# LOOKING BACK AT 2022

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*Health Products Regulation Group*

*Health Sciences Authority*

# OUTLINE

- GCP Inspection Framework
  - *Objectives*
  - *Scope*
  - *Criteria*
  - *Inspectee*
  - *Classification of GCP Inspection Findings*
- GCP Inspections conducted in 2022
- GCP Inspection Findings for 2022
  - Important Points to Note
- Maintaining quality of clinical trials
- 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.

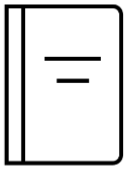
Assess compliance to protocol and applicable regulations, guidelines and standard operating procedures for clinical trials.

# 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)*

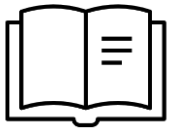
- GCP inspections may either be protocol-specific or systems-based.

# GCP Inspection Criteria



Study protocol

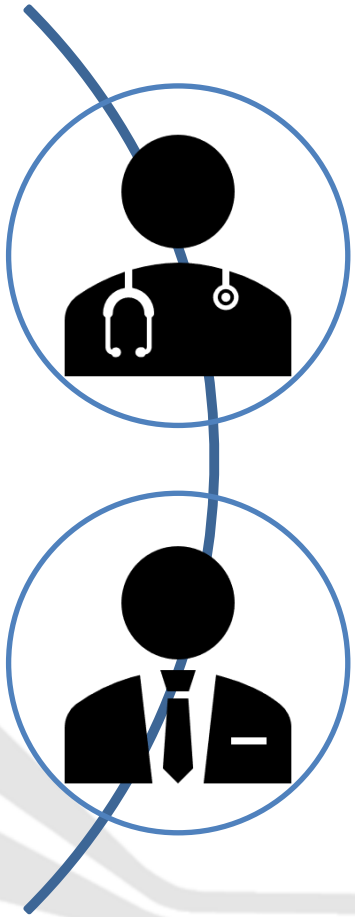
Regulations



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 prevent a non-compliance from occurring in future.

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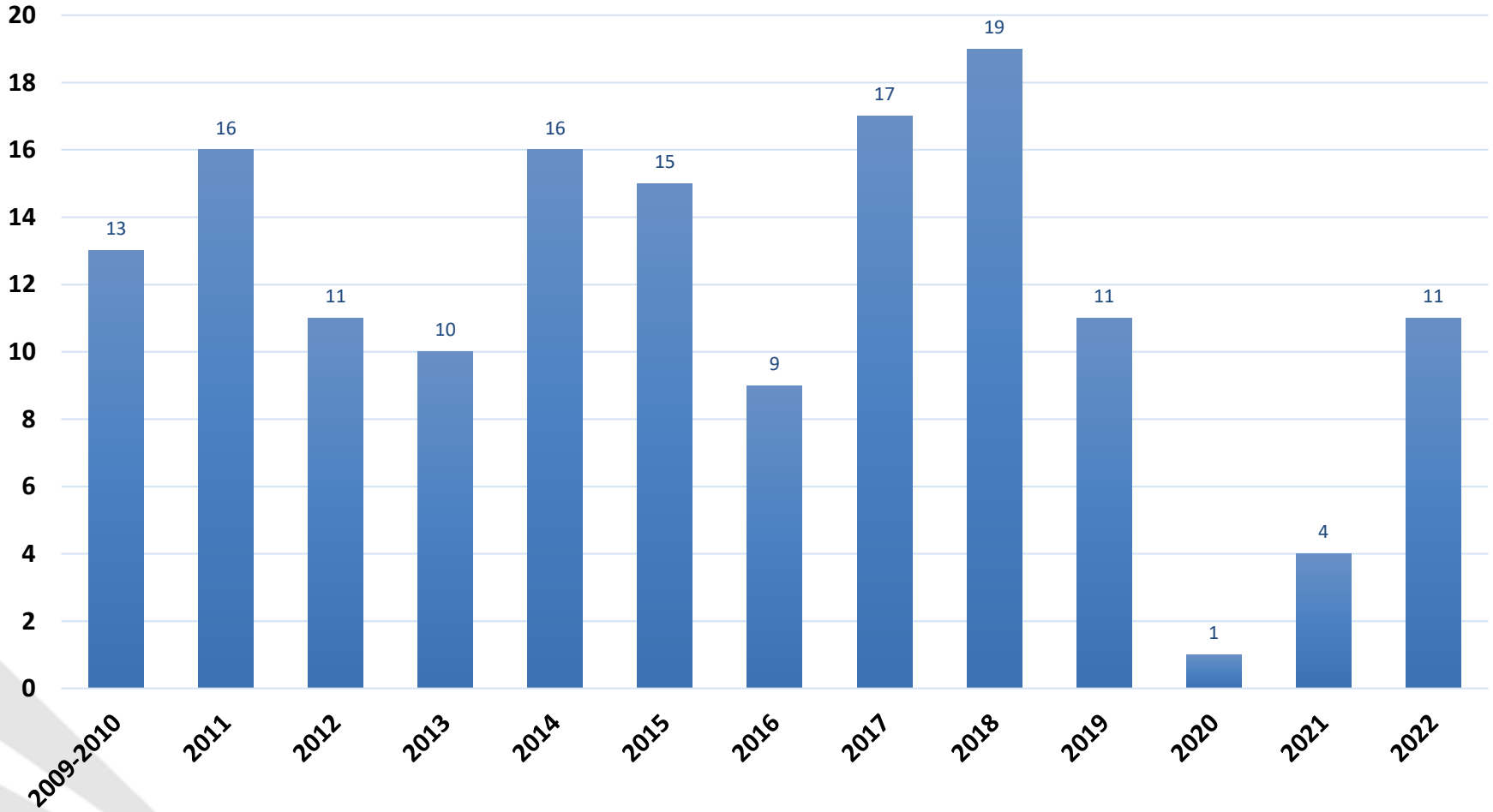
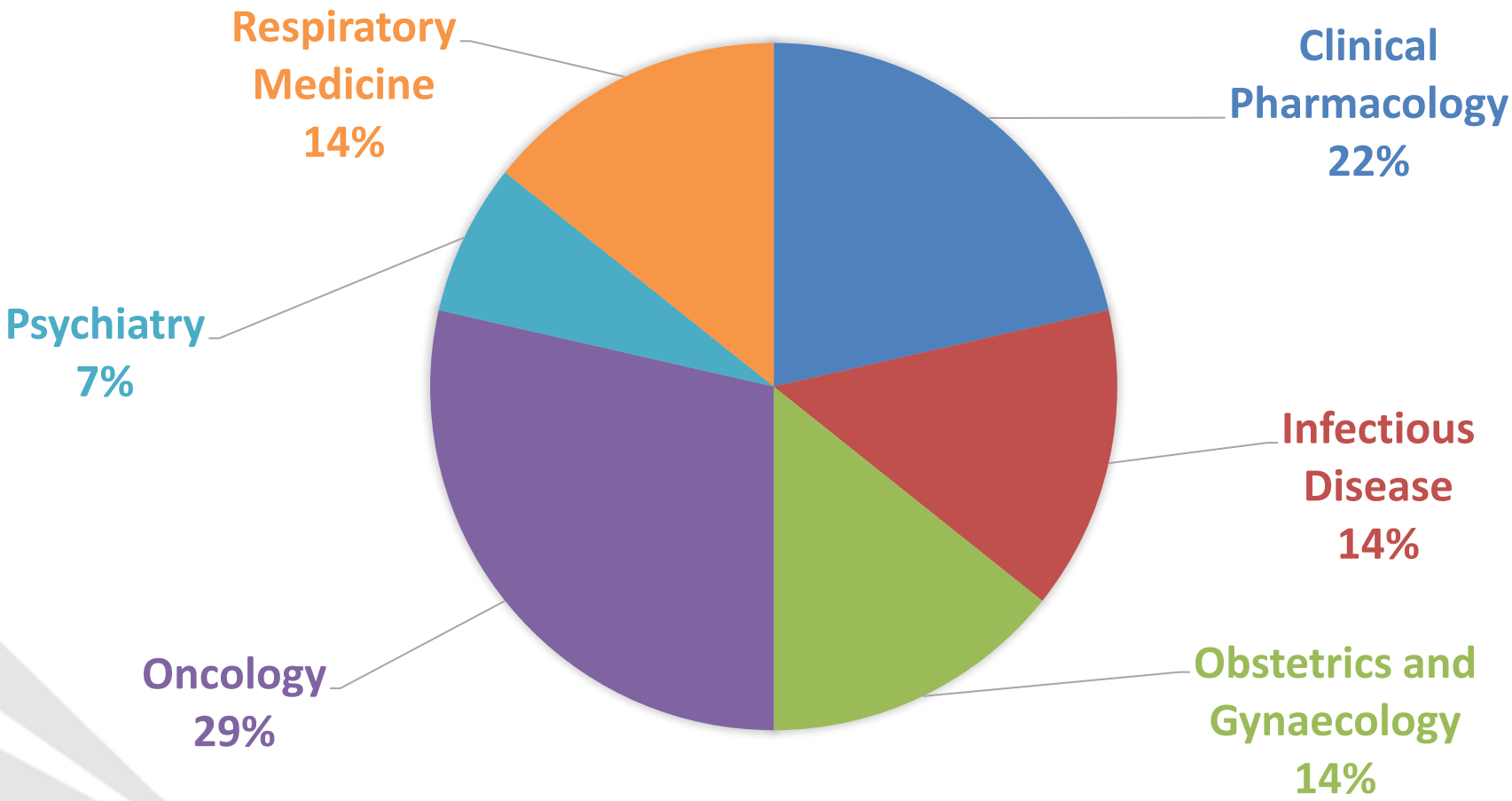
# GCP Inspections (2009-2022)



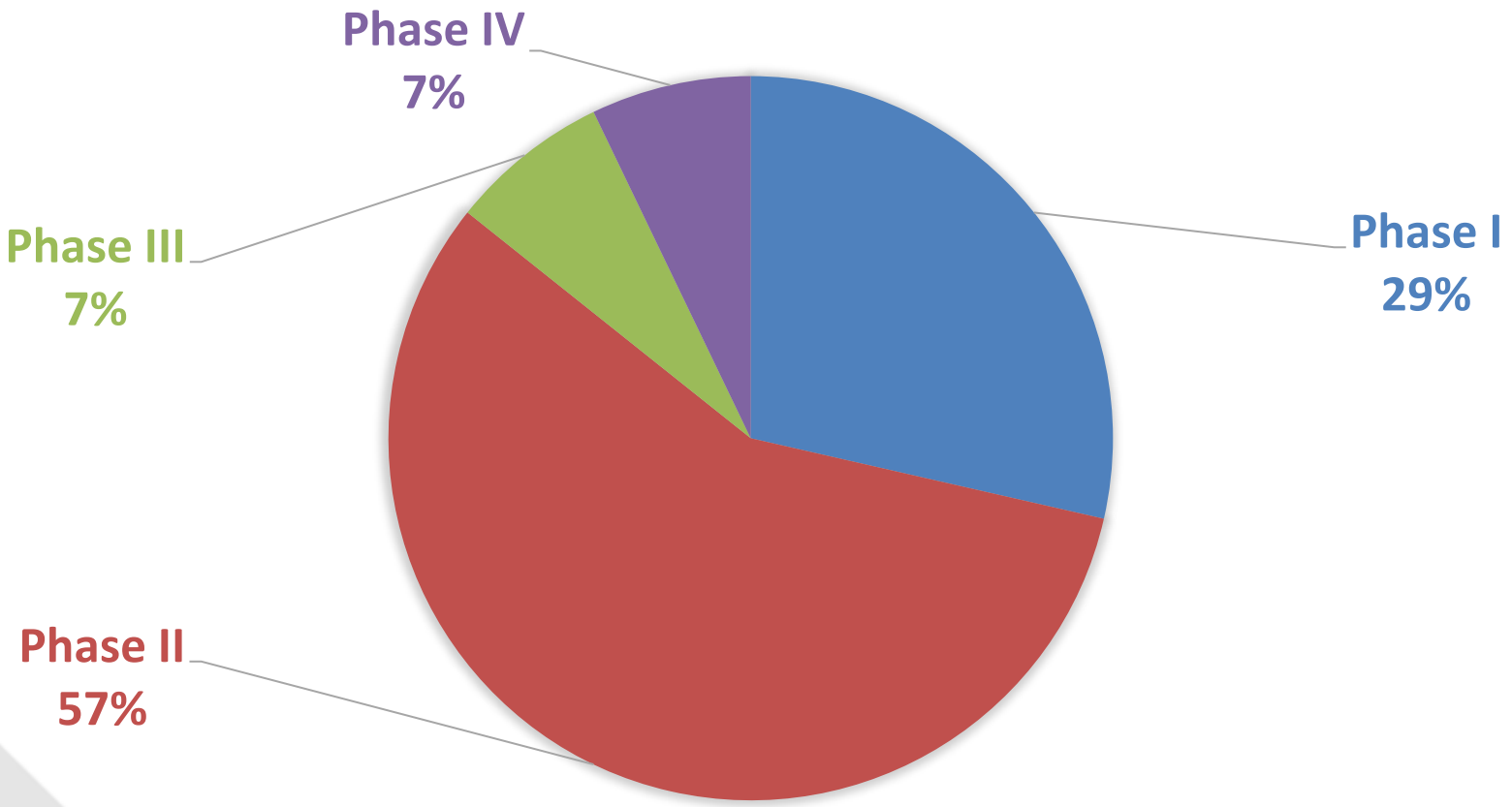
# GCP Inspections (2022)

## *Distribution by Therapeutic Area*



# GCP Inspections (2022)

## *Distribution by Phase of Clinical Trial*



# GCP Inspections (2022)

## *Study termination / suspension*

- **Study termination**
  - No clinical trials were terminated through GCP Inspections.
- **Study suspension**
  - 1 clinical trial was suspended through a GCP Inspection.
    - 3 critical GCP Inspection Findings
      - Study Staff
      - Informed Consent
      - Monitoring

*NB: Refer to GCP Site Inspection slides for further details.*

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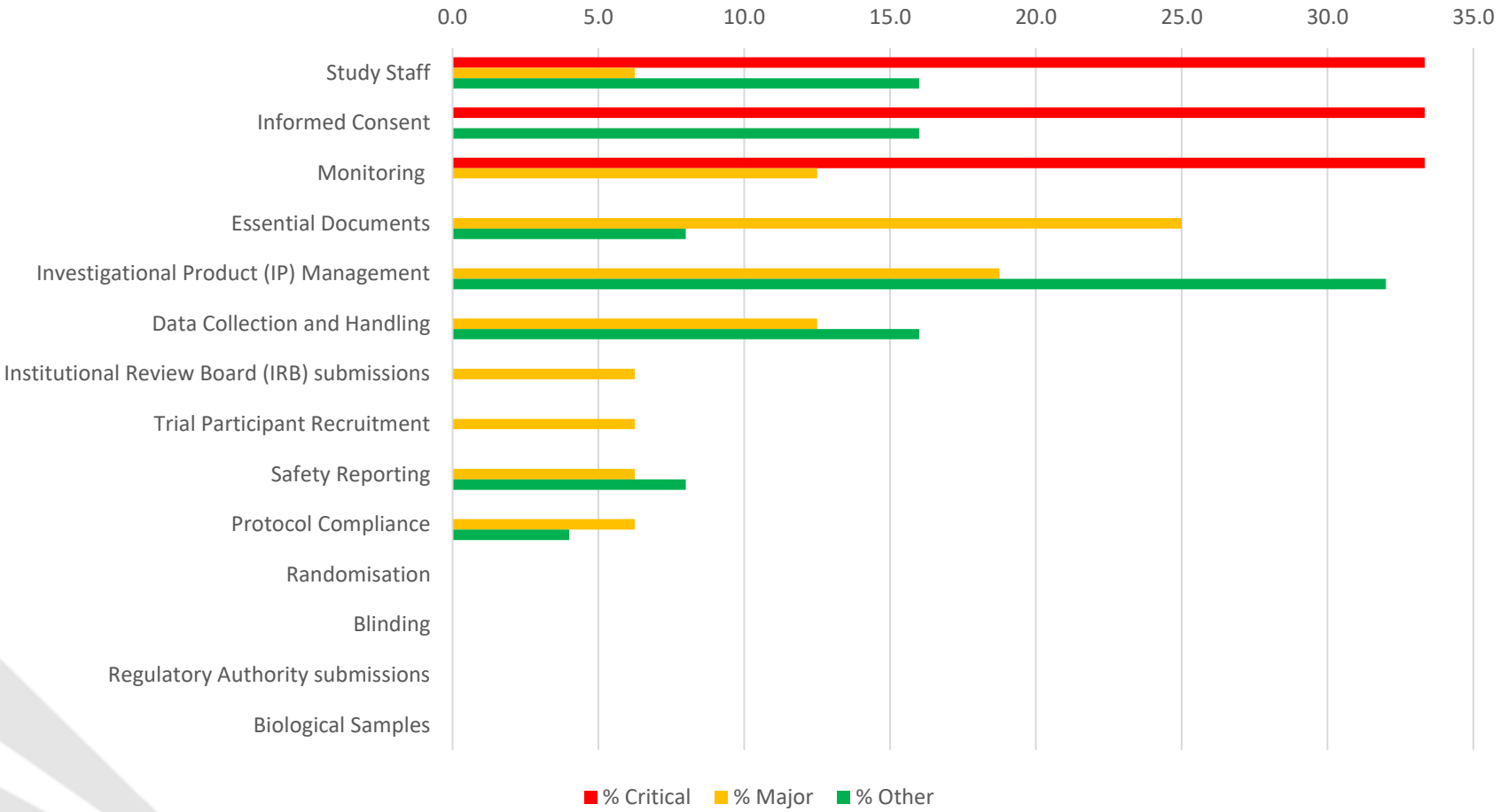
# GCP Site Inspections (2022)

## (N = 6)



# IMPORTANT POINTS TO NOTE
## *GCP Site Inspections*

- **Study Staff**
  - **Lack of adequately qualified and delegated study staff:**

❑Study staff should be trained:
- ❑*Good Clinical Practice (GCP)*
- ❑*Standard Operating Procedures (SOPs)*
- ❑*Study-specific matters*
- ❑*Applicable regulations*
- ➢ *Training should be documented.*

❑Study staff should be delegated by the PI to perform significant study tasks.
- ➢ *Signature Sheet / Delegation Log should be maintained.*

# IMPORTANT POINTS TO NOTE

## *GCP Site Inspections*

- **Informed Consent**
  - **Inadequate informed consent process for adults lacking capacity:**

❑The investigator and an independent medical doctor should assess the mental capacity of the trial participants prior to informed consent.

❑The investigators should be delegated to assess the mental capacity of the trial participant.

❑The investigator, who is delegated and qualified, must obtain informed consent from the trial participant's legal representative.

# IMPORTANT POINTS TO NOTE

## *GCP Site Inspections*

- **Monitoring**
  - **Lack of adequate trial monitoring by sponsor:**

❑The sponsor should develop a monitoring plan tailored to the specific trial participant protection and data integrity risks of the trial.

❑The Monitor should be:

❑Independent of the study team.

➢ *Study staff should not be appointed to monitor the same clinical trial.*

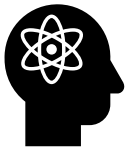
❑Adequately qualified to monitor the clinical trial.

➢ *GCP, SOP, study-specific training and applicable regulations*

➢ *CV, Job Description and Training Documentation should be maintained.*

# IMPORTANT POINTS TO NOTE

## *GCP Site Inspections*

- **Monitoring**
  - **Lack of adequate trial monitoring by sponsor:**
    - ❑The Monitor should:
      - 
      - ❑Conduct the monitoring visits on-site and/or remotely, in accordance with the monitoring plan.
      - 
      - ❑Adopt a systematic, prioritized and risk-based approach in monitoring the processes and data that are critical to ensure trial participant protection and the reliability of trial results.
      - 
      - ❑Complete a Monitoring Visit Report to document what was reviewed, the significant findings, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

# IMPORTANT POINTS TO NOTE

## *GCP Site Inspections*

- **Essential Documents**
  - **Missing essential documents**

❑Refer to Section 8 of ICH E6 (R2) GCP guidelines for list of essential documents.

  - **Lack of quality systems in the maintenance of the essential documents for the clinical trial.**

❑Document control (e.g. version number and/or version date).

❑Audit trail

❑ALCOA+ principles (i.e., attributable, legible, contemporaneous, original, accurate and complete)

# IMPORTANT POINTS TO NOTE

## *GCP Site Inspections*

- **Investigational Product (IP) management**
  - **The roles and responsibilities of the blinded and unblinded study teams were not clearly delineated.**

❑For double-blinded clinical trials:

❑Blinded study team: All study tasks excluding IP management*

**NB: Blinded study team may be involved in IP dispensing if adequate safeguards are available to maintain the study blind.*

❑Unblinded study team: IP management

  - **The IP supply at site was inadequately managed by the sponsor.**

❑Sponsor should ensure there is adequate supply of IP at the trial sites even if IP supply is managed via Interactive Response Technology (IRT).

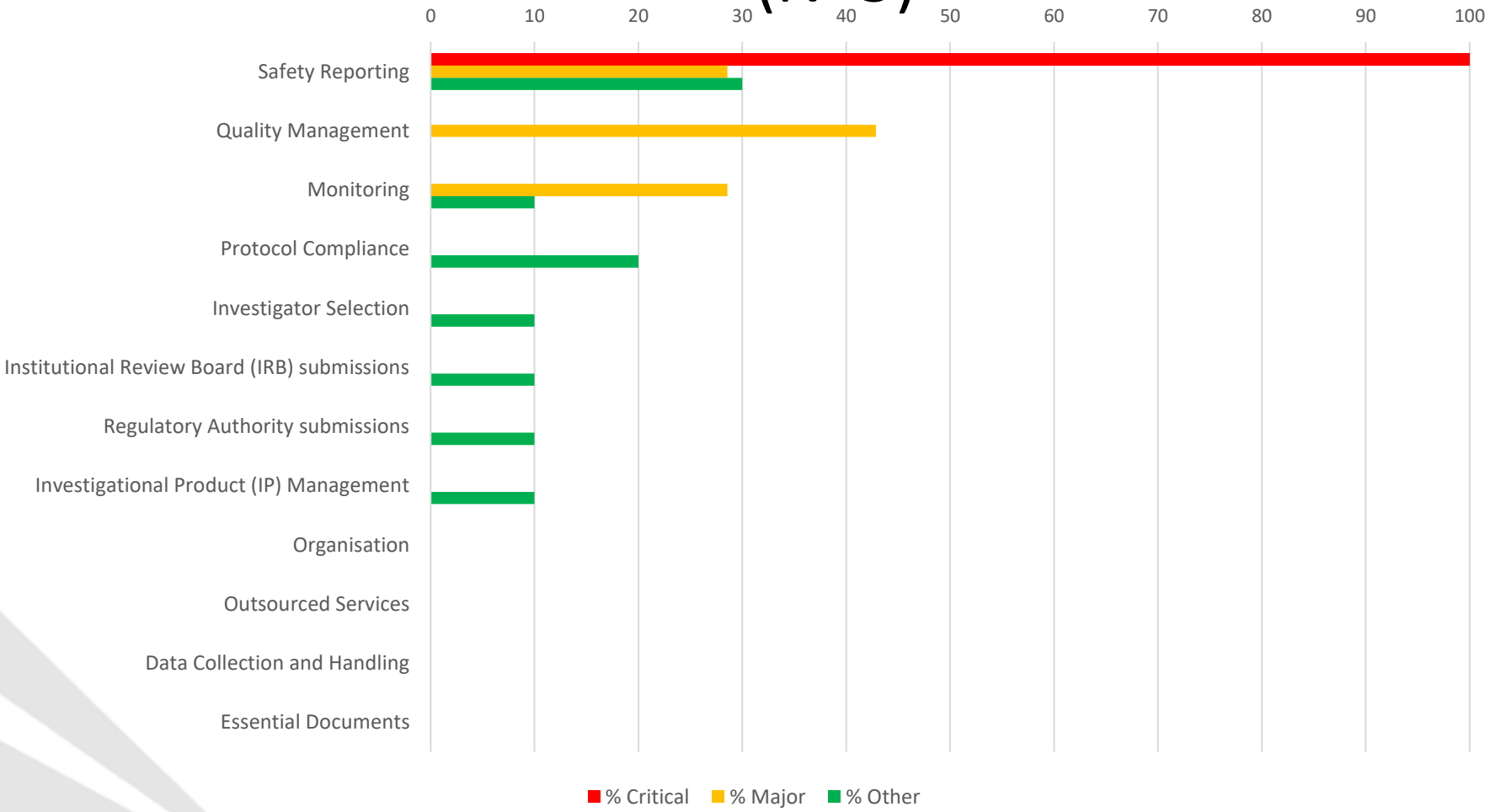
# IMPORTANT POINTS TO NOTE
## *GCP Site Inspections*

- **Investigational Product (IP) management**
  - **The IP was not repackaged in accordance with Good Manufacturing Practice (GMP) requirements.**

    - ❑ SOP
    - ❑ Delegated and trained study staff
    - ❑ Line clearance
    - ❑ Witness
    - ❑ Label reconciliation
    - ❑ Documentation
  - **The IP was not labelled in accordance with regulatory requirements for IP labelling.**

    - ❑ IP should be labelled in accordance with the regulatory requirements throughout the IP supply chain.

# Sponsor Inspections (2022) (N=5)



# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

- **Safety Reporting**
  - ***Management of Serious Adverse Events***
    - **The unblinded treatment assignment entered into the Safety Database was incorrect, thereby resulting in the over- or under-reporting of Expedited Safety Reports (ESRs), or the submission of inaccurate ESRs, to HSA that is not in compliance with local regulatory requirements, potentially compromising the promptness of regulatory review and/or actions taken to mitigate any emerging safety risks.**

❑Second person verification is recommended for critical data and critical processes, where applicable.

❑Systematic review of trends and outliers is recommended.

# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

- **Safety Reporting**
  - ***Management of Serious Adverse Events***
    - **Lack of compliance to sponsor's safety reporting SOPs.**

❑Sponsor staff should be familiar with and comply with applicable safety reporting SOPs.

    - **Inaccurate information was reported to IRB and HSA.**

❑Sponsor should remind PIs to report accurate information to the IRB.

❑Sponsor should ensure that accurate quality checks are performed

    - **Lack of documentation of review of medical reports by investigator.**

❑Sponsor should remind investigators to document their review of medical reports.

# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

- **Quality Management**

✓ **Applicable for management of Investigator-initiated trials (IITs)**

- **Inadequate quality assurance system to ensure adherence to quality standards:**
  - **Inadequate SOPs for key sponsor oversight activities, including:**
    - Trial Monitoring;
    - Handling SAEs;
    - Handling non-compliances, Serious Breaches and Urgent Safety Measures, including impact assessment, root cause analysis and corrective action and preventive action (CAPA) plans;
    - Submitting trial status reports to HSA; and
    - Auditing (i.e., study reviews / quality reviews).
  - **Training documentation of sponsor staff not maintained.**

# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

- **Quality Management**

✓ **Applicable for management of Investigator-initiated trials (IITs)**

➢ **Inadequate quality control system to secure compliance.**

- Lack of documentation of review of non-compliances and SAEs;
- Lack of an efficient system to maintain sponsor oversight.

➢ **Inadequate risk-based quality management**

➢ Lack of documentation of risk assessment of clinical trial applications.

# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

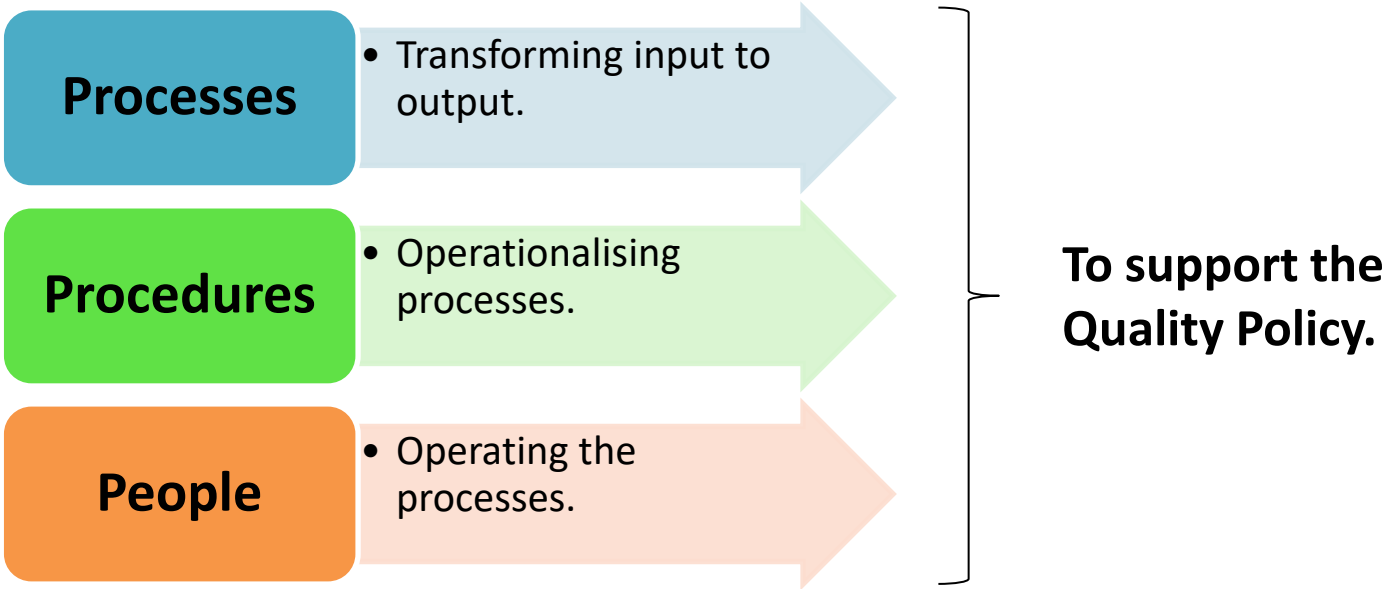
- **Monitoring**
  - **Lack of a systematic, prioritised and risk-based approach in trial monitoring, thereby being unable to ensure appropriate conduct of IITs in accordance with GCP.**
    - Not all IITs were monitored.
    - Monitoring Plans and Monitoring Visit Reports were not reviewed for IITs, which were not monitored by the institution.

# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

- **Quality Management for IITs**

**1** **Develop a Quality Management System (QMS):**



# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

- **Quality Management for IITs**

**2** **Develop an adequate quality assurance system to ensure adherence to quality standards :**

**Study start-up**

- Sponsorship of IITs
- Budgeting
- Clinical Trial Agreements
- 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

**Sponsor SOPs & Training**

*NB: These are some examples, and not intended to be complete or exhaustive.*

# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

- **Quality Management for IITs**

### 3 Use a Proportionate and Risk-Based Approach to Quality Management

| Sponsorship Risk Assessment and Management<br>By Institution | Trial Risk Assessment and Management<br>By Principal Investigator |
|---|---|
| • Type of clinical trial<br>• Contractual Agreements<br>• Funding<br>• Study population<br>• PI qualifications<br>• Resources<br>• Facilities<br>• Monitoring strategy | • Risk Identification<br>• Risk Evaluation<br>• Risk Control<br>• Risk Communication<br>• Risk Review<br>• Risk Reporting |

*NB: These are some examples, and not intended to be complete or exhaustive.*

# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

- **Quality Management for IITs**

**4** **Implement an adequate quality control system to secure compliance:**

**Study start-up**

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

**Study Conduct**

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

**Study Closure**

- Review Final Clinical Study Reports

*NB: These are some examples, and not intended to be complete or exhaustive.*

# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

- **Quality Management for IITs**

**5** **Develop a risk-based approach to trial monitoring:**

**Selection of Monitors**

- Monitors should be adequately trained to monitor the clinical trial.
  - *e.g., GCP, SOPs, study-specific training and applicable regulations*.

**Monitoring Plan**

- The sponsor should develop a Monitoring Plan describing the:
  - *Monitoring strategy;*
  - *Monitoring responsibilities;*
  - *Monitoring methods (i.e., on-site / remote);*
  - *Critical data and processes to be monitored;*
  - *Timelines for drafting and reviewing Monitoring Visit Reports; and*
  - *Applicable policies and procedures.*

# IMPORTANT POINTS TO NOTE

## *Sponsor Inspections*

- **Quality Management for IITs**

**5** **Develop a risk-based approach to trial monitoring:**

**Review of Monitoring Visit Reports**

- The sponsor should establish a system for reviewing Monitoring Visit Reports and document the review.

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# Managing Quality of Clinical Trials

- **Definition of quality (in the context of a clinical trial)**
  - Fitness for purpose and ability to generate reliable information to answer research questions and support good decision making.

- **GCP Principle on assuring quality of clinical trials**
  - Systems with procedures that assure the quality of every aspect of the trial should be implemented.
    - With focus on aspects of the trial that are essential to ensure trial participant protection and reliability of trial results.

# Managing Quality of Clinical Trials

## ❑ Quality Management System

- ➢ System to manage quality throughout all stages of the trial process.
- ➢ Focus on trial activities essential to trial participant protection and reliability of trial results.
- ➢ Incorporate **Quality By Design.**
- ➢ Adopt a **Proportionate** and **Risk-Based Approach.**
- ➢ Establish, implement and maintain **Quality Assurance** and **Quality Control** processes and documented procedures.

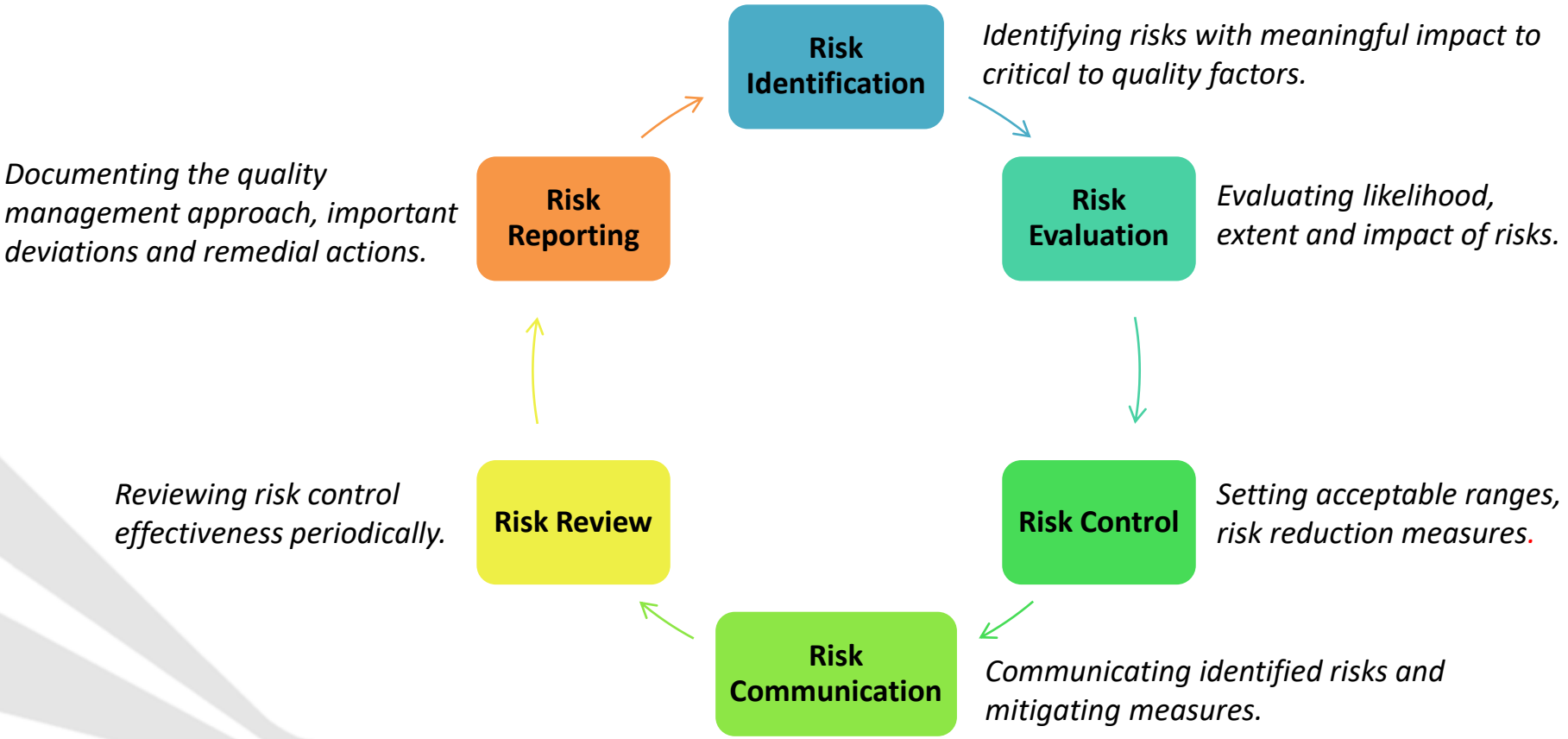
# Managing Quality of Clinical Trials

## ❑ Quality by Design

- Ensure quality of a clinical trial is driven proactively by designing quality into the study protocol and processes.
- Focusing on **critical to quality factors** to ensure the:
  - *Protection of the rights, safety, and well-being of trial participants;*
  - *Generation of reliable and meaningful results; and*
  - *Management of risks to those factors using a risk-proportionate approach.*

# Managing Quality of Clinical Trials

## ❑ Proportionate and Risk-Based Approach (Risk Based Quality Management)



# Managing Quality of Clinical Trials

## Quality Assurance

- Planned and systematic processes and documented procedures that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s)

  E.g.

  - *Protocols, Case Report Forms, SOPs and other documents should be clear, concise and consistent; and*
  - *Staff should be trained on GCP, SOPs, study-specific training and applicable regulations.*

# Managing Quality of Clinical Trials

## ❑ Quality Control

- Operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled. E.g.,

| | |
|---|---|
| • **Trial Monitoring**<br>  ➢ *On-site and/or remote monitoring*<br>• **Centralised monitoring**<br>  ➢ *Remote evaluation of accumulating data*<br>• **Safety Monitoring**<br>  ➢ *Ongoing safety evaluation and safety reporting* | • **Quality and Compliance Metrics**<br>  ➢ *Review of IP Release Status*<br>  ➢ *Review of Trial Master Files*<br>  ➢ *Review of study-specific training status*<br>  ➢ *Review of Non-compliances*<br>  ➢ *Review of Serious Breaches*<br>  ➢ *Review of Urgent Safety Measures*<br>  ➢ *Review compliance with Site Visit Schedules*<br>  ➢ *Review of Site Visit Reports*<br>  ➢ *Review of data entry / source document verification (SDV) status*<br>  ➢ *Review of issues*<br>  ➢ *Conducting accompanied visits etc.* |

# 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:
  - *Quality Management System*
  - *Quality by Design*
  - *Proportionate and Risk-Based Approach (Risk-Based Quality Management)*
  - *Quality Assurance and Quality Control*
- 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
- ICH E8 Guidelines on General Considerations for Clinical Studies
  https://www.ich.org/page/efficacy-guidelines
- Regulatory Guidances
  https://www.hsa.gov.sg/clinical-trials/regulatory-guidances
- VCCC Alliance - Investigator-initiated Trials
  https://vcccalliance.org.au/our-work/research-and-translation/clinical-trial-innovations/investigator-initiated-trials/

*THANK YOU!*

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