UPDATES FROM THE GCP INSPECTION TEAM

Ms Sumitra Sachidanandan
GCP Inspection Consultant
Clinical Trials Branch
Health Products Regulation Group
Health Sciences Authority

Outline

- Common GCP Inspection Findings for 2015
- Serious Breaches
- ICH E6 Addendum Update
- Quality Improvement Initiatives

COMMON
GCP INSPECTION FINDINGS
FOR 2015

GCP Inspection Framework

- **Launched in Sep 2009;**
- **Completed 82 GCP Site Inspections to date:**
  - *2009-2010 : 13 (Protocol-specific)*
  - *2011 : 15 (Protocol-specific), 1 (Systems on ICF and IP)*
  - *2012: 10 (Protocol-specific), 1 (Systems on ICF and IP)*
  - *2013: 10 (Protocol-specific)*
  - *2014: 15 (Protocol-specific), 1 (Systems on ICF and IP)*
  - *2015: 15 (Protocol-specific)*

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

~ adopted from EMEA SOPs on GCP Inspection.

- **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.

Classification of GCP Inspection Findings

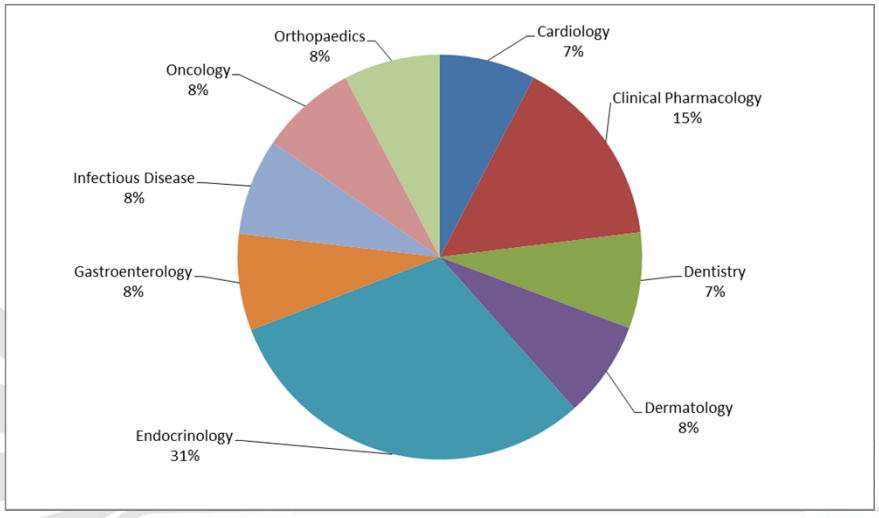
~ adopted from EMEA SOPs on GCP Inspection.

- **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.

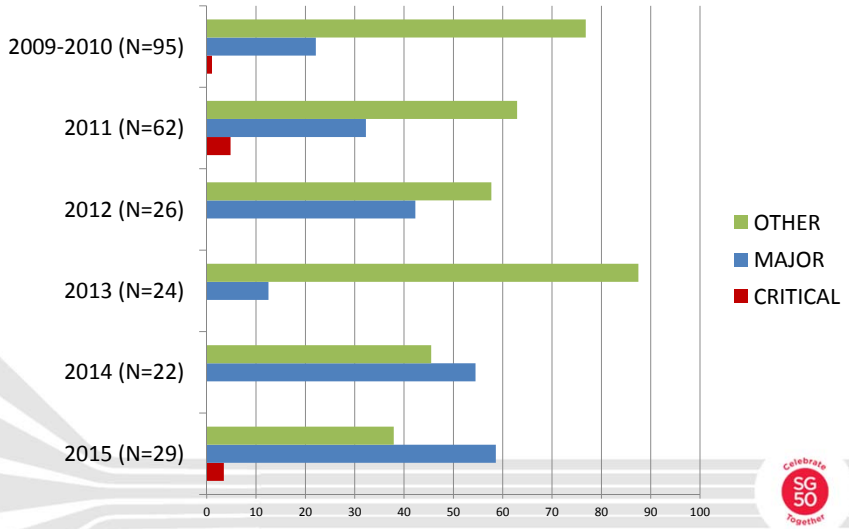
- **Comments**: The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

GCP Inspections in 2015

- Distribution of Therapeutic Areas (N=15)



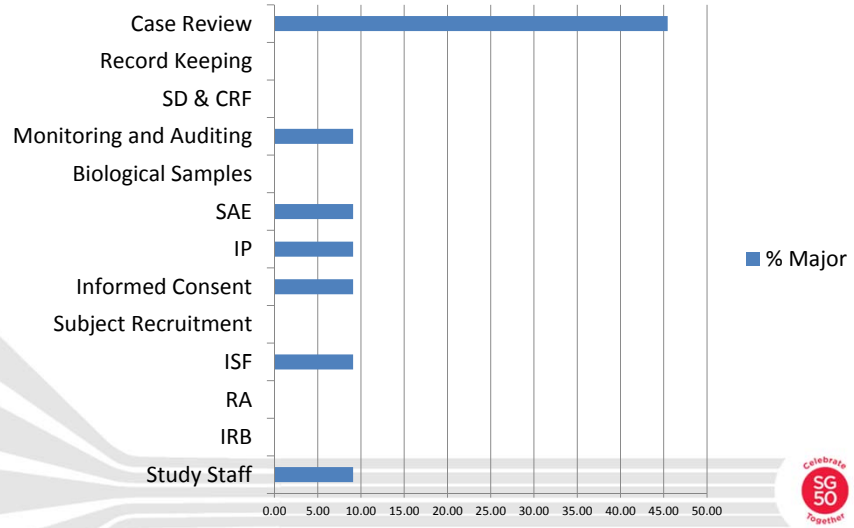
Distribution of GCP Inspection Findings



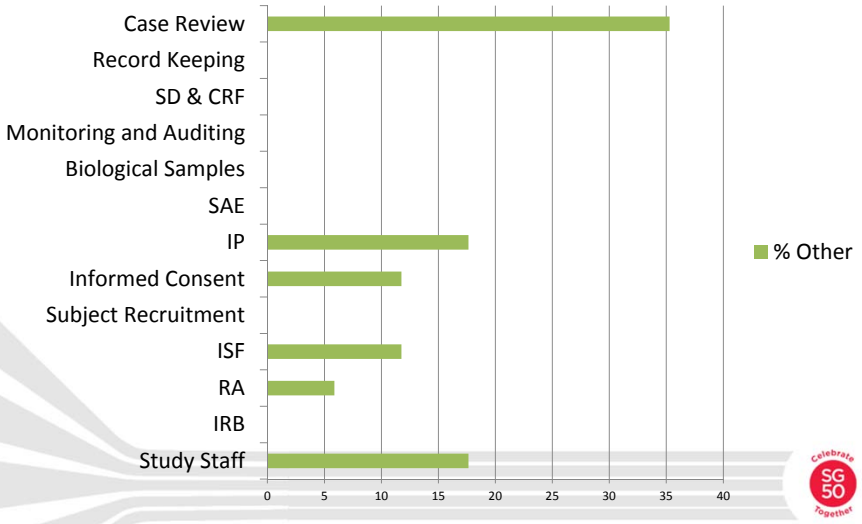
CRITICAL GCP Inspection Finding (N = 1)

- **Triggered GCP Site Inspection**
  - Conducted due to a Serious Breach
  - Wrong strength of IP administered to subjects
  - Lack of quality systems in IP management:
    - *Lack of IP Management SOPs*
    - *Inadequate staff training*
    - *Site staff unaware of strengths of IP available for use*
    - *Various strengths of IP not clearly labelled*
    - *Inadequate counter-checking by witness*
    - *Discrepancies in IP documentation*

MAJOR
GCP Inspection Findings (N=11)



OTHER
GCP Inspection Findings (N=17)



MAJOR GCP INSPECTION FINDING

Case Review

Traceability

Protocol ABC

DATA COLLECTION FORM

Subject Identifiers required if DCF is used as SD.

Subject ID: 59001
Visit No.: 1

Subject Initials: ABC
Visit Date.: 3 Dec 2015

Data should be captured in accordance with study protocol.

- Study Procedures
  - ✓ A – Attributable
  - ✓ L - Legible
  - ✓ C -Contemporaneous
  - ✓ O - Original
  - ✓ A - Accurate

✓ Purpose: SD / CRF?

✓ Requires IRB approval

✓ May be required to be updated for protocol amendments.

Completed by: _____

Version Control

Version Dated: 1 Dec 2015 Page 1

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Source Documents

TIP

ATTRIBUTABLE	• *Traceable to the authorised study staff who had collected the source data*
LEGIBLE	• *Handwriting should be readable*
CONTEMPORANEOUS	• *Completed prospectively* • *No retrospective entries*
ORIGINAL	• *Point of first capture*
ACCURATE	• *Amendments should be initialled and dated* • *No correction tape or pencil* • *Data should be captured in accordance with Protocol*

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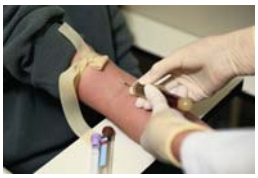
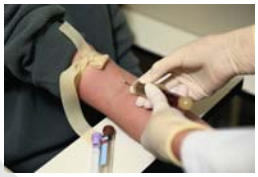
MAJOR GCP INSPECTION FINDING

Informed Consent


Informed Consent should be obtained BEFORE any study-specific procedures!

[Ref: Medicines (CT) Regs 11(1) and SGGCP 4.8.8]

Regulatory Document Tracking Log

TIP

Version No/ Date	Language	Present in ISF?	Translation Certificates Present (if applicable)?	IRB Submission Date	IRB Approval Date	HSA Submission Date	HSA Approval Date

Informed Consent Review

TIP

- Was the **correct version** of ICF used? [Medicines CT Regs 11(4); SGGCP 4.4.1]
- Did the subject, personal obtaining consent and impartial witness (if applicable) **personally sign and date the ICF**? [SGGCP 4.8.8]
- Did the subject require **substituted consent**? [Medicines CT Regs 11(1-3); SGGCP 4.8.12]
- Was the person obtaining consent **authorised** to do so? [SGGCP 4.8.5]
- Did the subject require an **impartial witness**? [Medicines CT Regs 11(5); SGGCP 4.8.9]
- Did the subject require **translation**? [SGGCP 4.8.6]
- Was a **signed copy** of the ICF provided to the subject?[SGGCP 4.8.11]
- Was there **documentation of informed consent**?

Informed Consent Tracking Log

TIP

Subject ID	Subject Initials	ICF version ref. (include language used)	Informed Consent Date	ICF version ref. (include language used)	Informed Consent Date	ICF version ref. (include language used)	Informed Consent Date

MAJOR GCP INSPECTION FINDING

Investigational Products

IP MANAGEMENT

Written procedures for IP management (SGGCP 5.14.3)

TRAINING

Study staff should be trained and training should be documented; nurses and/or pharmacy technicians should be trained (SGGCP 4.2.4)

IP STORAGE

Limited and secure access; storage temperature should be monitored; temperature excursions should be managed (SGGCP 4.6.4)

IP ADMINISTRATION

IP should be administered in accordance with the protocol (SGGCP 4.6.5)

IP DOCUMENTATION

IP documentation should be maintained in accordance with SGGCP 4.6.3.

Involvement of Allied Hospital Staff in IP management

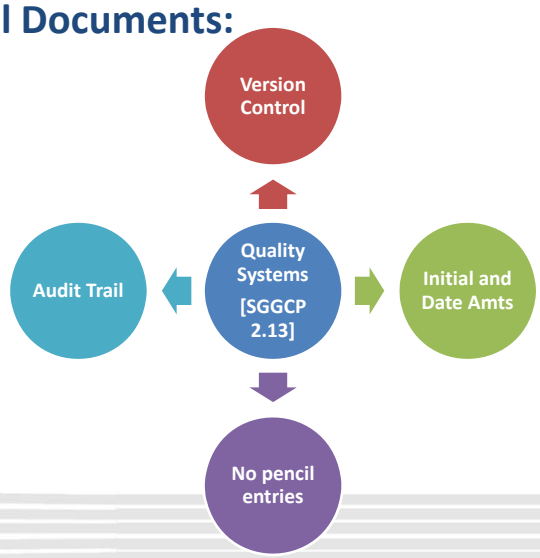
TIP

- **Nurses and / or Pharmacy Technicians**
  - Representative should be part of study team and delegated by PI on Staff Delegation Log
  - Should be trained on protocol
  - Aide memoires would be useful
  - Training should be documented and maintained in Investigator Site File

MAJOR GCP INSPECTION FINDING

Investigator Site File

- Essential Documents:



MAJOR GCP INSPECTION FINDING

Monitoring

- Study staff are trained (SGGCP 5.18g)
- Study staff are adhering to study protocol (SGGCP 5.18d)
- Significant issues are communicated to the study staff (SGGCP 5.18q)

Study Staff Tracking Log

TIP

SIGNATURE SHEET			IRB	CV	**Forms for IND Study		TRAINING RECORDS		
Name of Investigator	Start Date	End Date	IRB Approval	CV	FDA 1572	Financial Disclosure	CITI	SGGCP	Study training

MAJOR GCP INSPECTION FINDING

Safety Reporting

- Ensure that Adverse Events that a Serious, Related and Unexpected are reported to IRB and HSA within the required timelines.
- SAE Tracking Log:

TIP

SUBJECT ID	SERIOUS ADVERSE EVENT	ONSET DATE	DATE SAE REPORTED TO SITE	DATE SAE REPORTED TO SPONSOR / CRO	IRB SUBMISSION DATE	HSA SUBMISSION DATE

SERIOUS BREACHES

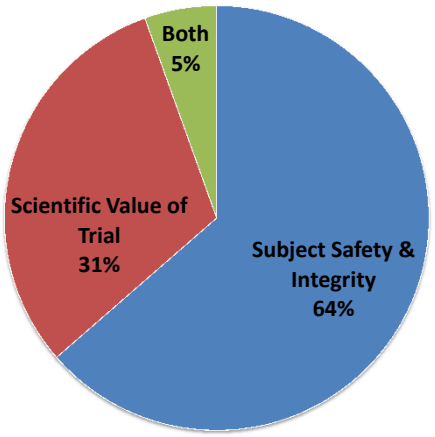
Serious Breach

A **serious breach** is a deviation which is **likely to** affect to **a significant degree**:

- The safety or physical or mental integrity of any subjects in a clinical trial; or
- The scientific value of the clinical trial.

Distribution of Serious Breach

(based on Impact)



Total number of reports = 55

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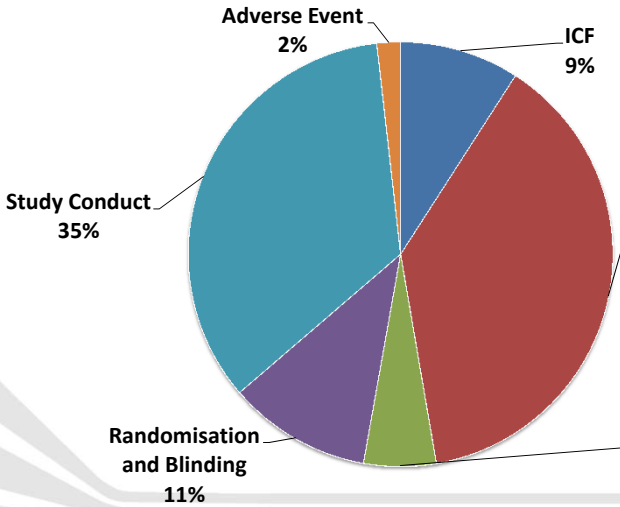
Distribution of Serious Breach

(based on Category)



Total number of reports = 55

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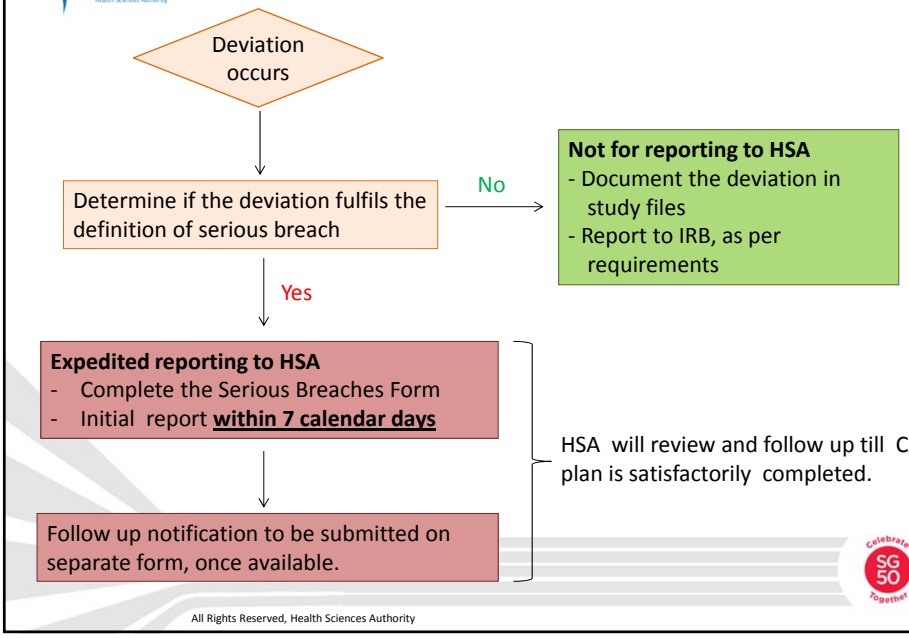
Examples of Serious Breaches

- **Investigational Product (IP):**
  - IP Packaging errors
  - Dispensing errors
  - Use of expired IP
- **Study Conduct:**
  - Enrollment of ineligible subjects
  - Key efficacy / safety parameters not performed

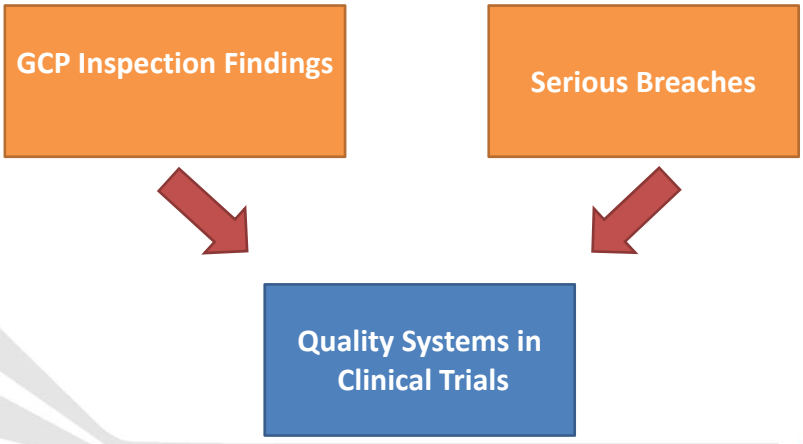
Examples of Serious Breaches

- **Randomisation and Blinding:**
  - Randomisation errors
  - Blinding procedures not adhered to
- **Informed Consent:**
  - Use of unapproved version of ICF
  - Subjects not re-consented with updated ICF
  - Lack of an impartial witness
- **Adverse Events:**
  - Use of prohibited medications
  - Dose modifications not performed

Notification of Serious Breaches



SUMMARY



ICH E6 ADDENDUM UPDATE

- Adapted from ICH E6 Webinar

Feedback deadline extended to 15 Jan 2016!

Send your feedback to HSA_CT@hsa.gov.sg

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Statement of the perceived problem– why do we need an addendum to ICH E6?

- **Since 1996 adoption of ICH E6 GCP, clinical trials have evolved substantially,**
- **Increases in globalisation, study complexity, and technological capabilities,**
- **Approach to GCP needs modernisation to keep pace with the scale and complexity of clinical trials and to ensure appropriate use of technology.**

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Statement of the perceived problem– why do we need an addendum to ICH E6?

- **ICH E6 gave sponsors flexibility to implement innovative approaches –but has been misinterpreted and implemented in ways that impede innovation**
  - e.g. emphasising less important aspects of trials (e.g., focusing on the completeness and accuracy of every piece of data) at the expense of critical aspects (e.g., carefully managing risks to the integrity of key outcome data).
- **Modernising ICH E6 by supplementing it with additional recommendations will better facilitate broad and consistent international implementation of new methodologies.**

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Addendum to ICH E6 - Objective

- **This guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure human subject protection and data integrity**

Addendum-Integrated Format

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

ADDENDUM

(e) Monitoring results should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up as indicated. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan.

ADDENDUM

5.18.7 Monitoring Plan

The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used and the rationale for their use. The plan

Addendum Content

- Introduction
- Glossary
  - certified copy,
  - monitoring plan,
  - monitoring report,
  - validation of computerized systems
- GCP Principles
  applicability of GCP standards when using electronic media

Addendum Content

- Investigator responsibilities:
  - Supervision of tasks delegated
  - Ensure qualification and implement procedures to ensure integrity
  - Source documents and trial records for each trial subject
    - Attributable, legible, contemporaneous, original, accurate, and complete

Addendum Content

- Sponsor responsibilities
  - Quality Management
    - Sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting, and archiving of clinical trials
    - Sponsors should focus on essential trial activities
    - Methods used to assure and control quality of trial should be proportionate to risks
    - Avoid unnecessary complexity, procedures and data collected

Addendum Content

- Sponsor responsibilities
  - Quality Management
    - risk-based approach to quality management,
      - Critical process & data identification
      - Risk Identification
      - Risk Evaluation
      - Risk Control
      - Risk Communication
      - Risk Review
      - Risk Reporting

Addendum Content

- Sponsor responsibilities
  - oversight,
  - subcontracting by contract research organizations (CROs),
  - use of computerized systems,
  - follow-up of non-compliance

Addendum Content

- Sponsor responsibilities
  - Monitoring- including risk based, centralised and on-site monitoring approaches,
    - Sponsor should develop a systematic, prioritised, risk-based approach
    - Permission of varied approaches e.g combination of on-site and centralised monitoring to improve effectiveness & efficiency
    - Rationale for chosen strategy should be documented
    - Documentation of monitoring results
    - Sponsor should develop monitoring plan tailored to the human subject protection and data integrity risks of the trial

Addendum Content

- Essential Documents/(e)TMF
  - Sponsor and investigator should maintain record of location(s) of their respective essential documents. Storage system should provide for document identification, search and retrieval
  - Individual trials may require additional documents not mentioned in essential document list. Sponsor and/or investigator should include these as part of trial master file (TMF)
  - Investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during and after the trial
  - When copy used to replace original document, it should fulfil requirements for certified copies

ICH harmonisation for better health

Addendum Content

- Sponsor should not have exclusive control of CRF data
  - Sponsor should ensure that investigator has control of and access to CRF data reported to sponsor

HSA Health Sciences Authority

QUALITY IMPROVEMENT INITIATIVES

Celebrate SG 50 Together

Quality Improvement Initiatives

- Training
- CTB FAQs on HSA website
- Engaging stakeholders
- Observation of GCP Site Inspections
- Upstream consultation on IP management
- Sharing of Best Practices
- ICH E6 Workgroup
- Template Forms Repository
- Review of Serious Breaches

THANK YOU!

We welcome your queries!

Mr Foo Yang Tong
foo_yang_tong@hsa.gov.sg

Ms Sumitra Sachidanandan
sumitra_sachidanandan@hsa.gov.sg

Ms Poh Cuiqin
poh_cuiqin@hsa.gov.sg