LOOKING BACK AT 2025

Sumitra Sachidanandan

Regulatory Consultant

Innovation Office & Clinical Trials Branch

Health Products Regulation Group

Health Sciences Authority

OUTLINE

- GCP Inspection Framework
- GCP Inspections conducted in 2025
- Regulatory Actions Taken in 2025
- Important Points to Note
  - Site Inspections
  - Sponsor Inspections
- Implementation of ICH E6 (R3) GCP guideline
- Conclusion

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.

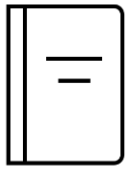
Assess compliance to protocol and applicable regulations, guidelines and standard operating procedures for clinical trials.

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



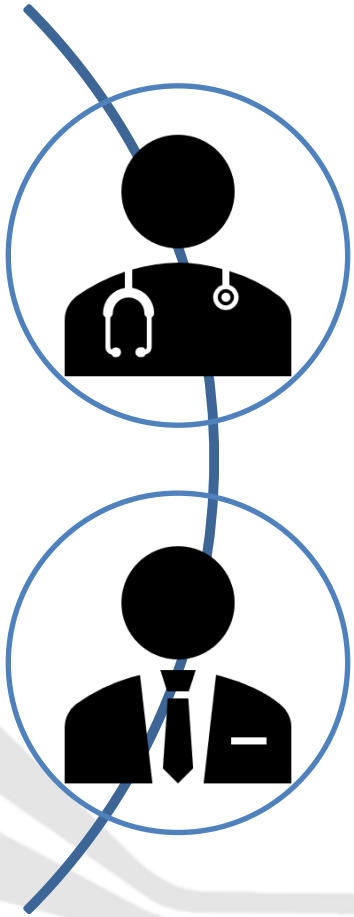
Trial protocol

Regulations

ICH E6 GCP Guideline

Standard Operating Procedures

Inspectee



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

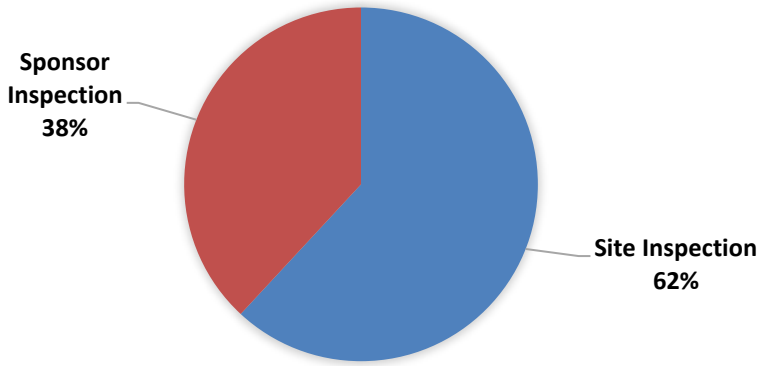
- Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the trial participants and/or the quality and integrity of data.

COMMENTS

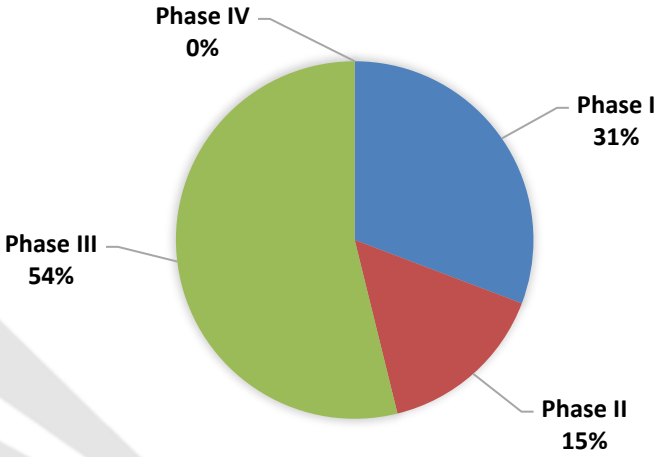
- Suggestions to improve quality or to reduce the potential for a non-compliance from occurring in future.

GCP Inspections (2025)

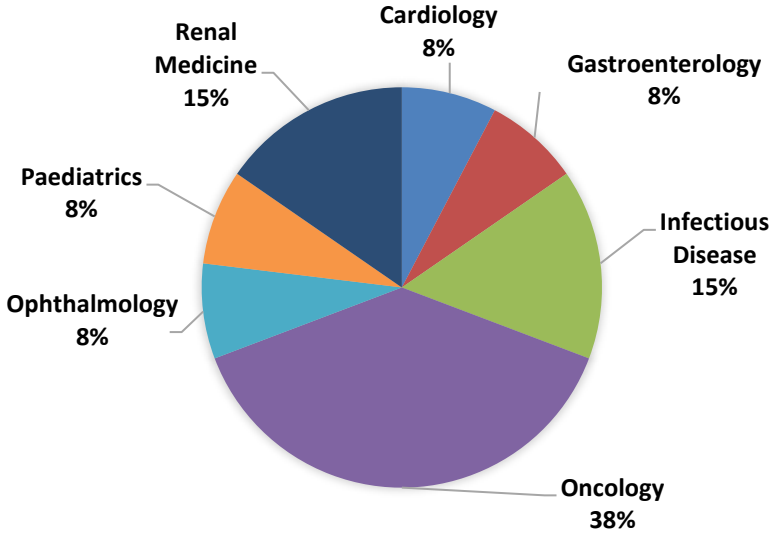
TYPE OF INSPECTEE (N=21)



DISTRIBUTION BY PHASE OF CLINICAL TRIAL



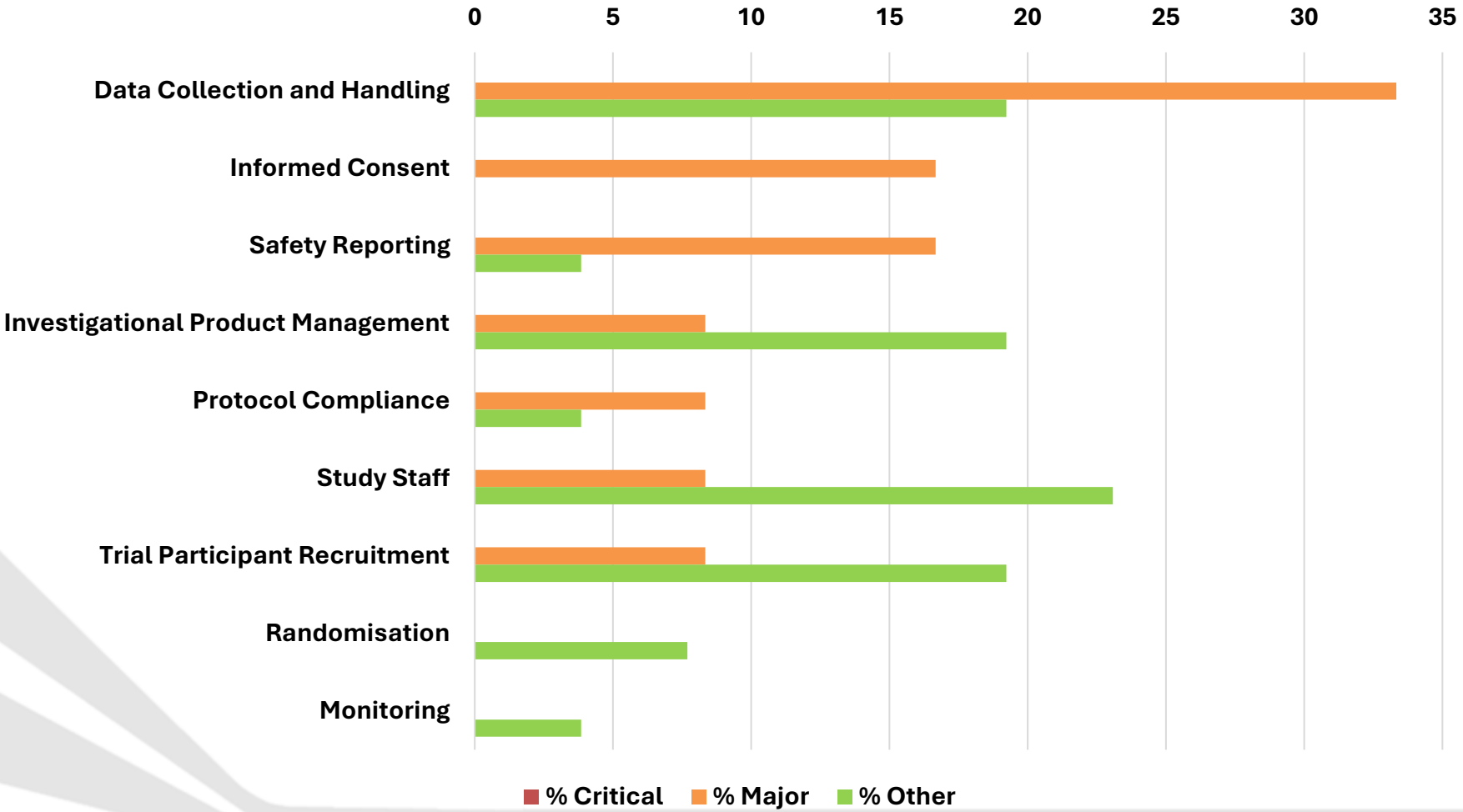
DISTRIBUTION BY THERAPEUTIC AREA



Regulatory Actions Taken in 2025

Type of Regulatory Action	No. of clinical trials	Reason(s)
Trial Termination	0	NA
Trial Suspension	0	NA
Recruitment Suspension	1	• Failed sterility testing from IP manufacturing, thereby potentially impacting the quality of the IP.
Suspension of Investigational Product (IP) Manufacture	2	• Environmental Monitoring failure noted during IP manufacturing, thereby potentially impacting the quality of the IP.

Site Inspections (2025) (N = 13)



Data Collection and Handling

- **Major GCP Inspection Findings:**

  - There was **no audit trail maintained in MS Excel (clinical database),** thereby potentially impacting data integrity.

  - The **audit trail** in the electronic Case Report Form (eCRF) was **not made accessible** to the investigator, Monitor and GCP Inspectors.

How does data flow from source records?

Can MS Word / MS Excel be used as electronic source records or electronic CRFs?

- **Lack of data integrity*, thereby significantly impacting the reliability of trial results.**
  - Attributability
  - Contemporaneousness
  - Accuracy
  - Security
  - Reliability

➢ **NB: Data integrity includes the degree to which data fulfil key criteria of being **attributable, legible, contemporaneous, original, accurate, complete, secure and reliable** such that data are **fit for purpose**.*

Should access be provided to audit trails from computerised systems?

- **Access to metadata, including audit trails, from computerised systems should be provided.**
  - Allow the **appropriate evaluation of the course of events** by capturing details on actions (manual or automated) performed relating to information and data collection and, where applicable, to activities in computerised systems.
  - The **audit trail should show activities**, **initial entry** and **changes to data fields or records**, **by whom, when** and, **where applicable, why.**
  - In **computerised systems**, the **audit trail** should be **secure, computer-generated and time stamped.**

Informed Consent

- **Major GCP Inspection Findings:**

  - It was not possible to ascertain if the **informed consent material** had been **accurately explained to**, and **informed consent freely given by, the legal representative**, as the **impartial witness** was **illiterate in the local language** understood by the legal representative.

  - The investigators **did not sign the informed consent forms (ICFs) in a contemporaneous manner** with the participants, as they did not sign the ICFs with the participants in the same setting.

What is the role of an impartial witness during an informed consent process?

IMPARTIAL WITNESS

- A person who **is independent of the trial** who **cannot be unfairly influenced by people involved with the trial.**
- Required when participant / their legal representative is **unable to read the informed consent material:**
  - **By signing the consent form,** the witness **attests** that the consent information was **accurately explained to and apparently understood** by the participant or the participant's legally acceptable representative and **that informed consent was freely given by the participant / their legal representative.**
- Also required if participant or participant's legal representative is **unable to sign / date the informed consent form.**
  - Verifies that **informed consent was freely given by the participant / their legal representative.**

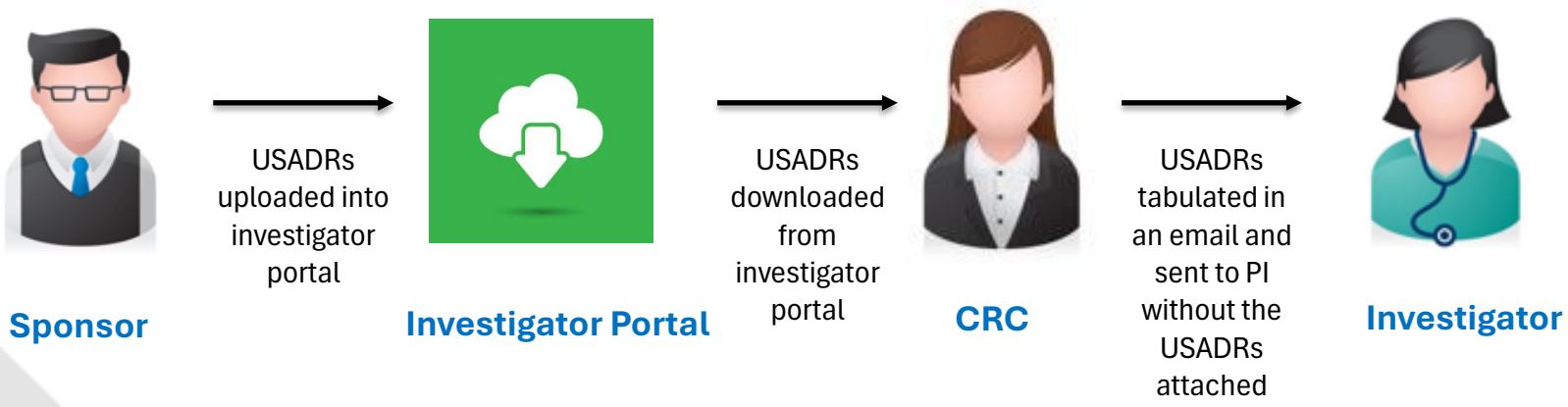
When should the Informed Consent Form be signed and dated?

- **The informed consent form should be signed and dated prior to trial participation.**
  - All relevant parties should sign and date the informed consent form **contemporaneously.**
  - There are no regulatory provisions for the order of signing and dating the informed consent form.

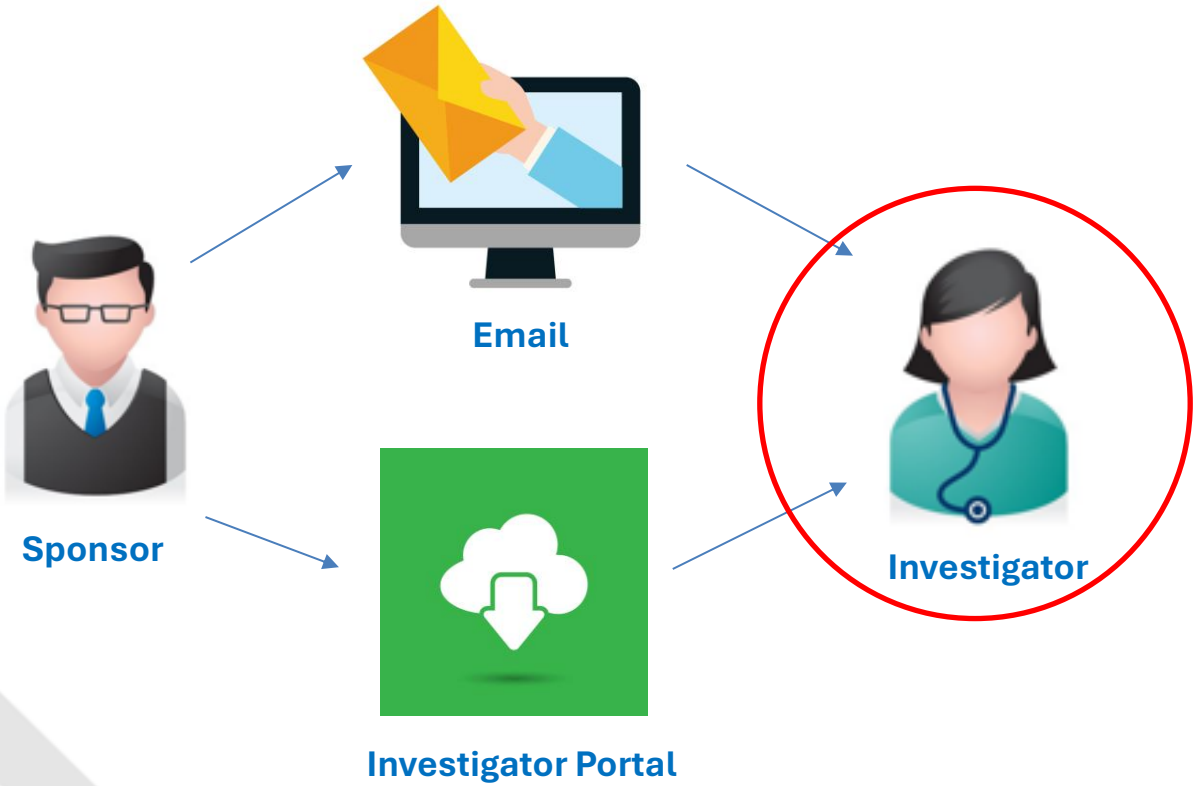
Safety Reporting

- **Major GCP Inspection Finding:**

  - The **CRC did not circulate the full Unexpected Serious Adverse Drug Reaction (USADR) reports to the PI for review**, as only Notes to File summarising the USADR reports had been provided for review.



How should USADRs be circulated to the Principal Investigator (PI)?



Investigator should:

- **Review the USADR** to determine if it requires IRB reporting.
- **Document the review** of the USADR.
- **If the investigator is accessing the USADRs via an investigator portal**, the investigator would still be required to **retain the USADRs at the end of the trial**.

Investigational Product (IP) Management

- **Major GCP Inspection Finding:**

  - The IP was **prescribed by a doctor, who was not part of the investigator site team.**

*The **delegated investigator should prescribe the IP for the participant.***

Protocol Compliance

- **Major GCP Inspection Finding:**
  - The trial was not conducted in compliance with the trial protocol.

Investigator should:

- ***Conduct the clinical trial*** *strictly in* ***compliance with the approved trial protocol.***
- ***Implement amendments to the trial protocol*** *only* ***after IRB and HSA approvals*** *(where applicable) have been obtained.*

Study Staff

- **Major GCP Inspection Finding:**

  - The PI did not adequately maintain a **delegation log** of investigator site staff authorised to perform **significant trial-related activities**.

- ***Delegation***
  - *The investigator may **delegate trial-related activities to other persons or parties**.*

  - *The investigator should ensure a **record is maintained of the persons and parties to whom the investigator has delegated trial-related activities**.*
    - ***Documentation of delegation** should **be proportionate to the significance** of the **trial-related activities**.*
    - ***In situations where the activities are performed as part of clinical practice, delegation documentation may not be required.***

Delegation, Training and Investigator Oversight

Example	Delegation Documentation	Trial-related training	Investigator Oversight
Phlebotomist draws blood for haematology and biochemistry tests	Not required, if there is nothing outside of routine clinical practice.	Not required, if there is nothing outside of usual training and experience.	Less
Phlebotomist draws blood for pharmacokinetic testing	Required	Required	More
Pharmacist dispenses a locally registered IP	Not required, if there is nothing outside of routine clinical practice. *(Alternative documentation recommended, as it is a significant trial-related activity)*	Not required, if there is nothing outside of usual training and experience.	Less
Pharmacist dispenses an unregistered IP	Required	Required	More
Research Nurse measures blood pressure	Not required, if there is nothing outside of routine clinical practice.	Not required, if there is nothing outside of usual training and experience.	Less
Research Nurse administers questionnaire	Required	Required	More

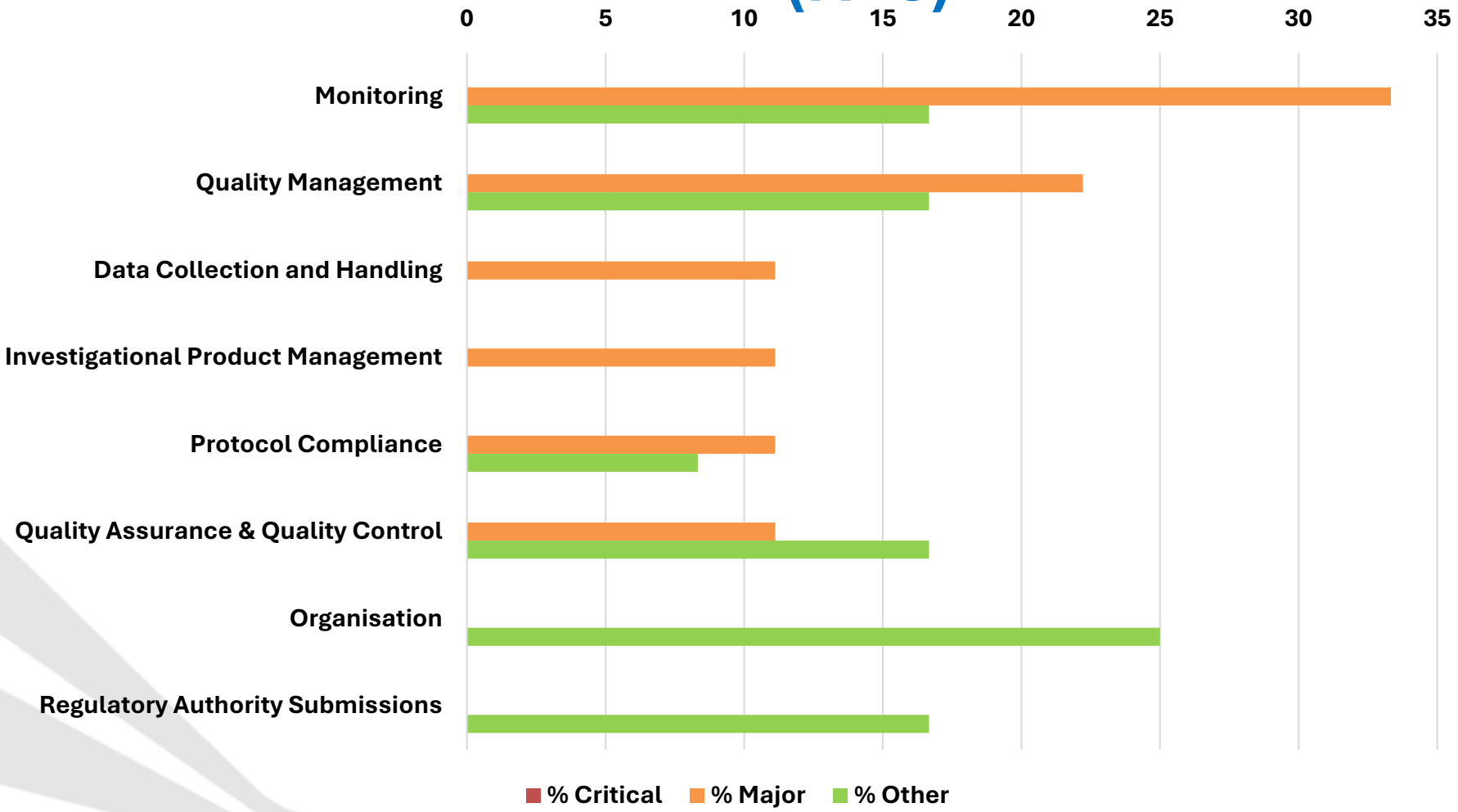
Trial Participant Recruitment

- **Major GCP Inspection Finding:**

  - There was a **lack of attributability, contemporaneousness** and **accuracy** in the completion of the **eligibility checklists**.

  - **Eligibility checklists:**
    - *Include **version control** (e.g., version date);*
    - ***Corroborate with latest approved trial protocol;***
    - ***Completed by the investigator performing eligibility assessment prior to enrollment;***
      - *Checkboxes should be manually completed, unless a validated computerised system with audit trail is used.*
    - *Completed **accurately;***
    - ***Signed and dated via a physical / electronic signature and date.***
      - *Image of manuscript signature should not be copied and pasted!*

Sponsor Inspections (2025) (N=8)



Monitoring

- **Major GCP Inspection Findings:**

  - The sponsor **did not maintain adequate oversight of IITs** regulated by HSA.

  - The Monitor **did not promptly escalate issues to the sponsor** to secure compliance.

What are the requirements of sponsor oversight for IITs?

Allocation of sponsor's trial-related duties and functions

- Allocation between sponsor and investigator

Risk-Based Quality Management

- Risk identification
- Risk Evaluation
- Risk Control
- Risk Communication
- Risk Review
- Risk Reporting

Quality Assurance

- Documented procedures
- Clear, concise, scientifically sound and operationally feasible protocol

Quality Control

- Investigator Site Monitoring
- Securing compliance through continuing review, amendments, deviation / non-compliance / serious breach reporting, urgent safety measures, safety reporting

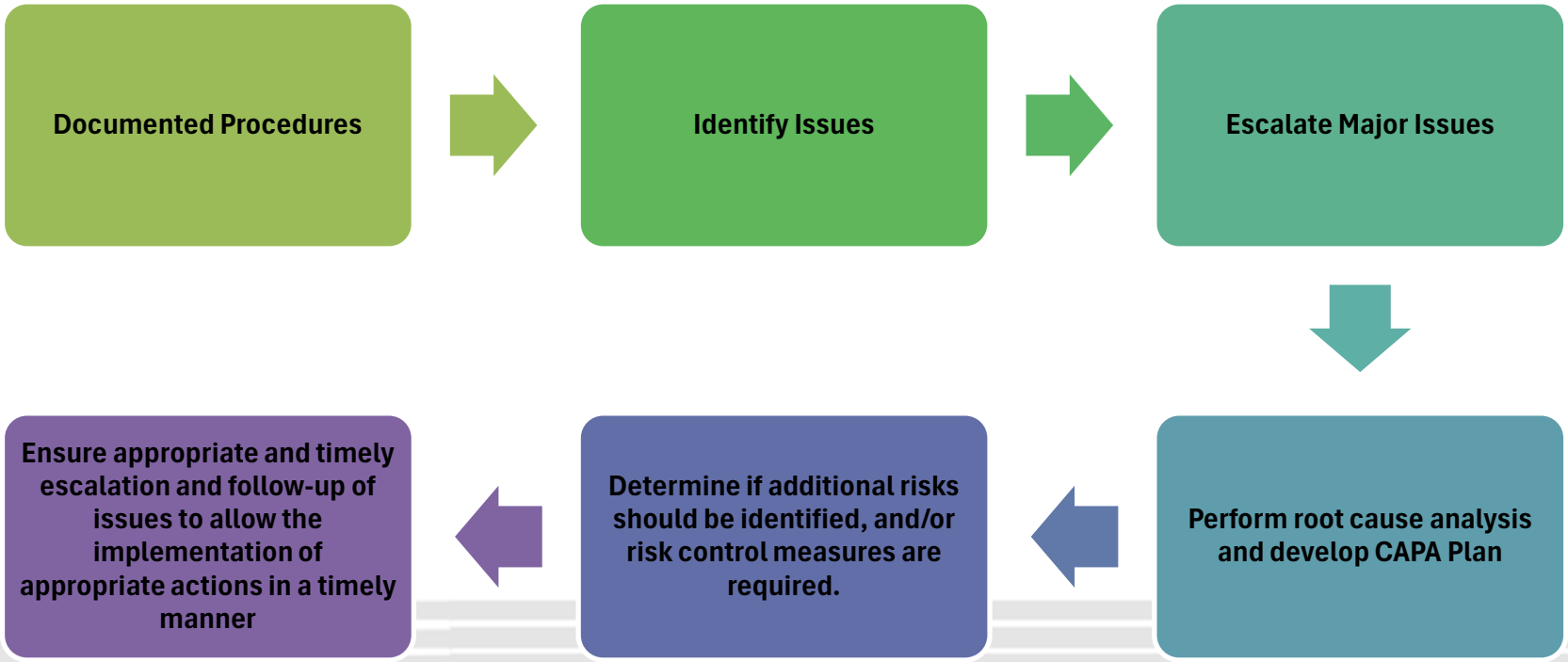
Ref.: IOCTB Learn slide decks on Sponsor Oversight of IITs workshop
https://www.hsa.gov.sg/clinical-trials/learning

OFFICIAL OPEN

How should the sponsor manage issues in a clinical trial?

- **Quality Issues**
  - Usually defined in sponsor's documented procedures. For e.g.,
    - Quality Issues may be defined as **an incident, event, behavior, or activity** that may have a **meaningful impact** on the **safety or privacy of participants**, the **credibility of trial results**, or the **confidentiality of sponsor information**.

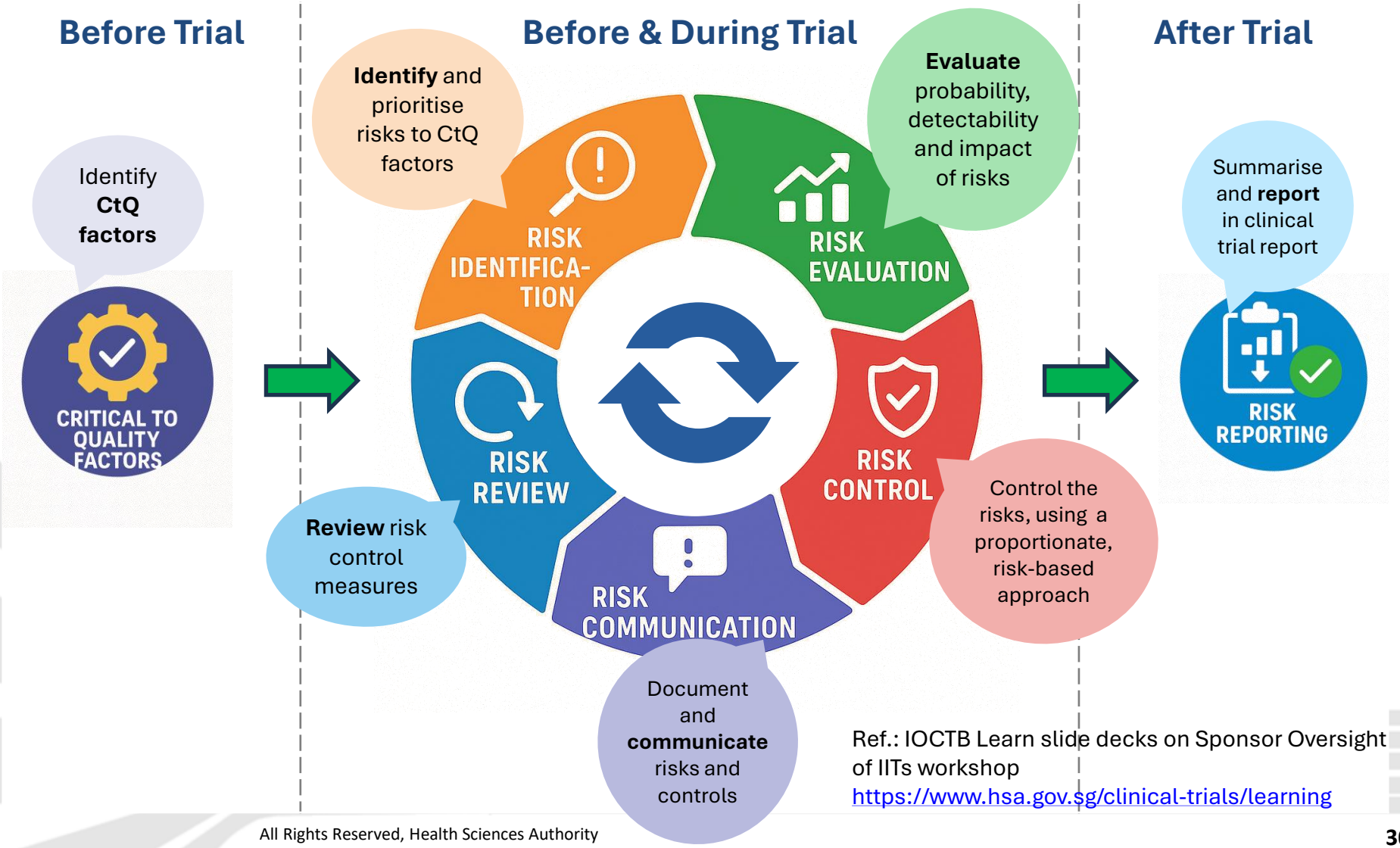
  - **Issue Management**



Quality Management

- **Major GCP Inspection Findings:**
  - The sponsor **did not adopt an adequate risk-based approach to quality management** to ensure the quality of IITs regulated by HSA.
    - **Lack of documented procedures** for **risk-based quality management for IITs regulated by HSA**.
    - Lack of risk assessment of **IITs**

What are the requirements for risk-based quality management (RBQM) for clinical trials?



Ref.: IOCTB Learn slide decks on Sponsor Oversight of IITs workshop
https://www.hsa.gov.sg/clinical-trials/learning

How are risks usually assessed for a clinical trial?

Critical to Quality (CtQ)Factor	Risk Identification	Risk Evaluation					Risk Control
		Probability	Impact	Detectability	Risk Score	Risk Classification	

- Probability: Low (1), Medium (2), High (3)
- Impact: Low (1), Medium (2), High (3)
- Detectability: High (1), Medium (2), Low (3)
- Risk Score = Probability x Detectability x Impact

Risk Score Matrix
1-3: Low risk
4-17: Medium risk
18-27: High risk

How can risks be assessed for IITs that are not intended to support product registration?

Aspects of a Clinical Trial	Risk	Probability (P)	Impact (I)	Risk Score (P x I)	Risk Classification (Low/Medium/High)	Risk Controls
Trial Design						
Phase of Clinical Trial						
Trial Population						
PI's Experience						
Resources						
Facilities						
Informed Consent Requirements						
Registration Status of IP						
Randomisation						
Blinding						
Data Collection and Handling						
Trial Monitoring						

- Probability: Low (1), Medium (2), High (3)
- Impact: Low (1), Medium (2), High (3)

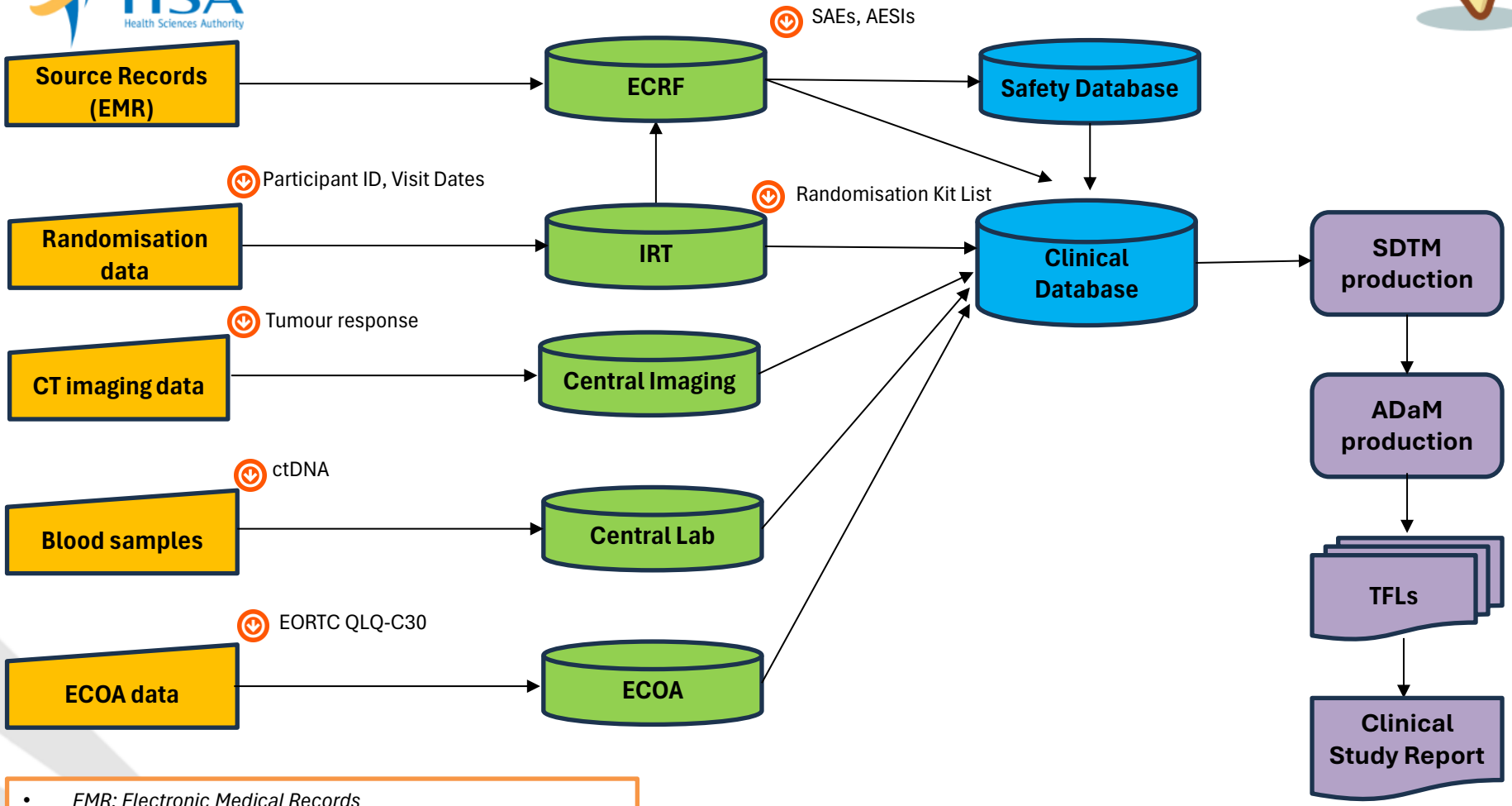
Risk Score Matrix (P x I)
1: Low risk / 2-4: Medium risk / 6-9: High risk

Data Collection and Handling

- **Major GCP Inspection Findings:**

  - **Lack of adequate documentation** maintained for the **validation of the electronic Case Report Form (eCRF)** for an IIT.

Example of a Data Flow Diagram



- *EMR: Electronic Medical Records*
- *ECOA: Electronic Clinical Outcome Assessments*
- *IRT: Interactive Response Technology*
- *ECRF: Electronic Case Report Form*
- *SDTM: Study Data Tabulation Model*
- *ADaM: Analysis Data Model*
- *TFL: Tables, Figures & Listings*
- *Critical Data (e.g., primary and key secondary endpoint data)*

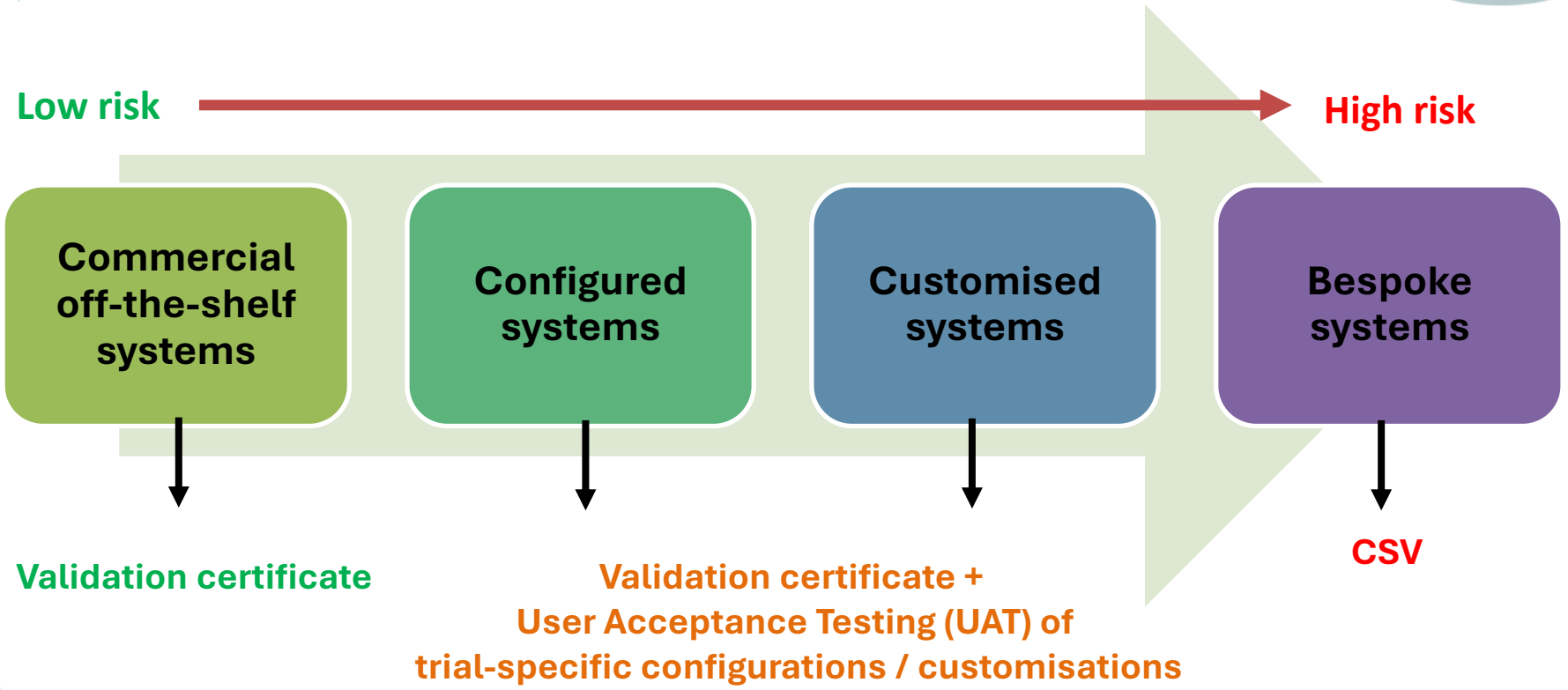
What are the requirements for Computerised System Validation?

- A **process** of **establishing and documenting** that the **specified requirements** of a **computerised system** can be **consistently fulfilled** from **design until decommissioning** of the system or **transition** to a new system.
- The **approach to validation** should be **based on a risk assessment** that takes into consideration the **intended use of the system** and the **potential of the system to affect trial participant protection** and the **reliability of trial results**.
  - **Focus on the important computerised systems used for the clinical trial.**
- **Comprises:**
  - ❑ User requirements and specifications
  - ❑ Validation plan
  - ❑ Test execution and reporting
  - ❑ System release
  - ❑ Periodic review
  - ❑ Change control

❑ The trial-specific systems (including updates resulting from protocol amendments) should only be **implemented, released or activated for individual investigator sites after all necessary approvals for the clinical trial relevant to that investigator site have been received.**

Ref.: IOCTB Learn slide decks on Sponsor Oversight of IITs workshop
https://www.hsa.gov.sg/clinical-trials/learning

How can a proportionate, risk-based approach be applied to CSV?



- **Configuration** sets up a system **using existing (out-of-the-box) functionality without altering the underlying code**. It **does not require programming knowledge** and **may be performed by a trained user**. For e.g., adding text fields in an eCRF (e.g., REDCap) in accordance with the trial protocol.

- **Customisation modifies and/or adds to existing functionality by custom coding.** It **requires programming knowledge**, and is **usually performed by an IT personnel**.

Ref.: IOCTB Learn slide decks on Sponsor Oversight of IITs workshop
https://www.hsa.gov.sg/clinical-trials/learning

How can a proportionate, risk-based approach be applied to CSV for IITs?

Configuration of computerised system

Quality Control (QC) check by another staff

Approval by Principal Investigator (PI)

Ref.: IOCTB Learn slide decks on Sponsor Oversight of IITs workshop
https://www.hsa.gov.sg/clinical-trials/learning

Investigational Product (IP) Management

- **Major GCP Inspection Finding:**

  - **Information relating to IP release** was **not recorded, handled and stored** in a way that allowed its **accurate reporting, interpretation and verification.**

    - IP release was performed via a computerised system:
      - Lack of documentation of the essential records that had been reviewed for IP release.

How should IP release be performed via a computerised system?

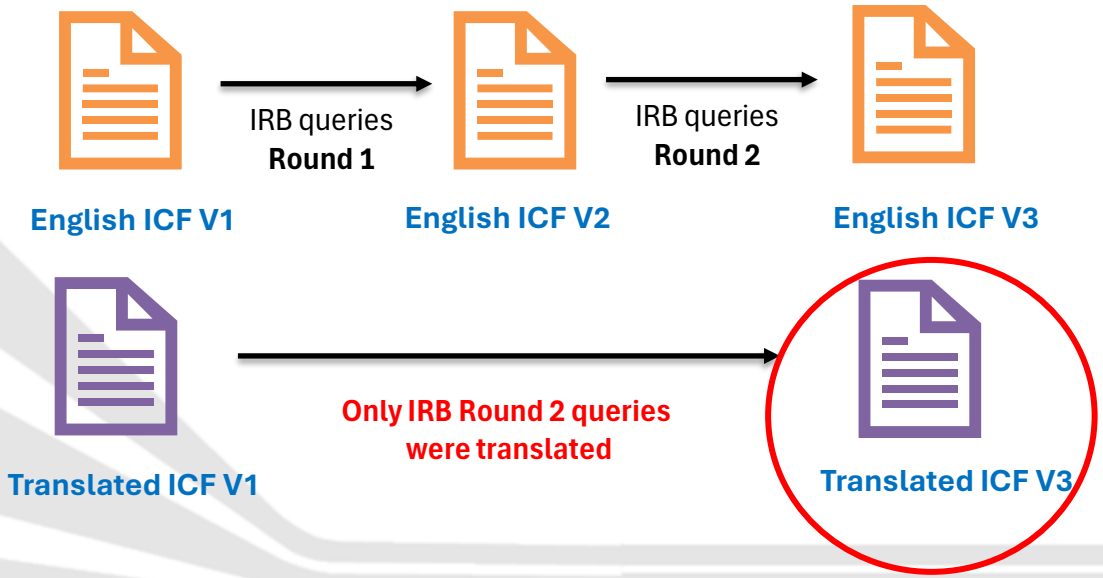
- **IP release – via paper format**

- **IP release via a computerised system**
  - E.g., via sponsor's Clinical Trial Management System (CTMS) / Electronic Trial Master File (eTMF)
  - Computerised system should **be fit for purpose**.
    - Specify the **essential records (including version references)** that were reviewed for IP release;
    - Enable **comments** to be included, if applicable; and
    - Demonstrate **attributability** of the approval (e.g., who and when)

Protocol Compliance

- **Major GCP Inspection Finding:**

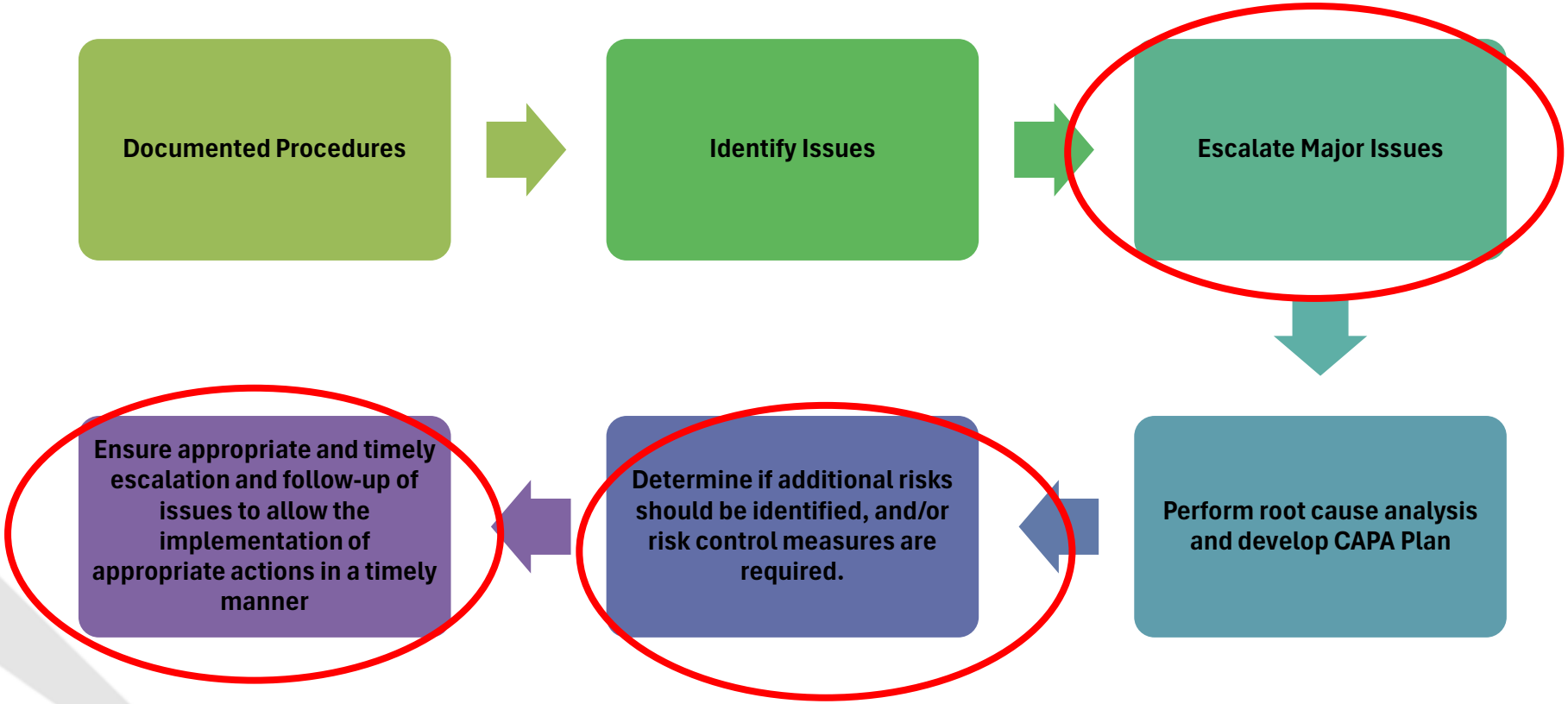
  - The sponsor **did not maintain adequate sponsor oversight of the service provider,** and **take prompt actions to secure compliance** for the deviations and non-compliances involving errors in preparing and translating informed consent materials.



- **Red flags:**
  - Investigator site staff alerted Monitor about translation errors.
  - Monitor did not promptly escalate the issue to the sponsor.
  - Initial CAPA Plan was ineffective, as translation errors were repeated.

How should major issues be managed?

- **Issue Management**



Quality Assurance & Quality Control

- **Major GCP Inspection Finding:**

  - The **sponsor did not maintain adequate SOPs** for the **sponsor's trial-related duties and functions** undertaken for HSA-regulated IITs.

What are the documented procedures that should be maintained by sponsors of IITs?

Trial start-up

- Clinical Trial Agreements
- Budgeting
- Risk-based Quality Management
- Initial application to IRB
- Initial application to HSA
- Data collection and handling
- Using Computerised Systems
- Trial Master Files

Trial Conduct

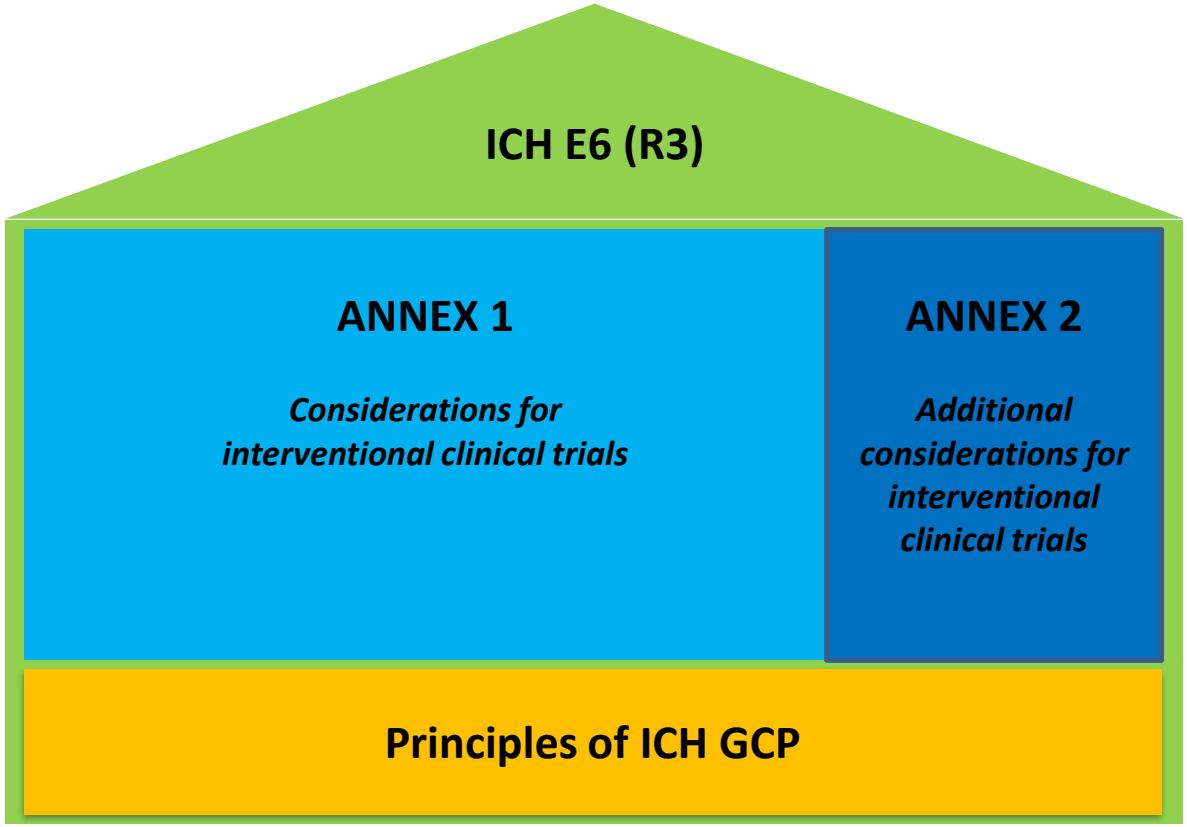
- Investigator Site Monitoring
- Continuing Review / Trial Status Reports
- Study / Substantial amendments
- Deviations, Non-compliances, Serious Breaches & Urgent Safety Measures
- Safety Assessment and Safety Reporting

Trial Completion

- Trial Completion / Termination

Ref.: IOCTB Learn slide decks on Sponsor Oversight of IITs workshop
https://www.hsa.gov.sg/clinical-trials/learning

ICH E6 (R3) GCP guideline Overview



Principles and Annex 1 of ICH E6 (R3) GCP guideline were implemented in Singapore w.e.f. 1 Jan 2026!

Looking Back at 2025

- **Stakeholder engagement**
  - Training
    - HSA-SCRI Public Webinar [28 Feb 2025]
    - Workshop of Sponsor Oversight of IITs [14 Nov 2025]
  - Feedback
  - Queries
- **Updates to HSA website**
  - Regulatory Guidances
  - IOCTB Learn
  - Conducting Clinical Trials
  - Template Forms
  - GCP Inspections
- **ICH E6 (R3) Expert Working Group**
  - Development of training materials [Refer to ICH training library]
- **Updates to internal SOPs**

Looking ahead in 2026

- **Step 4 of Annex 2 of ICH E6 (R3) GCP guideline** – [Additional considerations for interventional clinical trials involving use of decentralised elements, pragmatic elements or Real World Data (RWD)]
  - Targeted to be published ~ Q2 2026
- **Continued involvement in ICH E6 (R3) Expert Working Group**
  - Check out the ICH training library!
- **Assessing the transition to the ICH E6 (R3) GCP guideline through GCP inspections**
  - Reviewing sponsor's gap analysis
  - Adopting a facilitatory approach to plug gaps
- **Development of new regulatory guidances**
  - Tell us your wish list!

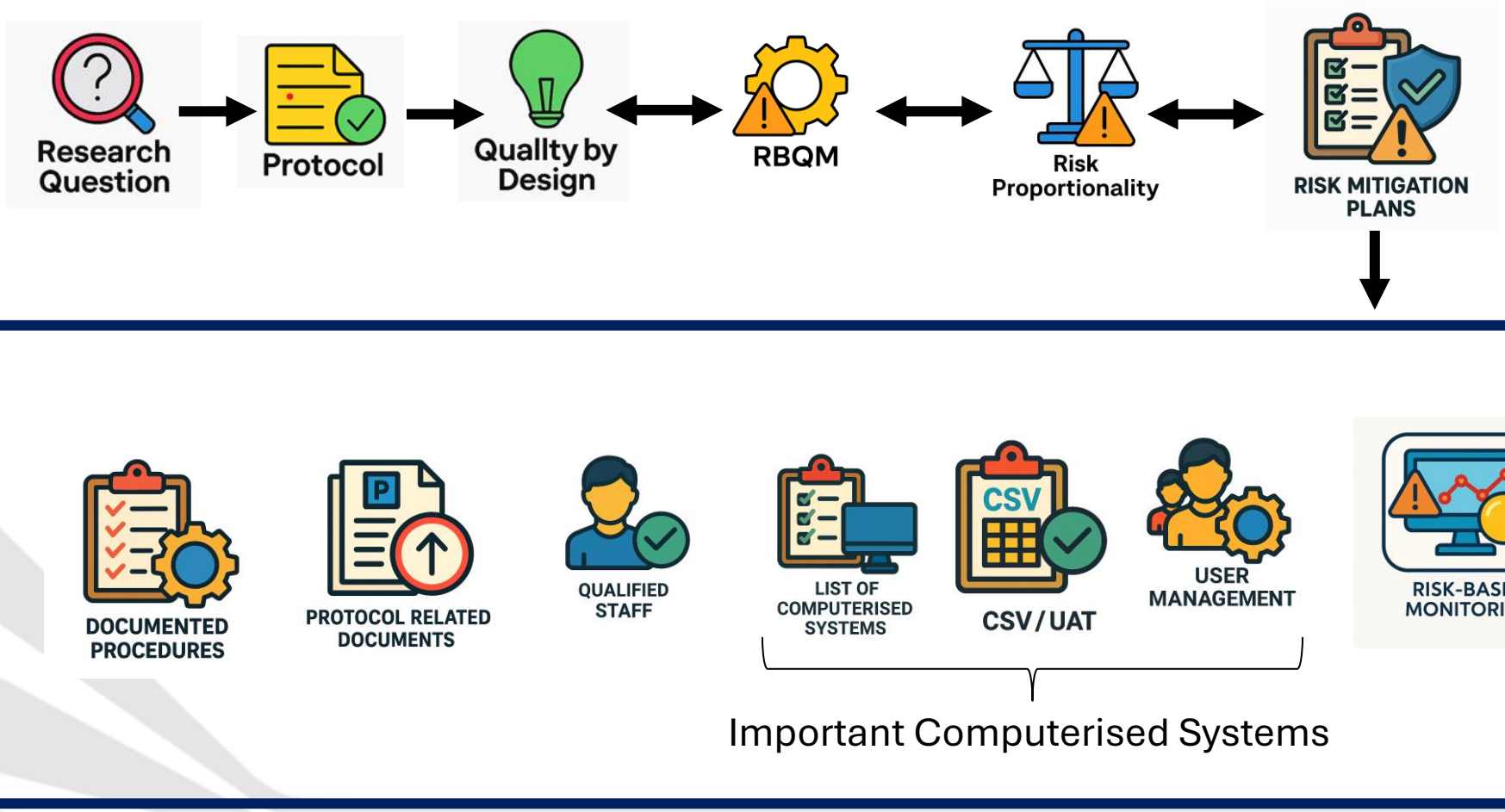
Conclusion

- **ICH E6 (R3) GCP guideline:**
  - Implemented in Singapore since 1 Jan 2026!
  - Applies to interventional clinical trials of investigational products that are intended to be submitted to Regulatory Authorities.
  - Principles of GCP may be applicable for other interventional clinical trials of investigational products that are not intended to support marketing authorisation applications, in accordance with local requirements.

- **Important to apply the key concepts throughout the ICH E6 (R3) GCP guideline:**
  - Fitness for Purpose
  - Quality by Design (QbD)
  - Proportionate, risk-based approach
  - Risk-based Quality Management (RBQM)

- It is always better to prepare, than repair!

Achieving Fit for Purpose Clinical Trial Quality



References

- **ICH E6 (R3) Good Clinical Practice (GCP) guideline**
  https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

- **ICH training library for ICH E6 (R3) training modules**
  https://www.ich.org/page/training-library

- **HSA website**
  - Clinical trials and Clinical Research Materials regulations
  - Regulatory Guidances
  - IOCTB Learn
  - Conducting Clinical Trials
  - Template Forms
  - GCP Inspections

Thank you!

www.hsa.gov.sg

We welcome your queries!

HSA_CT@hsa.gov.sg