



LOOKING BACK AT 2019

Sumitra Sachidanandan
Regulatory Consultant
Innovation Office & Clinical Trials Branch
Health Products Regulation Group
Health Sciences Authority Singapore

Copyright HSA 2019



2

OUTLINE

- GCP inspection findings for 2019
- ICH E6 (R3)
- Launch of new HSA website

Copyright HSA 2019



Objectives of GCP Inspection

To safeguard the **rights, safety and well-being** of trial subjects

To verify the **quality and integrity** of the clinical trial data submitted to the Regulatory Authority.

To assess **compliance to protocol and applicable regulations, guidelines and standard operating procedures** for clinical trials

Classification of GCP Inspection Findings



CRITICAL

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



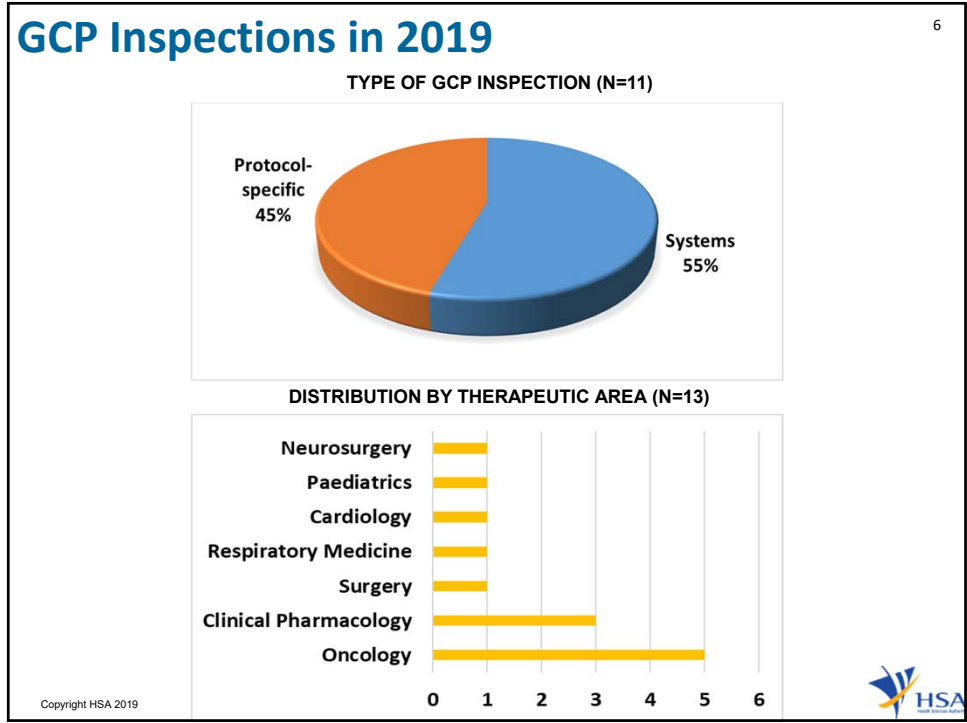
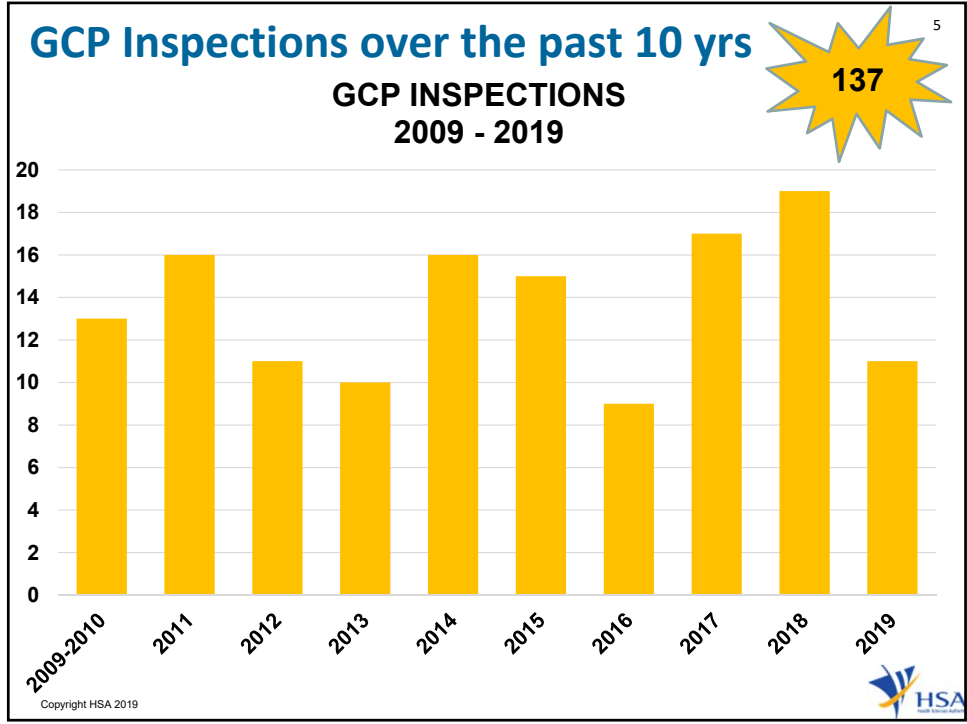
OTHER

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



COMMENTS

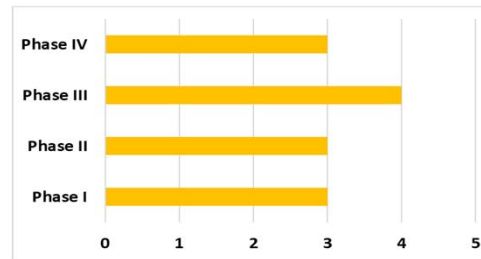
- Suggestions to improve quality or to prevent a non-compliance from occurring in future.



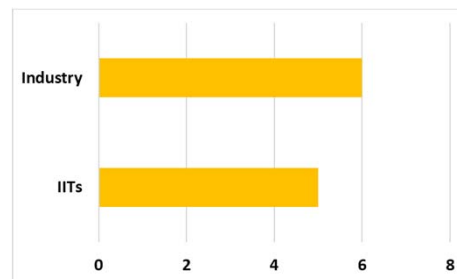
GCP Inspections in 2019

7

DISTRIBUTION BY PHASE OF CLINICAL TRIAL (N=13)



DISTRIBUTION BY SPONSOR (N=11)

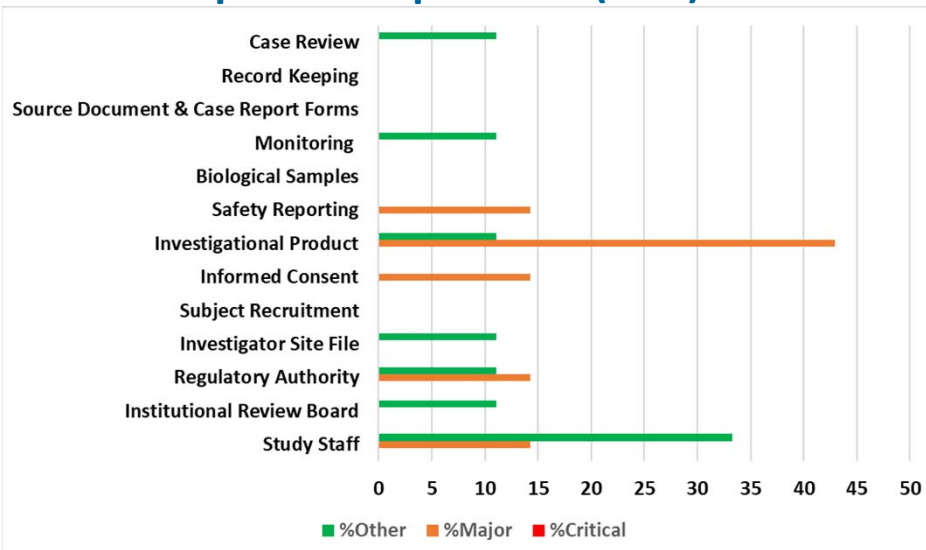


Copyright HSA 2019



GCP Inspection Findings in 2019 Protocol-specific Inspections (N=5)

8



Copyright HSA 2019



Protocol-specific Inspections

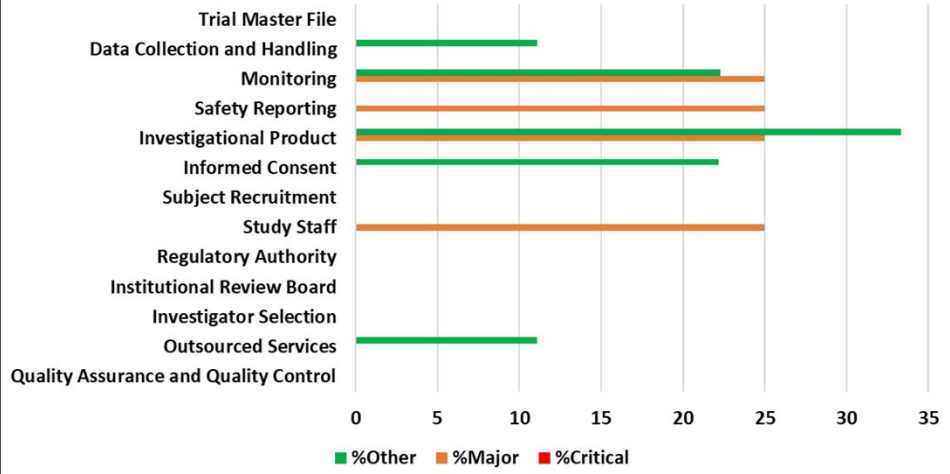
- **Investigational Product**
 - ▶ Delegation and training of study staff
 - *Lacking during IP receipt*
 - ▶ Written procedures for handling IP
 - *Lack of SOPs for handling IP*
 - ▶ IP documentation
 - *No document control*
 - *No ALCOA principles*
 - *Lack of traceability*
 - *Retrospectively created*
 - *Discrepancies*
 - ▶ IP repackaging and relabelling
 - *Non-compliance with GMP guidelines*
 - ▶ IP Labelling
 - *Non-compliance to clinical trials regulations*

Protocol-specific Inspections

- **Study Staff**
 - ▶ Lack of study-specific training.
- **Informed Consent**
 - ▶ Subject had signed on unapproved ICF.
- **Safety Reporting**
 - ▶ Delayed reporting of SAEs to sponsor.
- **Regulatory Authority**
 - ▶ Serious Breach not notified to HSA.

GCP Inspection Findings in 2019 Sponsor Inspections (N=4)

11



Copyright HSA 2019



Sponsor Inspections in 2019

12

- **Study Staff**
 - ▶ Study staff had been delegated by Sub-investigator instead of PI.
- **Investigational Product**
 - ▶ Significant discrepancies in IP documentation.
 - Lack of ALCOA principles
 - Discrepancies in IP accountability.
 - Discrepancies in IP preparation for calculation of volume of IP.
- **Safety Reporting**
 - ▶ Lack of adequate oversight of safety review process by sponsor and CRO.
- **Monitoring**
 - ▶ Monitors had not reviewed eligibility criteria thoroughly and carefully.

Copyright HSA 2019



Sponsor Inspections in 2019

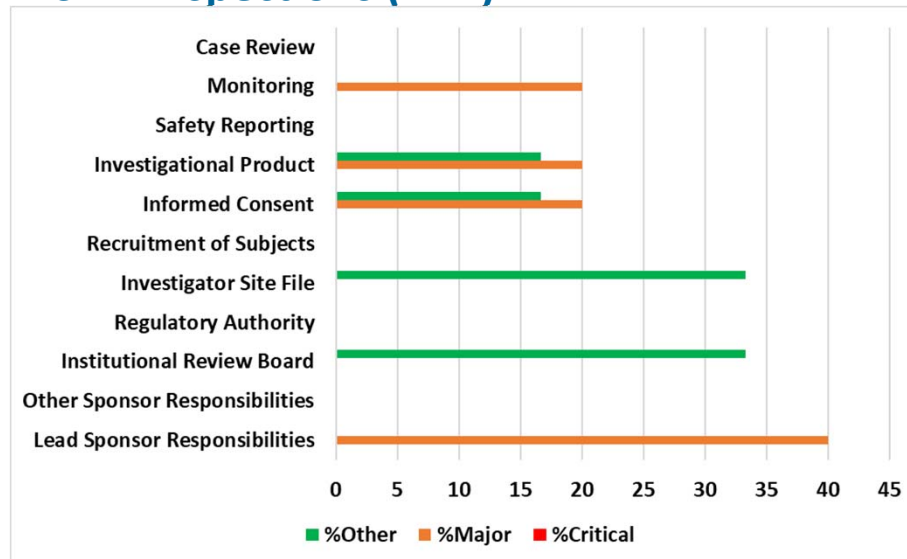
- **Inadequate oversight of Investigator-initiated trials (IITs) by local sponsor**
- **Note:**
 - ▶ Institution is the local sponsor of IITs
 - ▶ Sponsors of IITs should ensure there are proper processes and systems in place to:
 - *Keep track of all clinical trials conducted within the institution*
 - *Screen clinical research studies to determine whether they are regulated by HSA*
 - *Ensure that non-compliances, serious adverse events and urgent safety measures are promptly notified to the local sponsor's Research Office / Clinical Research Unit*
 - *Monitor clinical trials*
 - *Maintain oversight of IITs under the mutual recognition of IRBs*

Copyright HSA 2019



GCP Inspection Findings in 2019

MS IIT Inspections (N=2)



Copyright HSA 2019



MS IIT Inspections in 2019

- **Lead Sponsor Responsibilities**

- ▶ Lead sponsor did not promptly assess the impact of the breaches and notify HSA of the serious breaches.
- ▶ Lead sponsor did not submit updated IB to HSA.
- ▶ Lead sponsor did not submit CRM Notification to HSA.

- **Informed Consent**

- ▶ Subject did not personally date the ICF.
- ▶ Subjects were not provided with signed copies of ICFs.
- ▶ Non-substantial amendments had been made to the ICF and used to consent a subject prior to IRB approval.

MS IIT Inspections in 2019

- **Investigational Product**

- ▶ Study staff had not been delegated to handle IP.
- ▶ Discrepancies in IP documentation
 - *No document control*
 - *Photocopies were not certified as true copies*
 - *Lack of traceability to Subject ID between IP documentation*
 - *Actual IP storage temperature was not recorded, but plotted in 5°C intervals*

- **Monitoring**

- ▶ Lead sponsor did not maintain adequate oversight of the satellite site.

ICH E6 (R3) – update of ICH E6

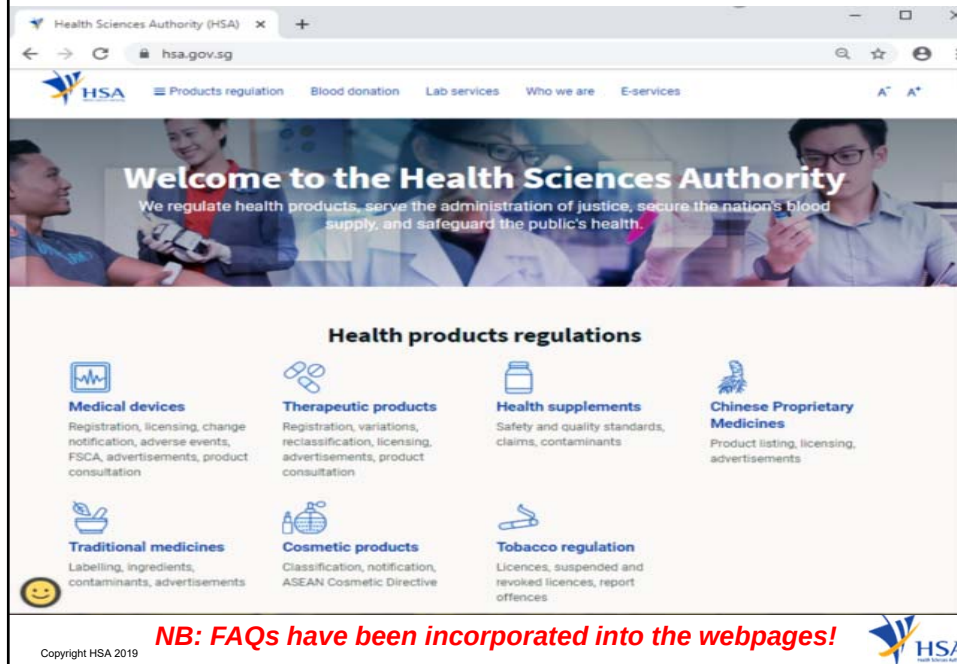
- Clinical trials have become more complex with respect to trial design, use of technology, quantity of data collected and involvement of central testing facilities or other service providers.
- ICH E6 (R1) was amended to ICH E6 (R2) in Nov 2016 to incorporate electronic data sources and quality risk management (e.g. Quality by Design, Risk-based Monitoring).
- ICH E6 (R2) will be amended to ICH E6 (R3) in future. The development of ICH E6(R3) will consider the flexibilities needed for a variety of trial designs and will focus on key principles.
- HSA is a member of the ICH E6 (R3) EWG.

ICH E6 (R3) – update of ICH E6

- **Concept Paper for ICH E6 (R3)**
 - ▶ **Annex 1 – Interventional clinical trials**
 - Principles and objectives document; and GCP guidelines
 - Include use of unapproved / approved drugs in a controlled setting with prospective allocation of treatment to participants and collection of trial data.
 - NB: ~18-24 months to reach Step 1 (i.e. draft Technical Document).
 - ▶ **Annex 2 – Additional considerations for non-traditional interventional clinical trials**
 - Include designs such as pragmatic clinical trials, decentralised clinical trials, and trials that incorporate real world data sources.
 - NB: Work will commence when Annex 1 reaches Step 1.
- **Stakeholder engagement**
 - ▶ Academia
 - ▶ Patient-advocacy groups – Not applicable for Singapore

Launch of new HSA website

19



Conclusions

20

- Both sponsors and site staff play a crucial role in maintaining the quality of clinical trials.
 - ▶ Quality systems should be implemented in every aspect of the clinical trial.
 - ▶ Risk-based approach should be adopted in quality systems.
 - ▶ Adequate oversight is key.
 - ▶ Sponsors and site staff should work in tandem to maintain the quality of clinical trials.
 - Be aware of non-compliances, and learn from them to prevent a recurrence.

Copyright HSA 2019



We welcome your enquiries and feedback!

HSA_CT@hsa.gov.sg

THANK YOU!