Sponsor Oversight of Investigator-Initiated Trials (IITs)

14 Nov 2025

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OUTLINE

- Definition of a Sponsor
- Clarifying differences between ‘delegate’ and ‘transfer’
- Clarifying differences between ‘responsibility’ and ‘oversight’
- Sponsor Oversight
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Definition of a Sponsor

- An **individual, company, institution, or organisation** that takes responsibility for the **initiation, management and/or financing** of a clinical trial.

- The sponsor is responsible to **implement and maintain quality assurance and quality control systems** to ensure that clinical trials are conducted in **compliance** with the protocol, Good Clinical Practice, applicable regulatory requirements and documented procedures.

- The sponsor should be a **locally registered business entity registered** with the Accounting and Corporate Regulatory Authority **(ACRA)** in Singapore.

Understanding the Role of the Local Sponsor in Investigator-Initiated Trials (IITs)

Who is the local sponsor for an IIT?

- Usually the local healthcare institution, where the clinical trial is conducted.

What are the responsibilities of the local sponsor of an IIT?

- All the sponsor responsibilities, as outlined in the applicable regulations and GCP.
- The sponsor's duties and functions for IITs are usually shared between the sponsor and the investigator.

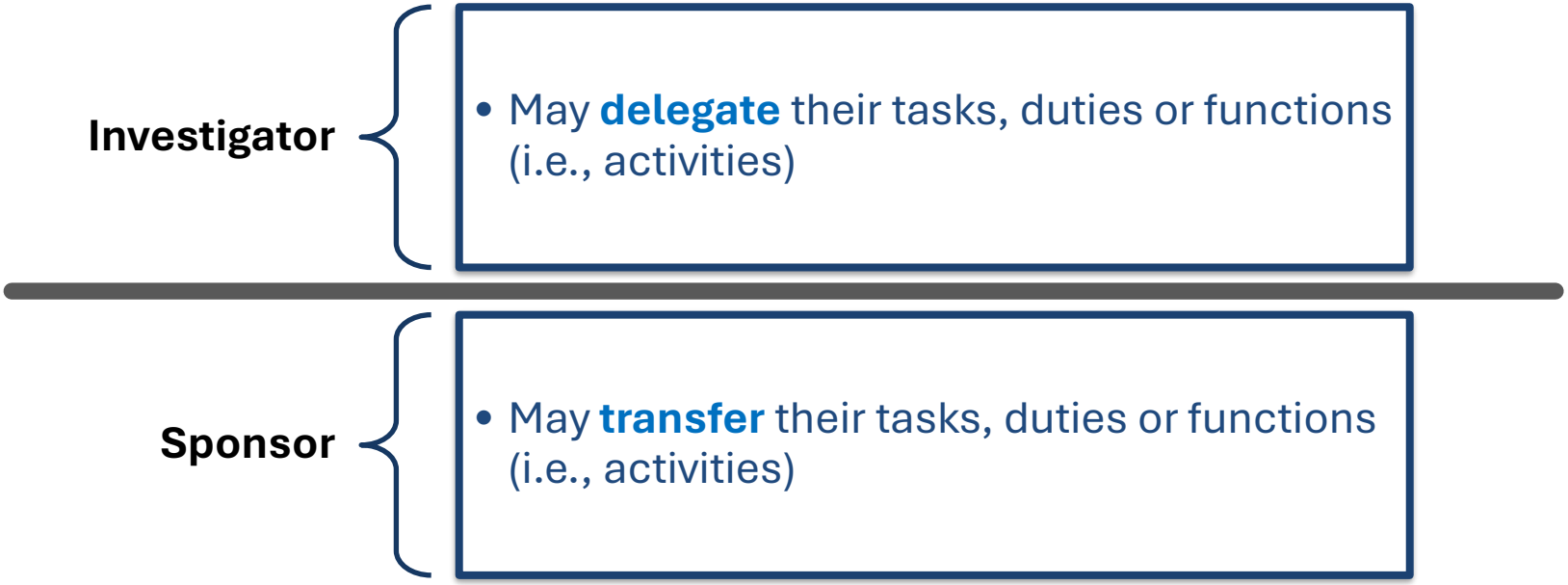
How can the local sponsor of an IIT maintain sponsor oversight?

- Consider setting up a Research Office or authorising a department to maintain sponsor oversight of IITs.

Sponsor Declaration in CT Application Form

Declaration for Sponsor/Lead Sponsor	
1.	I, on behalf of my company, confirm that the information submitted in this application is true and accurate.
2.	I, on behalf of my company shall abide by the Health Products Act, the Health Products (Clinical Trials) Regulations, any requirement imposed by the relevant Institutional Review Board, and any other conditions imposed by the Health Sciences Authority in the conduct of the clinical trial.
3.	I, on behalf of my company agree to the publication of information provided in the fields marked ^, and subsequent changes to such information, in a publicly accessible Clinical Trials Register.
4.	I, on behalf of my company, shall inform the Health Sciences Authority of any substantial changes to the information submitted in the application.
5.	I, on behalf of my company, shall submit status reports of the clinical trial every 6 months and when there is a change to the status of the clinical trial to the Health Sciences Authority.
6.	I, on behalf of my company, undertake to indemnify and hold the Health Sciences Authority harmless against all actions, claims or proceedings in respect of any loss, injury or death of any person whomsoever arising out of or in connection with the clinical trial.
7.	As a lead sponsor, I, on behalf of my company, shall evaluate on an on-going basis the safety of the investigational therapeutic product(s) being tested or used in the trial.
8.	As a lead sponsor, I, on behalf of my company, shall promptly notify all participating site sponsors and principal investigators of any information which suggests that the safety of subjects of the trial could be adversely affected (including any unexpected serious adverse drug reactions), and any findings which could impact the conduct of the trial.
9.	As a lead sponsor, I, on behalf of my company, shall ensure that all unexpected serious adverse drug reactions and serious breaches of the trial protocol, the principles of Good Clinical Practice, or the Health Products (Clinical Trials) Regulations are reported to the Health Sciences Authority in accordance with applicable regulatory requirements.
10.	As a lead sponsor, I, on behalf of my company, shall be responsible for all trial-related regulatory submissions and notifications to the Health Sciences Authority.

Clarifying differences between ‘delegate’ and ‘transfer’

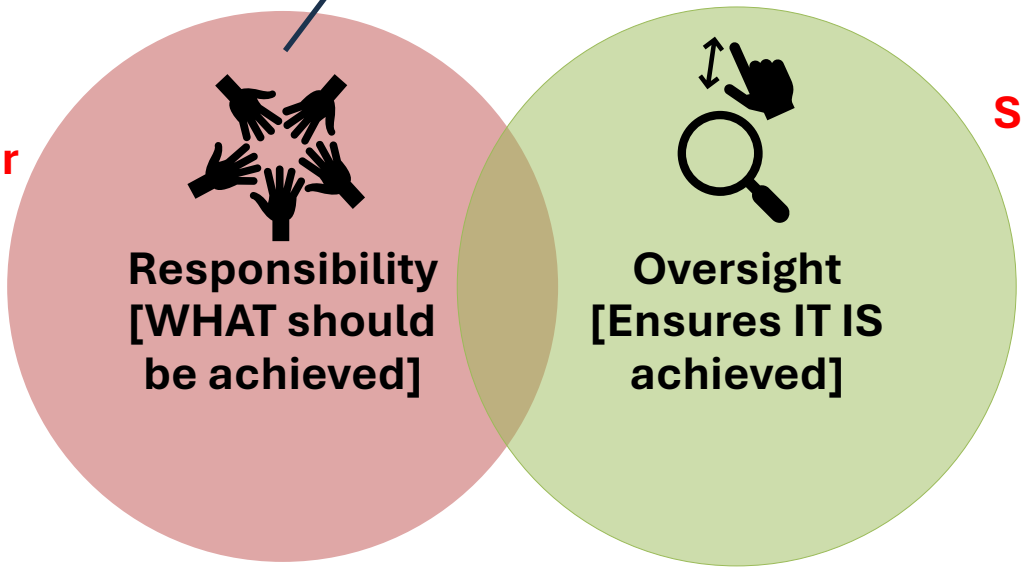


The sponsor and investigator retain overall responsibility for their respective activities, and should maintain appropriate oversight of the activities.

Ref: Principle 10 of ICH E6 (R3) GCP Guideline

Clarifying differences between ‘responsibility’ and ‘oversight’

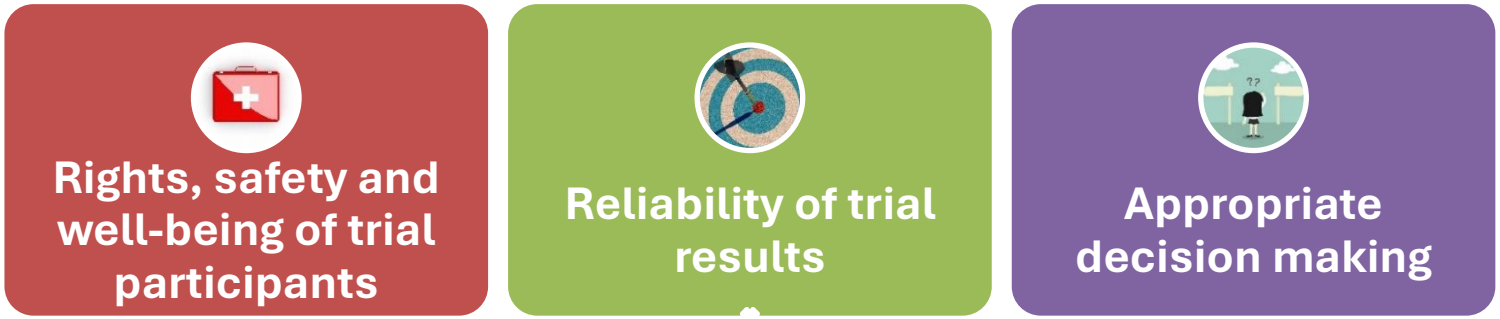
Tasks, duties and functions (i.e., activities) of parties involved in a clinical trial – primarily the investigator and sponsor



Ensures that the activities are performed in compliance with the protocol, GCP, applicable regulations and documented procedures.

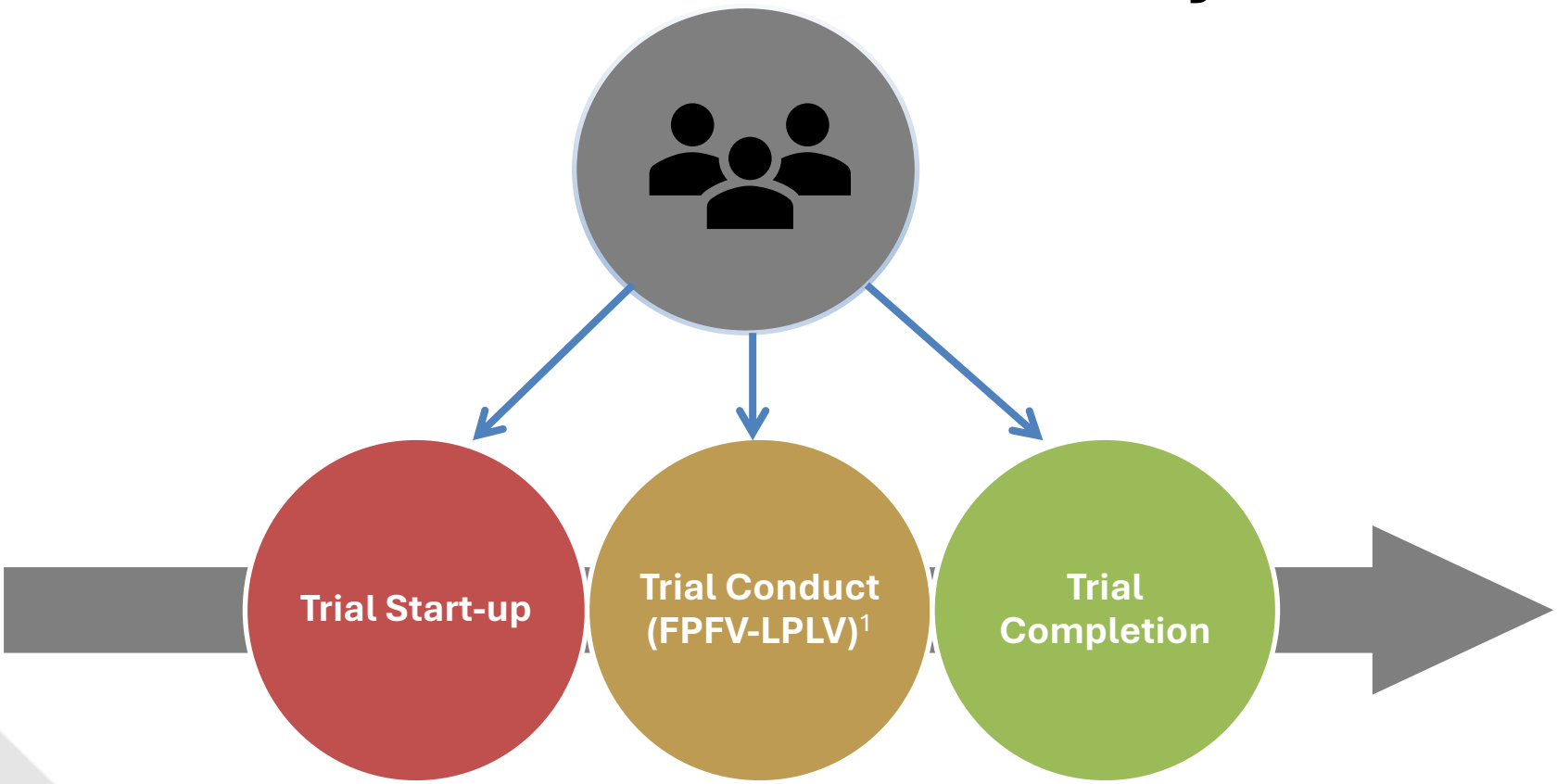
Sponsor Oversight
WHY is it important?

- **Why is sponsor oversight important?**
  - To ensure that the **trial design**, **trial conduct**, **processes** and **information and data generated** are of **sufficient quality** to ensure:

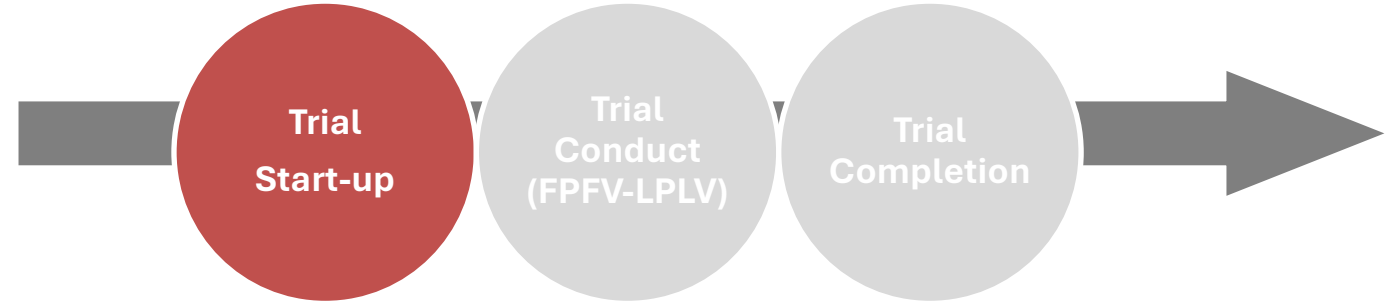


- **Approach:**
  - The **range and extent of oversight** measures should be **fit for purpose,** and tailored to the **complexity of and risks associated with the trial**.

Sponsor Oversight Across the Clinical Trial Lifecycle



1: ***First Patient First Visit (FPFV); Last Patient Last Visit (LPLV)***



RISK-BASED QUALITY MANAGEMENT

★★★

Adopt a **proportionate** and **risk-based approach** to **quality management**.

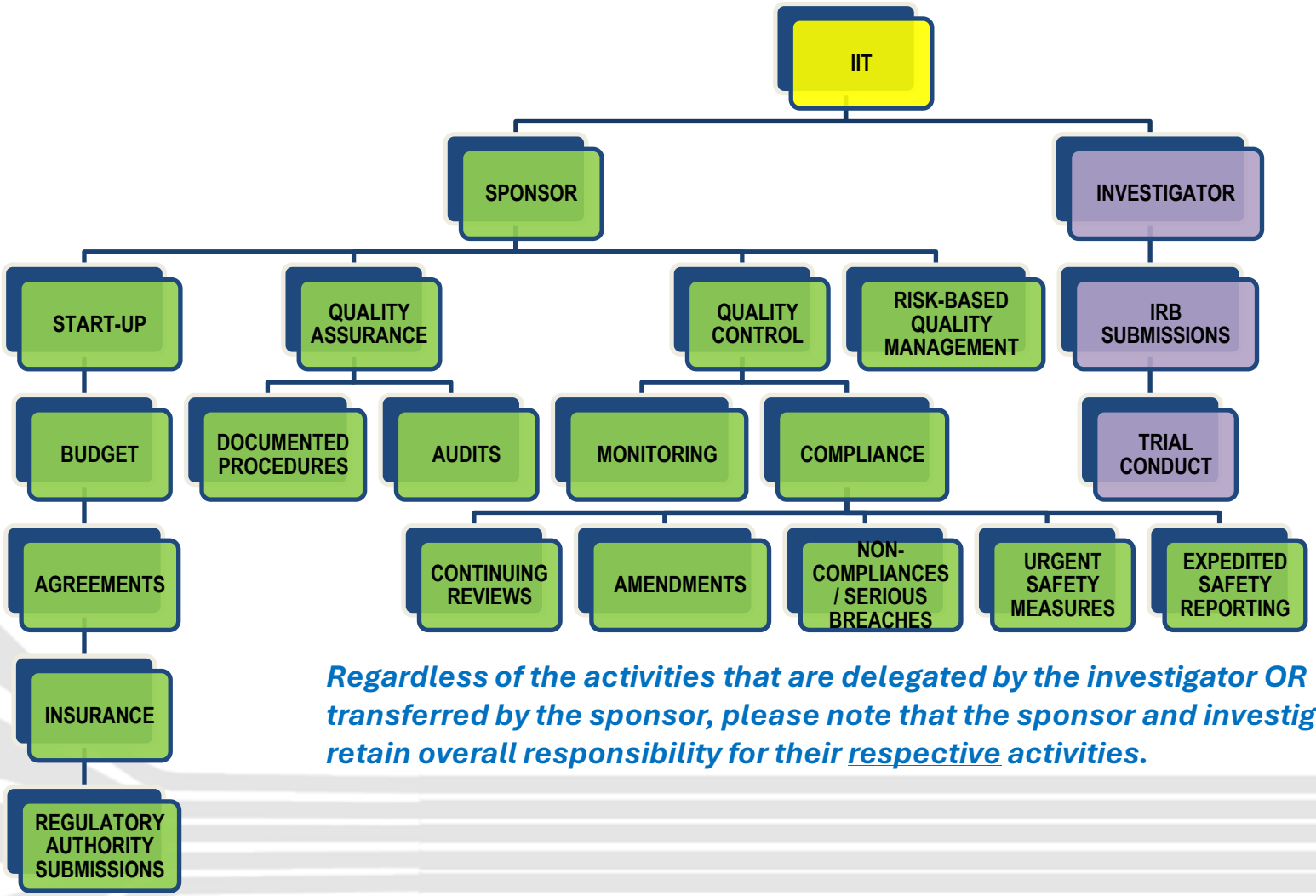
ALLOCATION OF ACTIVITIES

Prior to initiating clinical trial activities, the sponsor should **determine the roles and allocate their trial-related activities** accordingly.

The allocation of trial-related activities **between the sponsor and investigator** should be **documented.**

Allocation of sponsor's trial-related activities between sponsor and investigator for IITs

For example:



Regardless of the activities that are delegated by the investigator OR transferred by the sponsor, please note that the sponsor and investigator retain overall responsibility for their respective activities.

Regulatory Obligations of a sponsor as per CT regs (1)

	Suggested allocation for IITs regulated by HSA	
Regulatory obligations as per CT regs	**Sponsor**	**Investigator**
Obtain **Clinical Trial Authorisation (CTA), acceptance of Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC)** for the clinical trial.	✓	
Obtain approval for, or acceptance of notification of, **substantial amendments** to the clinical trial.	✓	
Ensure that information in the Investigator's Brochure (IB) is concise, objective and kept up to date.		✓
Ensure that the **clinical trial is conducted by or under the supervision of a qualified PI.**	✓	
Ensure that the **clinical trial is conducted at location(s) specified in the clinical trial application.**	✓	✓

Regulatory Obligations of a sponsor as per CT regs (2)

	Suggested allocation for IITs regulated by HSA	
Regulatory obligations as per CT regs	**Sponsor**	**Investigator**
Carry out **functions of the sponsor**, and ensures any person to whom the sponsor has delegated to carry out the functions of the sponsor carries out their respective functions, **in accordance with the principles of Good Clinical Practice (GCP).**	✓	✓
Put and keep in place arrangements to **ensure compliance with the principles of GCP.**	✓	✓
Ensure appropriate investigational and auxiliary product labelling.		✓
Keep adequate **essential documents.**	✓	✓
Notify HSA of the **trial status** (including the suspension, termination and/or conclusion of the trial) within the stipulated timelines.	✓	

Regulatory Obligations of a sponsor as per CT regs (3)

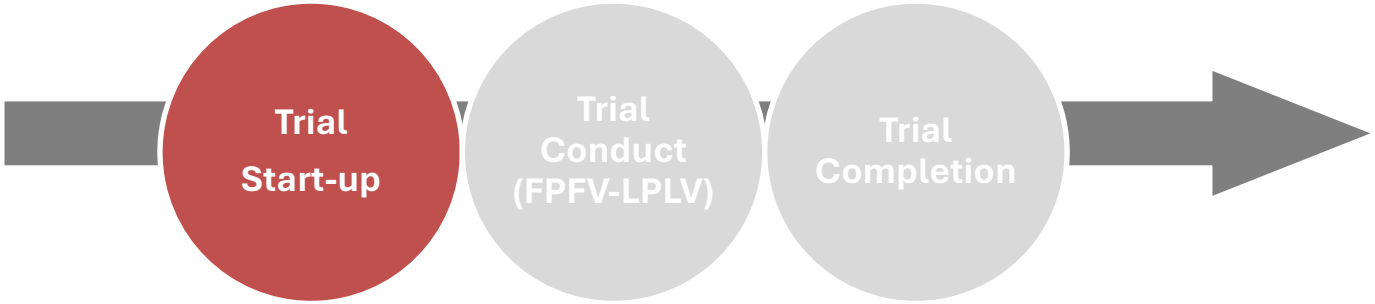
	Suggested allocation for IITs regulated by HSA	
Regulatory obligations as per CT regs	**Sponsor**	**Investigator**
Notify HSA of **serious breaches** within the stipulated timelines.	✓	
Notify HSA of **urgent safety measures** taken to protect trial participants against immediate hazard within the stipulated timelines.	✓	
Report **unexpected serious adverse drug reactions** and **medical devices adverse events** within the stipulated timelines.	✓	
Submit **final report** within the stipulated timelines.	✓	

Sponsor Responsibilities as per ICH E6 (R3) GCP Guideline (1)

	Suggested allocation for IITs regulated by HSA	
Sponsor Responsibility	**Sponsor**	**Investigator**
Trial Design		✓
Resources		✓
Allocation of activities	✓	
Qualification & Training	✓	
Financing		✓
Agreements	✓	
Investigator Selection		✓
Communication with IRB & RA	✓ (HSA)	✓ (IRB)
Sponsor Oversight	✓	
Risk-Based Quality Management	✓	

Sponsor Responsibilities as per ICH E6 (R3) GCP Guideline (2)

	Suggested allocation for IITs regulated by HSA	
Sponsor Responsibility	**Sponsor**	**Investigator**
Quality Assurance & Quality Control (including monitoring)	✓	
Non-compliance	✓	
Safety Assessment and Reporting	✓	
Insurance / Indemnification / Compensation to Participants and Investigators	✓	
Investigational Product		✓
Data and Records		✓
Reports	✓	



REGULATORY SUBMISSIONS

Submit clinical trial application to **HSA for review and approval** prior to trial initiation

Trial Start-up | Trial Conduct (FPFV-LPLV) | Trial Completion

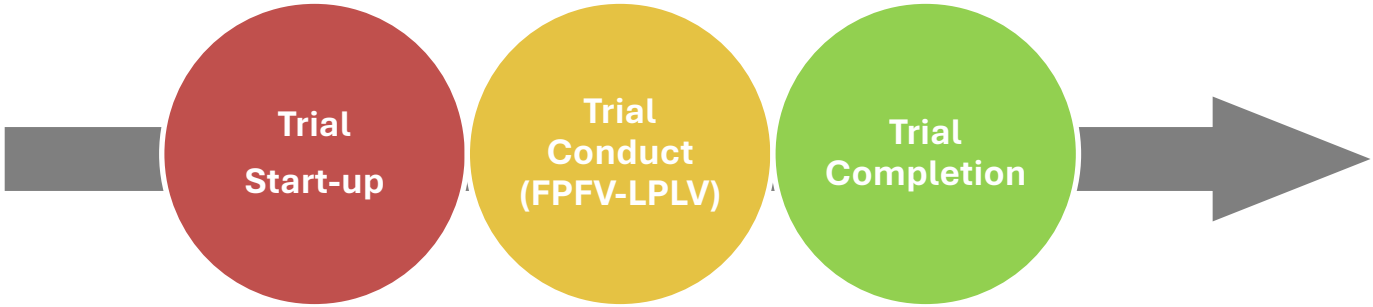
SERVICE PROVIDERS

Ensure that **agreements** are in place prior to initiating trial activities, and updated to **reflect significant changes** in the activities transferred.

Provide a copy of the **protocol and other protocol-related documents** for the service providers to perform their activities.

Ensure service providers provide **access to relevant information** to enable **selection and oversight by sponsor**.

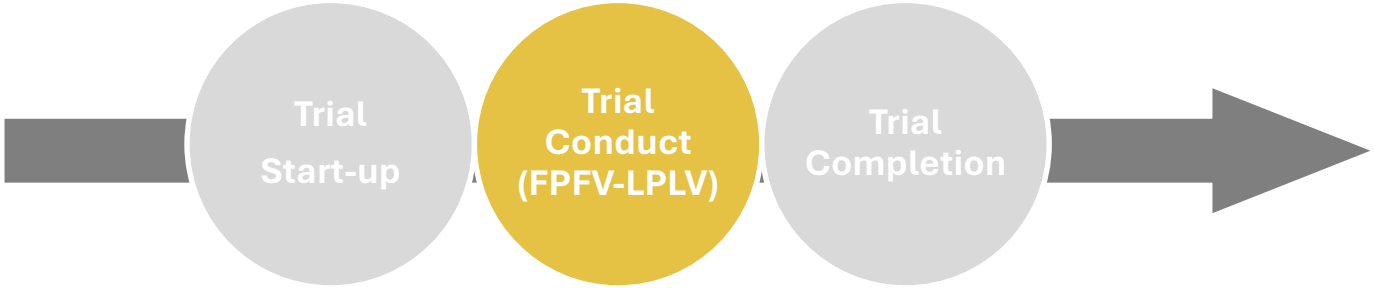
Ensure **trial-related activities performed by service providers** are conducted in accordance with relevant **GCP requirements.**



Sponsor responsibilities throughout the clinical trial lifecycle

QUALITY ASSURANCE AND QUALITY CONTROL

Establish, implement and maintain **appropriate quality assurance and quality control processes and documented procedures.**



MONITORING

Adopt a **proportionate, risk-based approach** to monitoring.

QUALITY CONTROL – Monitoring (1)

Monitoring is one of the principle **Quality Control (QC) activities** by a sponsor.

Monitoring

Appoint persons who are **not involved in the conduct of the trial** at the investigator site being monitored.

SELECTION OF MONITORS

Ensure that the **scope** of monitoring **adequately addresses** the **monitoring objectives**.

SCOPE OF MONITORING

Adopt a **proportionate, risk-based approach** to monitoring (i.e., adjust SDR/SDV plan depending on the risks to CTQ[2] factors).

MONITORING STRATEGY

[1]***: Source Data Review (SDR); Source Data Verification (SDV)***
[2]:***:Critical to Quality (CTQ)***

Monitoring

Monitoring Plan
(By the CRO / Sponsor's SOP)

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Monitoring

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Monitoring Visit Report
(Drafter: Monitor;
Approver: Monitor's line manager / Sponsor)

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Review and Documentation of review of the monitoring visit report by the sponsor

Monitoring Plan should be tailored to the identified potential safety risks, the risks to data quality, and/or other risks to the reliability of the trial results.

- ❑ **Type of monitoring** to be performed (e.g., on-site / remote)
- ❑ **Factors critical to quality** should be monitored *(i.e., attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results)*
- ❑ **Monitoring strategy** to ensure appropriate oversight of trial conduct
  - *Important to consider site capabilities and the potential burden (including frequency of monitoring, duration of monitoring, source data review (SDR) / source data verification (SDV) plan)*
- ❑ **Monitoring activities** to be performed
- ❑ **Monitoring methods and tools, and rationale** for their use
- ❑ **Applicable sponsor's SOPs** to be used

Monitoring

Monitoring Plan
(By the CRO / Sponsor's SOP)

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Monitoring

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Monitoring Visit Report
(Drafter: Monitor;
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Review and Documentation of review of the monitoring visit report by the sponsor

Monitoring involves a **broad range** of activities including, but **not limited to:**

- ❑ **Communication** with investigator sites;
- ❑ **Verification** of the investigator and investigator site staff qualifications and site resources, training
- ❑ **Review of essential records and information** using a range of approaches including source data review, source data verification, data analytics (for centralised monitoring) and visits to investigational site facilities undertaking trial-related activities

Monitoring

Monitoring Plan
(By the CRO / Sponsor's SOP)

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Monitoring

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Monitoring Visit Report
(Drafter: Monitor;
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Review and Documentation of review of the monitoring visit report by the sponsor

Monitoring Visit Report should include the following:

- ❑ **Summary** of what was reviewed;
- ❑ **Description** of significant findings;
- ❑ **Conclusions**
- ❑ **Follow-up actions**

Monitoring

Monitoring Plan
(By the CRO / Sponsor's SOP)

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Monitoring

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Monitoring Report
(Drafter: Monitor;
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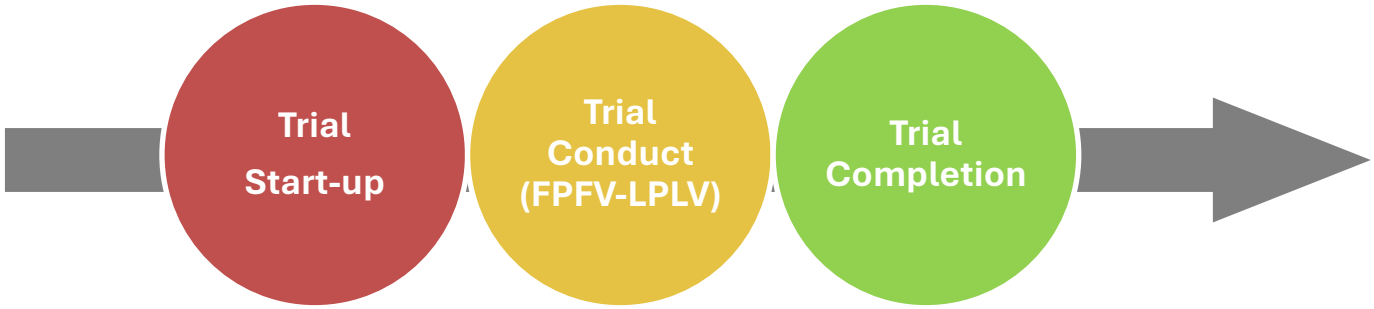
Review and Documentation of review of the monitoring visit report by the sponsor

The sponsor should **review** the monitoring visit reports in a timely manner, **document** their review and **take appropriate actions** on any issues requiring escalation.



SECURE COMPLIANCE

Perform a **root cause analysis, implement appropriate corrective and preventive actions** and **ensure adequacy of CAPA.**

QUALITY CONTROL – Secure Compliance (2)

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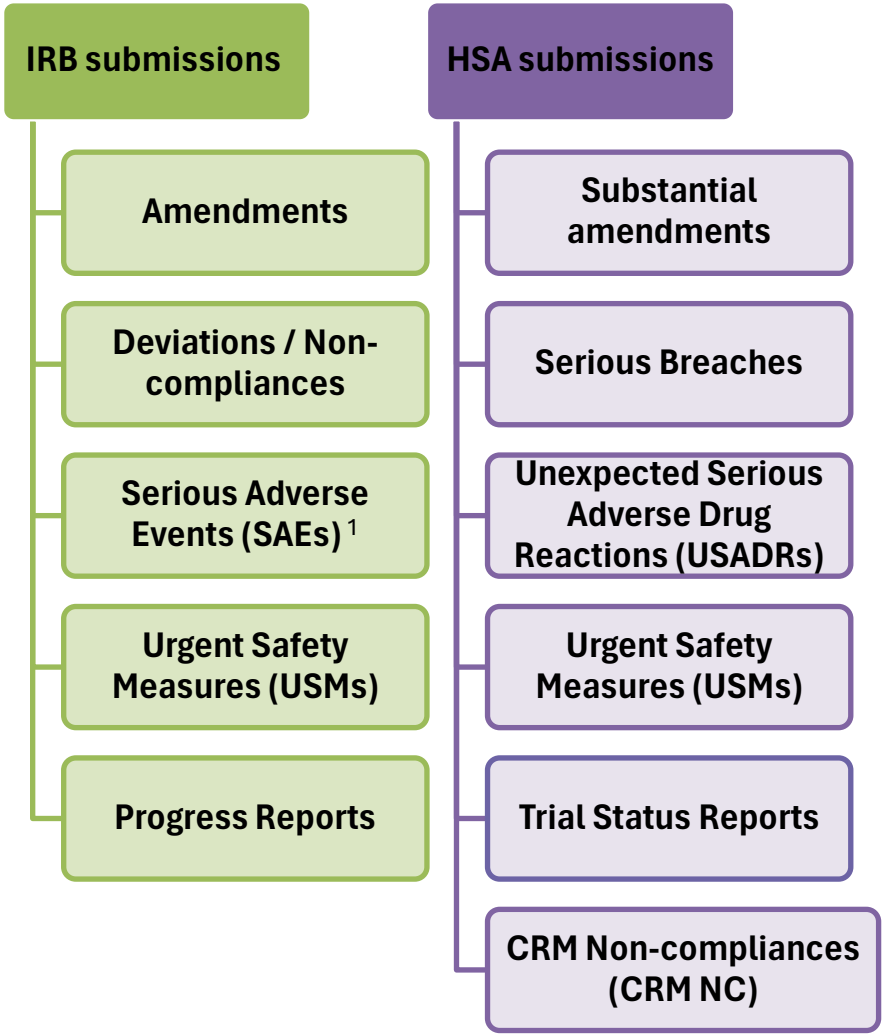


[1] : *In accordance with the respective IRB requirements;*
[2] : *If applicable*

QUALITY ASSURANCE

- **Having Documented Procedures**
  - ❑ Establishing Standard Operating Procedures (SOPs)
  - ❑ Training
- **Clear, concise, scientifically sound and operationally feasible protocol**
  - ❑ Training
- **Protocol-related documents (e.g., plans, manuals, work instructions, workflows, etc)**
  - ❑ Training
- **Audits (subject to availability of resources)**

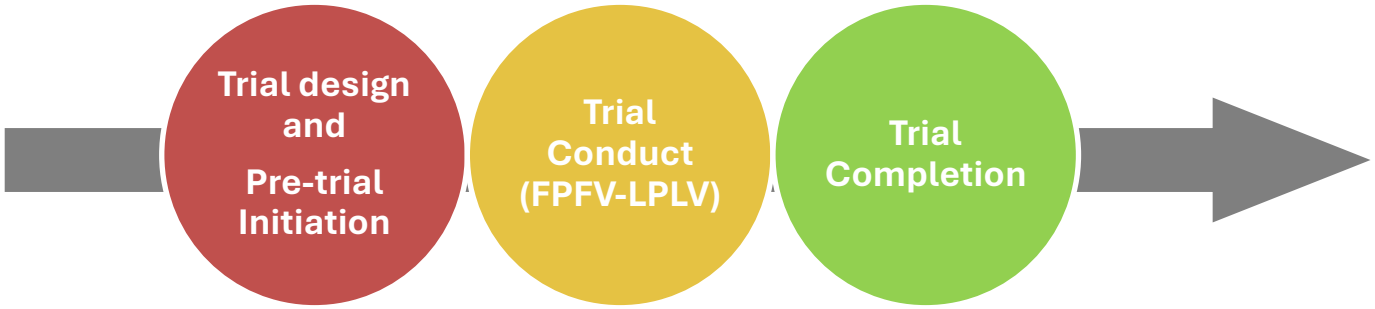
Trial Start-up

Trial Conduct (FPFV-LPLV)

Trial Completion

CLINICAL TRIAL REPORTS

Ensure that clinical trial reports, including interim reports, are provided to the regulatory authorities when the trial is completed or prematurely terminated.



Sponsor responsibilities throughout the clinical trial lifecycle

TIMELY ESCALATION / FOLLOW-UP OF ISSUES

The sponsor should ensure appropriate and timely escalation and follow-up of issues to allow implementation of appropriate actions in a timely manner.

Sharing of best practices for sponsor oversight

Tracking logs

- ❑ IRB and HSA approvals
- ❑ Trial monitoring status
- ❑ Trial Status Reports
- ❑ Serious breach (SB) notifications
- ❑ Urgent Safety Measure (USM) notifications
- ❑ Unexpected Serious Adverse Drug Reactions (USADR) notifications

Note: This list is non-exhaustive and these are just some of the examples.

Summary

The sponsor plays a critical and central role in the conduct and oversight of a clinical trial.

The local sponsor should maintain appropriate sponsor oversight of IITs regulated by HSA:

- **Allocation of sponsor's trial-related duties and functions**
- **Risk-based quality management**
- **Quality assurance**
  - Documented procedures for sponsor responsibilities
  - Protocol and protocol-related documents
- **Quality Control**
  - Investigator Site Monitoring
  - Securing compliance through continuing review, amendments, deviation / non-compliance / serious breach reporting, urgent safety measures, safety reporting

References

- Health Products (Clinical Trials) Regulations
- ICH E6 (R3) Good Clinical Practice (GCP) guideline
- ICH E8 (R1) Good Clinical Practice (GCP) Guideline
- HSA website
  - Conducting clinical trials [Sponsor]
  - Regulatory Guidance on Multi-Sponsor Investigator-initiated trials

Thank You!

We welcome your queries!

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