **Outsourced services**
  - Letter of Authorisation did not clearly describe the trial-related duties and functions that had been transferred to the local sponsor.
    - ➢ *Trial-related duties and functions should be included in the Letter of Authorisation accurately, in accordance with the contractual obligations between the global sponsor and local sponsor.*
  - No audit trail available for signatory dates on vendor agreements. Dates were either manually typed out or stamped.
    - ➢ *An audit trail should be available for signatory dates.*

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IMPORTANT POINTS TO NOTE

Sponsor Inspections

- **IRB**
  - Recruitment plan not provided to the IRB for review.
    - ➢ *Recruitment plan should be submitted to the IRB for review prior to implementation.*

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IMPORTANT POINTS TO NOTE

Sponsor Inspections

- **IP management**
  - Lack of written instructions for handling of IP.
    - ➢ *Written instructions for IP handling should be provided to trial sites.*
  - Lack of delegation of study staff for IP management.
    - ➢ *Study staff must be delegated by PI in Signature Sheet.*
  - Product defect not notified to HSA.
    - ➢ *Product defects must be notified to HSA.*

    https://www.hsa.gov.sg/therapeutic-products/defect-reporting-recall
  - IP label not compliant with labelling requirements.
    - ➢ *IP label must be compliant with regulatory requirements for IP labelling.*

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IMPORTANT POINTS TO NOTE

Sponsor Inspections

- **Monitoring**
  - Discrepancies noted in eCRFs.
    - ➢ *eCRFs should be verified accurately.*
  - Lack of documentation for sponsor review of site visit reports.
    - ➢ *Sponsor review of site visit reports should be documented.*
- **Essential documents**
  - Design of essential document template was amended by site staff without sponsor's approval.
    - ➢ *Unauthorised amendments to essential document templates should not be made.*

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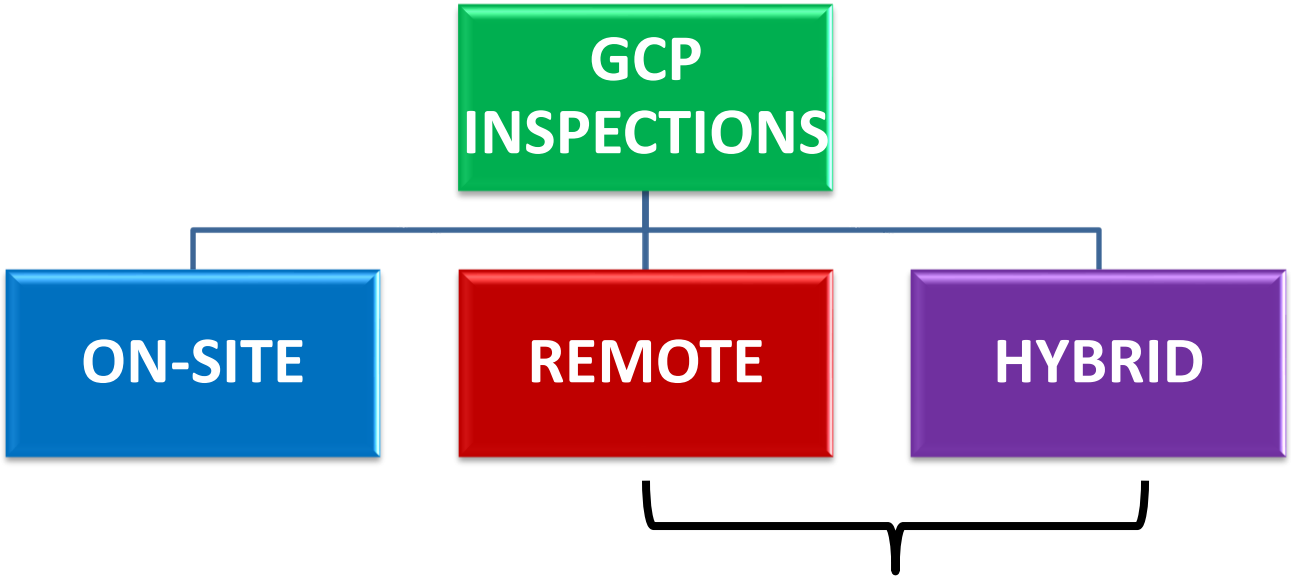
GCP Inspections

Moving forward



- *Same objectives, scope and criteria as on-site GCP Inspections.*
- *Similar process as on-site GCP inspections, except for remote interviews and document reviews.*

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Remote GCP Inspections

- **Logistical Considerations:**

- **Video conferencing platforms**
  - *For opening / interim / closing meetings, interviews, and document reviews;*
  - *Enable screen sharing and breakout rooms;*
  - *Disable recording.*

- **Remote access to electronic systems**
  - *For reviewing electronic Trial Master File (eTMF) and electronic Case Report Forms (eCRFs) etc.;*
  - *Enable downloading;*
  - *Ensure inspectors complete required training.*

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Remote GCP Inspections

- **Logistical Considerations:**

  - **Remote access to file sharing portals**
    - *For document sharing before, during and after GCP inspection;*
    - *Enable downloading.*

- **Modified Approaches:**

  - **Before GCP Inspection**
    - *Initial contact will be made to discuss logistical considerations;*
    - *Notice of GCP Inspection is sent thereafter.*

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Remote GCP Inspections

- **Benefits:**

- **Protects health and safety of GCP inspectors and inspectees**

- **Regulatory oversight maintained**

- **Allows**
  - *More flexibility in inspection schedule*
  - *More staff to be interviewed*
  - *More documents to be reviewed*

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Remote GCP Inspections

- **Challenges – Before GCP Inspection**

  - **Technological challenges**
    - *Scope of GCP inspection is contingent on technological capabilities of inspectee;*
    - *Access to electronic systems and file sharing portals:*
      - *Numerous User IDs and passwords;*
      - *Data Protection policies;*
      - *Cybersecurity restrictions;*
      - *Limited access rights;*
      - *Downloading restrictions;*
      - *Extend duration of access.*

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Remote GCP Inspections

- **Challenges – Before GCP Inspection**

- **Access to trial participant medical records**
  - *Subject to hospital policies*

- **Differing time zones of interviewees**
  - *GCP Inspection Agenda*

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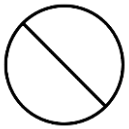
Remote GCP Inspections

- **Challenges – During GCP Inspection**
  - **Inability to:**



    - Assess facial expressions / body language of inspectee;
    - Perform facility tours;
    - Review trial participant medical records.

  - **Technological challenges:**

    - Internet problems;
    - Connection issues;
    - Long time for downloading documents (due to file size and internet speed)

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REGULATORY UPDATES

- **Regulatory Facilitation**
  - **Accelerating COVID-19 clinical trials**
    - Regulatory agility has been exercised during the pandemic in enabling rolling submissions and expedited approvals, as appropriate, to address the specific needs of the public health emergency.
    - COVID-19 clinical trials applications that are submitted to address the needs of the public health emergency have been prioritized and the review of such trials expedited.
    - HSA has been flexible in accommodating to sponsor's requests for a shortened review time of less than 15 working days, excluding stop-clock time, as and where appropriate.

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REGULATORY UPDATES

- **Regulatory Facilitation**
  - **Access to trial participants**
    - Telemedicine for remote consultation
    - Alternative ways of obtaining informed consent
      - Trial participants in isolation
      - Remote consent
      - Electronic consent
    - Investigational Product (IP) supply
      - Direct to Patient (DTP) service to trial participants' homes
    - Remote study visits
    - Electronic Data Capture
      - Electronic Clinical Outcome Assessments (eCOAs)

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REGULATORY UPDATES

- **Revision to the Clinical Trials Regulations**
  - New Cell, Tissue and Gene Therapy Products (CTGTPs) framework (1 Mar 2021)
  - Enabling pharmacists to be principal investigators for low risk trials of locally registered therapeutic products (1 Oct 2021)
  - Consent requirements for collection of human tissue from trial participants (1 Oct 2021)
- **New regulatory guidances (2020-2021)**
  - Conduct of clinical trials in relation to the COVID-19 situation (2020)
  - Electronic Consent (2020, updated 2021)
  - Consent requirements for clinical trials involving collection of human tissue (2021)
  - CMC Requirements for CTGTPs for Clinical Trials and Product Registration (2021)
  - Product defect reporting and and recall procedures for therapeutic products and cell, tissue and gene therapy products (2021)

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International Collaborations

- **ICH activities**
  - **Participation in Expert Working Groups**
    - **ICH E6 (R3) – Good Clinical Practice**

    Revision of GCP guidelines to address increasingly diverse trial types and data sources employed to support regulatory and healthcare-related decision making on drugs, and to provide flexibility to facilitate the use of technological innovations in clinical trials.

    - **ICH E20 – Adaptive Clinical Trials**

    New guideline on design, conduct, analysis and interpretation of adaptive clinical trials that provides a transparent and harmonized set of principles for the regulatory review of these studies in a global drug development programme.

    - **ICH M11 – Clinical electronic Structured Harmonised Protocol (CeSHarP)**

    New Guideline on harmonization of electronic CT protocol to pave the way for electronic exchange of protocol information and to facilitate the review of protocols by sponsor, IRB and Regulatory Authorities.

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International Collaborations

- **International Coalition of Medicines Regulatory Authorities**
  - Reflection paper on the regulatory experience of remote approaches to GCP and GMP regulatory oversight during the COVID-19 Pandemic
    - Published in ICMRA website on 10 Dec 2021.

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REFERENCES

- Clinical trials and CRM regulations
  https://www.hsa.gov.sg/clinical-trials/overview
- ICH E6 (R2) GCP guidelines
  https://www.ich.org/page/efficacy-guidelines
- Regulatory Guidances
  https://www.hsa.gov.sg/clinical-trials/regulatory-guidances
- ICH website
  https://www.ich.org/
- Reflection paper on the regulatory experience of remote approaches to GCP and GMP regulatory oversight during the COVID-19 Pandemic
  https://www.icmra.info/drupal/sites/default/files/2021 - 12/remote_inspections_reflection_paper.pdf

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