IOCTB LEARN

REGULATORY REQUIREMENTS FOR CLINICAL TRIALS OF THERAPEUTIC PRODUCTS AND CLASS 2 CELL, TISSUE AND GENE THERAPY PRODUCTS

Presented by:

Innovation Office & Clinical Trials Branch

Health Products Regulation Group

Health Sciences Authority

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Outline

- Scope of Clinical Trials Regulated Under the Clinical Trials Regulations
- Risk-Based Regulation of Clinical Trials
- Sponsor and Principal Investigator Responsibilities
- Clinical Trials Register

Learning Objectives

1. Describe the scope of clinical trials that are regulated under the Clinical Trials Regulations
2. Determine the correct submission route for a clinical trial application
3. Understand the roles and responsibilities of sponsors and principal investigators of clinical trials
4. Know how to access the Clinical Trials Register in Singapore

SCOPE OF CLINICAL TRIALS REGULATED UNDER THE CLINICAL TRIALS REGULATIONS

Regulatory Requirements for Clinical Trials

Singapore Statutes Online
https://sso.agc.gov.sg/

- **Health Products (Clinical Trials) Regulations**

  For clinical trials of:

  - *Therapeutic products, e.g., pharmaceutical drugs or biologics, PET radiotracers, contrast agents, contraceptives, anaesthetic agents*
  - *Class 2 Cell, Tissue and Gene Therapy Products (CTGTPs)*, e.g., Chimeric antigen receptor T cells (CAR T-cells), cultured chondrocytes*

- **ICH E6 Guideline for Good Clinical Practice (GCP)**

**CTGTPs are risk-stratified into two classes as follows:*

- *Class 2 CTGTP means a CTGTP other than a Class 1 CTGTP.*
- *Class 1 CTGTP means a CTGTP that*
  - *a) is the result of only minimal manipulation of human cell or tissue;*
  - *b) is intended for homologous use;*
  - *c) is not combined or used with a therapeutic product or a medical device; and*
  - *d) is assigned by HSA as a Class 1 CTGTP due to a lower health risk to a user of the product.*

Scope of Regulated Clinical Trials

Clinical Trials of **therapeutic products (TPs)** or **Class 2 cell, tissue and gene therapy products (CTGTPs)** intended to:

a) discover or verify its clinical, pharmacological or pharmacodynamic effects;

b) identify any adverse effects that may arise from its use;

c) study its absorption, distribution, metabolism and excretion; or

d) ascertain its safety or efficacy.

***Excluding Observational Trials*, i.e.,**

*A clinical trial of one or more **registered products**, where **all** of the following conditions are met in respect of each product:*

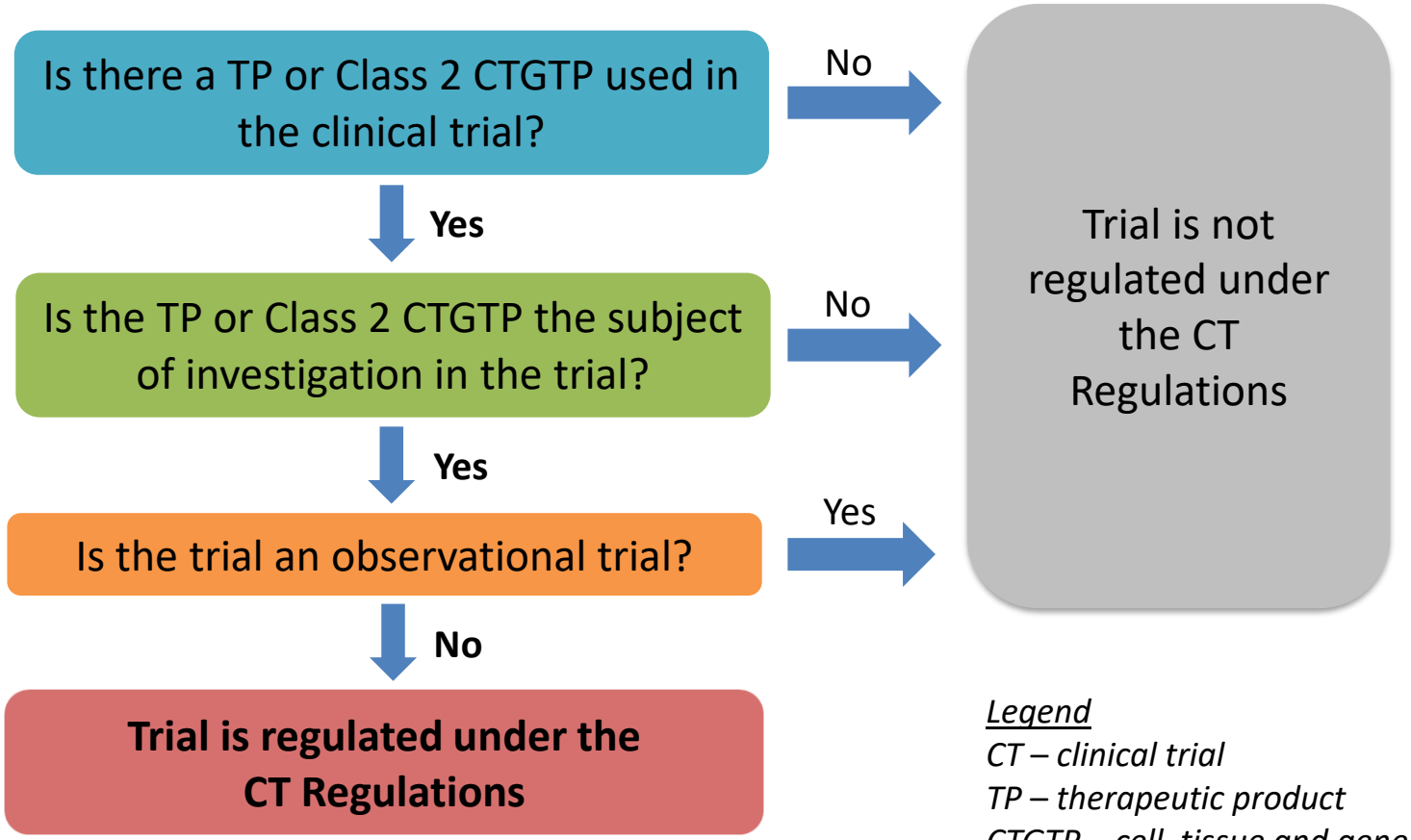
a) the product is prescribed in accordance with the terms of the product registration [i.e., on-label use]; and

b) decision to prescribe the product is clearly separated from decision to include patient in the trial; and

c) assignment of any patient in the trial to a particular treatment is not decided in advance by a protocol but falls within current practice [e.g., no randomisation].

Schematic Overview

Is the trial a regulated clinical trial?



Legend
CT – clinical trial
TP – therapeutic product
CTGTP – cell, tissue and gene therapy product

HSA Regulatory Guidance (GN-IOCTB-01): *Determination of Whether a Clinical Trial Requires Clinical Trial Authorisation, Clinical Trial Notification or Clinical Trial Certificate*

Case Study

Dr Tan is planning to undertake a clinical investigation to assess the safety and performance of a new endoscopic device that is US FDA-approved but not registered in Singapore yet.

Is this clinical trial regulated under the Health Products (Clinical Trials) Regulations?

- No. It is not regulated under the Clinical Trials Regulations.
- Currently, HSA does not regulate the conduct of clinical trials of **medical devices**. However, IRB approval should be obtained prior to conducting the trial.
- The import and supply of **medical devices** used is regulated.

  *(Please refer to the **Health Products (Medical Devices) Regulations** for details.)*

RISK-BASED REGULATION OF CLINICAL TRIALS

Risk-Based Regulation of Clinical Trials

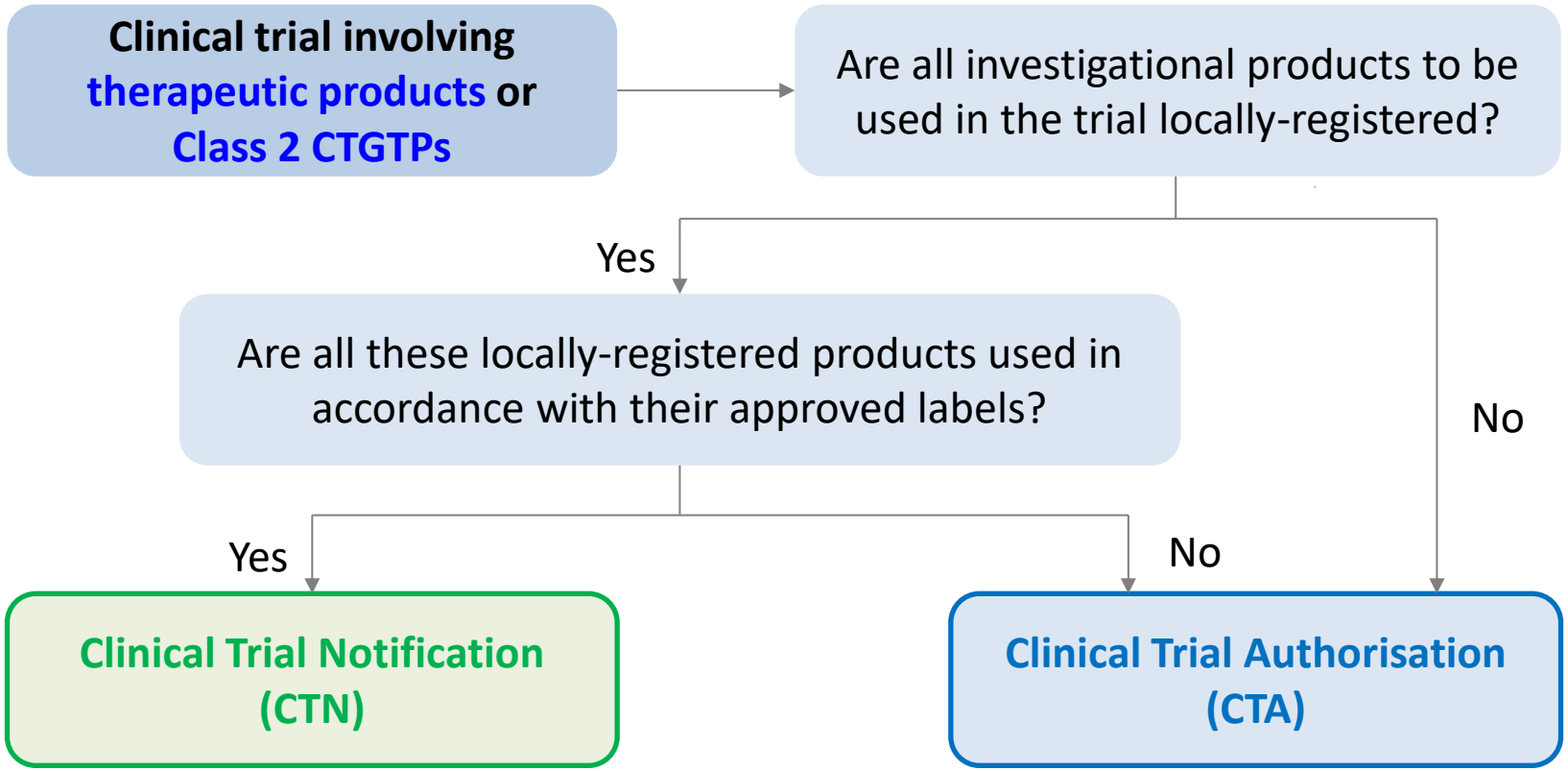
- **Clinical Trial Authorisation (CTA)**
  - Clinical Trials of
    - Locally unregistered TPs or Class 2 CTGTPs
    - Locally registered TPs or Class 2 CTGTPs not used in accordance with product registration*
    - Healthy volunteers (unless approved population is healthy individuals e.g. vaccine)

** Used for a different indication, patient population, dosing regimen, dosage form etc. from approved label*

- **Clinical Trial Notification (CTN)**
  - Clinical trials (including placebo-controlled trials) of locally registered TPs and Class 2 CTGTPs used in accordance with product registration

Schematic Overview

If regulated, which "submission route"?



HSA Regulatory Guidance (GN-IOCTB-01): *Determination of Whether a Clinical Trial Requires Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC)*

Summary of Submission Routes

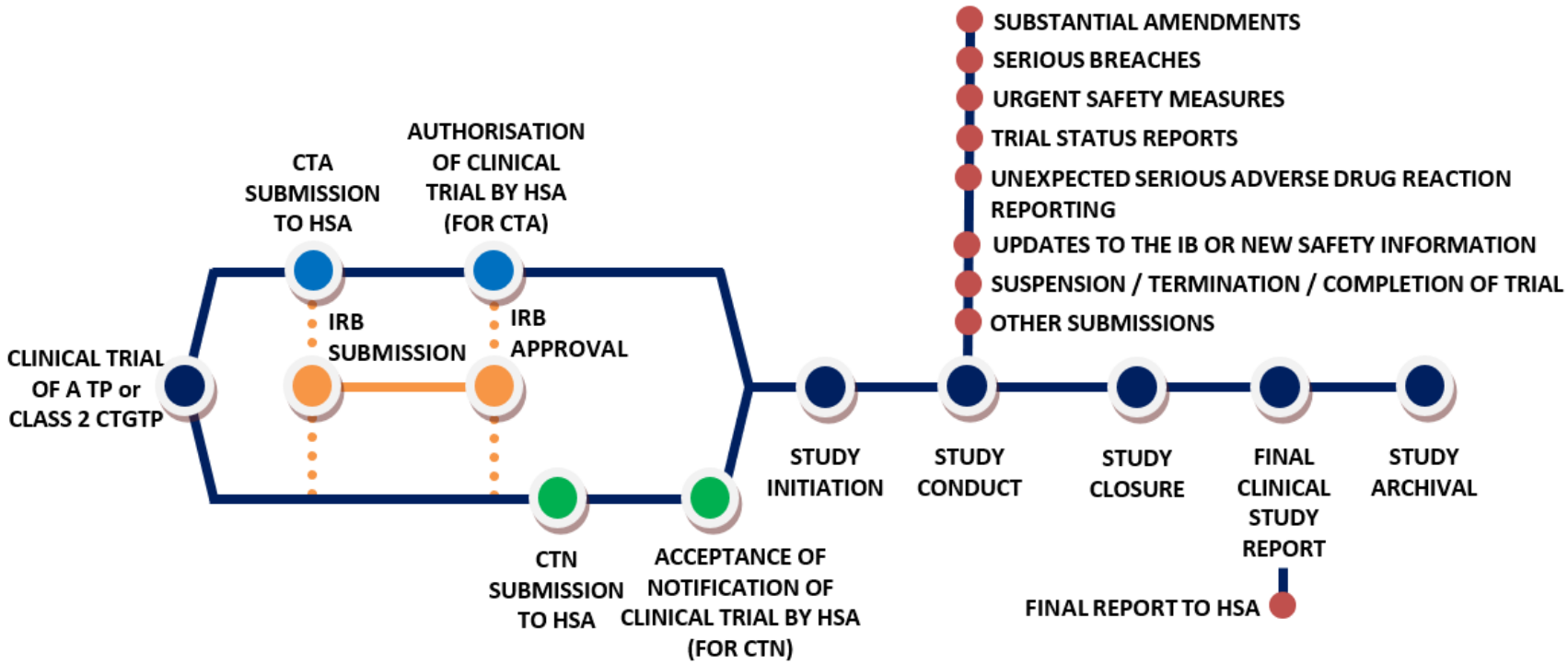
	Clinical Trial Authorisation (CTA)	Clinical Trial Notification (CTN)
Regulatory Processing Timelines (excluding stop-clock time)	• 30 working days • 15 working days (Phase 1 trials solely evaluating BE, BA, food effect, DDI) • 60 working days (CTGTP trials)	• 5 working days
Submission Dossier	• Trial Protocol • Informed Consent Form(s) • Investigator's Brochure / Approved Product Label • Principal Investigator's CV • GMP Certificate • Certificate of Analysis • CMC documents (when requested) • GMAC environmental risk assessment outcome, for CTGTPs or TPs containing genetically-modified organisms (e.g., viral vectors)	• Trial Protocol • Informed Consent Form(s) • Principal Investigator's CV • Approved Product Label • IRB Approval Letter
Substantial Amendments (e.g., Addition of Trial Site, Change of Sponsor or PI)	**Authorisation**	**Acceptance of Notification**

BE – Bioequivalence / BA – Bioavailability / DDI – Drug-drug Interaction
GMP – Good Manufacturing Practice
CMC – Chemistry, Manufacturing and Controls
GMAC – Genetic Modification Advisory Committee
CTGTP – Cell, Tissue and Gene Therapy Product
TP – Therapeutic Product
GCP – Good Clinical Practice

HSA Regulatory Guidance (GN-IOCTB-04): *Regulatory Requirements for New Applications and Subsequent Submissions*

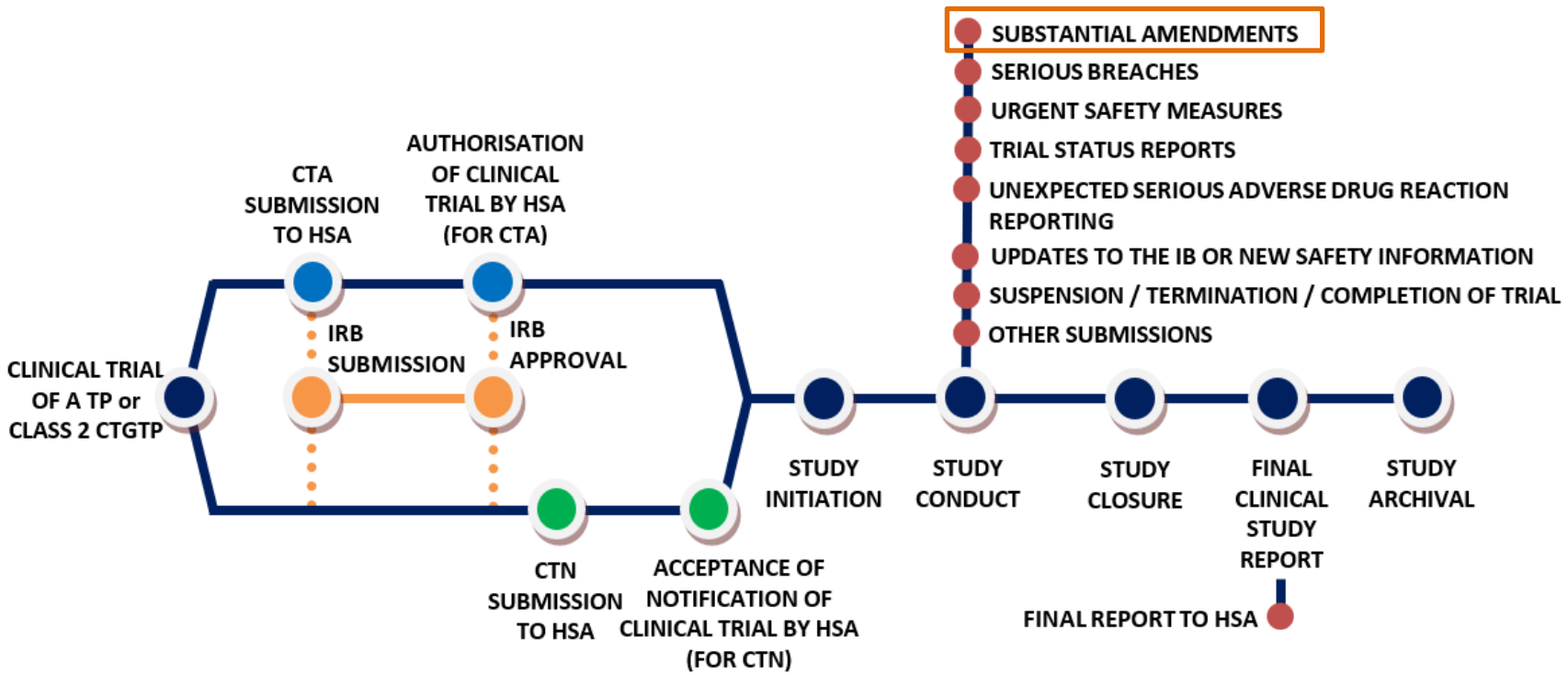
Regulatory Roadmap

Clinical Trial of a Therapeutic Product or a Class 2 CTGTP



Regulatory Roadmap

Clinical Trial of a Therapeutic Product or a Class 2 CTGTP



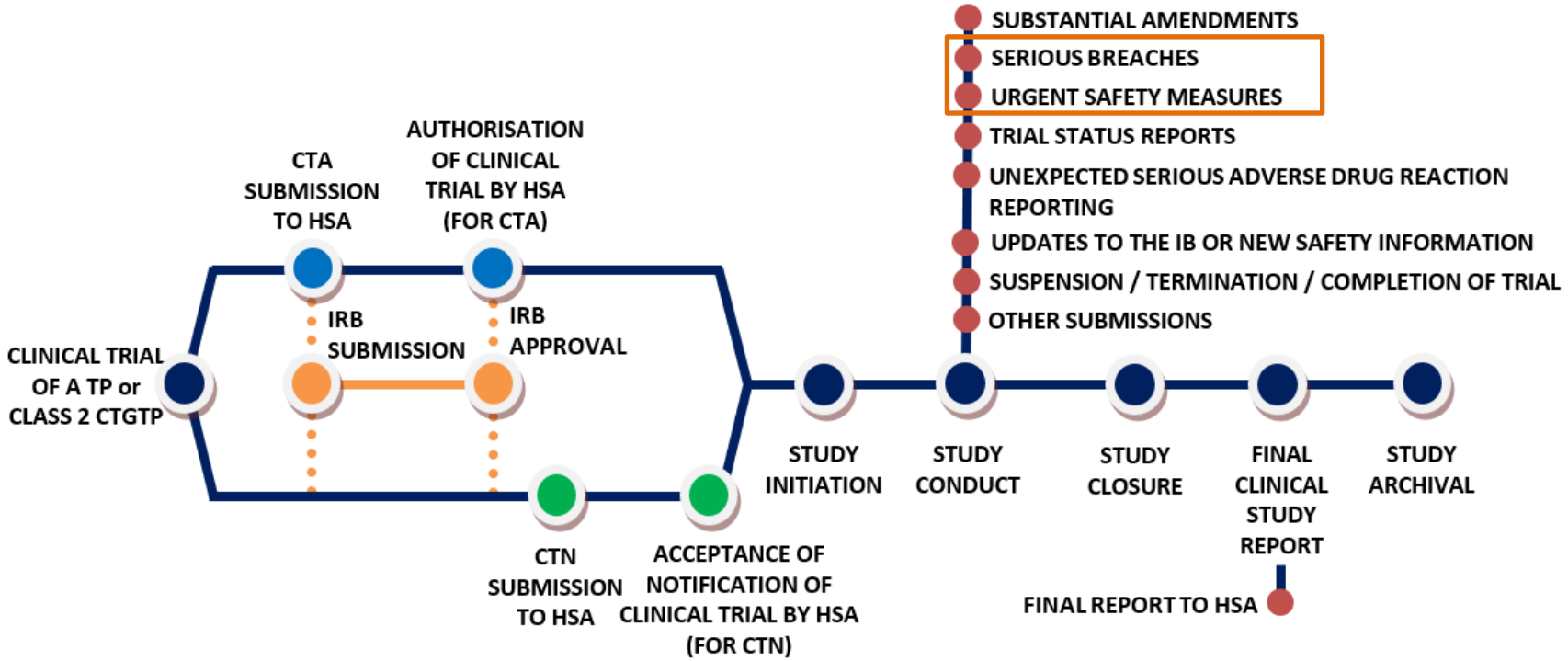
Substantial Amendments

- Change of sponsor or principal investigator;
- Any change likely to significantly affect
  a) the safety, physical or mental integrity of trial participants;
  b) the scientific value of the trial;
  c) the conduct or management of the trial; or
  d) the quality or safety of the investigational product.

*For details, refer to **HSA Regulatory Guidance (GN-IOCTB-05):** Determining whether an amendment to a clinical trial is a substantial amendment.*

Regulatory Roadmap

Clinical Trial of a Therapeutic Product or a Class 2 CTGTP



Serious Breach

- A breach of the principles of GCP, the protocol or the regulations that is likely to significantly affect:
  a) the safety, physical or mental integrity of trial participants; or
  b) or scientific value of the trial.

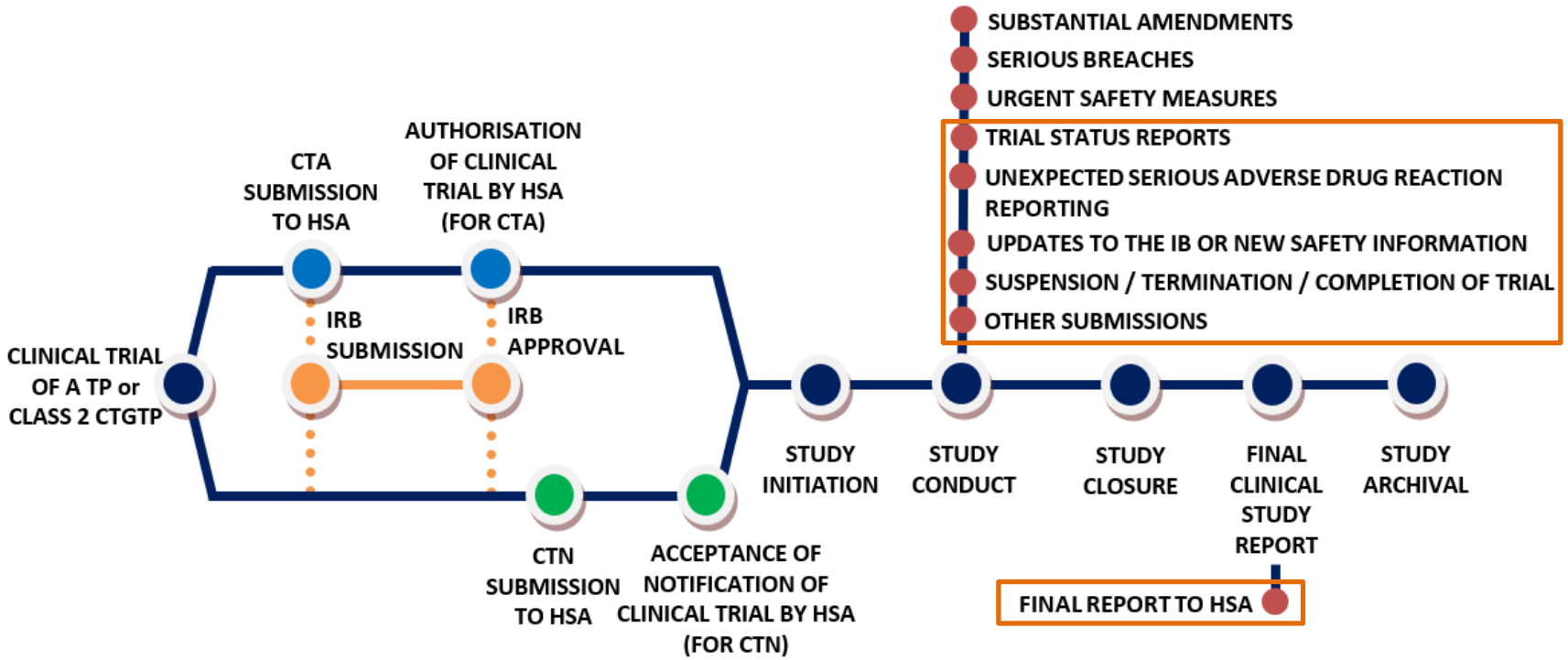
Urgent Safety Measures

- May be implemented without prior HSA or IRB approval if needed to eliminate an immediate hazard to participants

HSA Regulatory Guidance (GN-IOCTB-13): *Notification of Serious Breach*
HSA Regulatory Guidance (GN-IOCTB-04): *Regulatory Requirements for New Applications and Subsequent Submissions*

Regulatory Roadmap

Clinical Trial of a Therapeutic Product or a Class 2 CTGTP



HSA Regulatory Guidance (GN-IOCTB-13): *Notification of Serious Breach*

HSA Regulatory Guidance (GN-IOCTB-04): *Regulatory Requirements for New Applications and Subsequent Submissions*

Reporting Timelines

To be submitted by the sponsor to HSA:

	Reporting Timeline to HSA
Serious Breach	**As soon as possible**, and in any event **not later than 7 days** after becoming aware of the breach
Urgent Safety Measure	**As soon as possible**, and in any event **not later than 7 days** after the date on which the measure was taken
Trial Status Report	• **Every 6 months** starting from granting of CTA, acceptance of CTN or issuance of CTC, until trial conclusion or termination • Immediately or within such other time **as required by HSA**
Trial Suspension or Termination	Status report to be submitted **within 15 days** of the date of suspension or termination.
Trial Conclusion (Last Patient Last Visit, or if remote follow-up after LPLV, then Last Patient Last Contact)	• **Status report** to be submitted **within 30 days** of trial conclusion. • **Final clinical trial report** to be submitted **within 1 year** of the date of trial conclusion.

HSA Regulatory Guidance (GN-IOCTB-04): *Regulatory Requirements for New Applications and Subsequent Submissions*

Reporting Timelines

To be submitted by the sponsor to HSA:

Unexpected, Serious Adverse Drug Reactions (USADR)	Reporting Timeline to HSA
Fatal or life-threatening USADR	• **Initial report:** **as soon as possible**, and in any event, **not later than 7 days** after the sponsor's first awareness of the event • **Follow-up report:** **within 8 days** of the initial report
Other USADR	**As soon as possible**, and in any event, **not later than 15 days** after the sponsor's first awareness of the event

HSA Regulatory Guidance (GN-IOCTB-04): *Regulatory Requirements for New Applications and Subsequent Submissions*

Innovation Office

- Enables researchers, biotech and pharma companies to seek early scientific and regulatory advice on early-stage clinical product development with an intent to initiate clinical trials and ultimately pursue product registration in Singapore.

- Scope of advice that may be sought includes:
  - Non-clinical studies required to support clinical development
  - Clinical trial design and clinical development plans
  - Chemistry, manufacturing and controls (CMC)
  - Manufacturing requirements

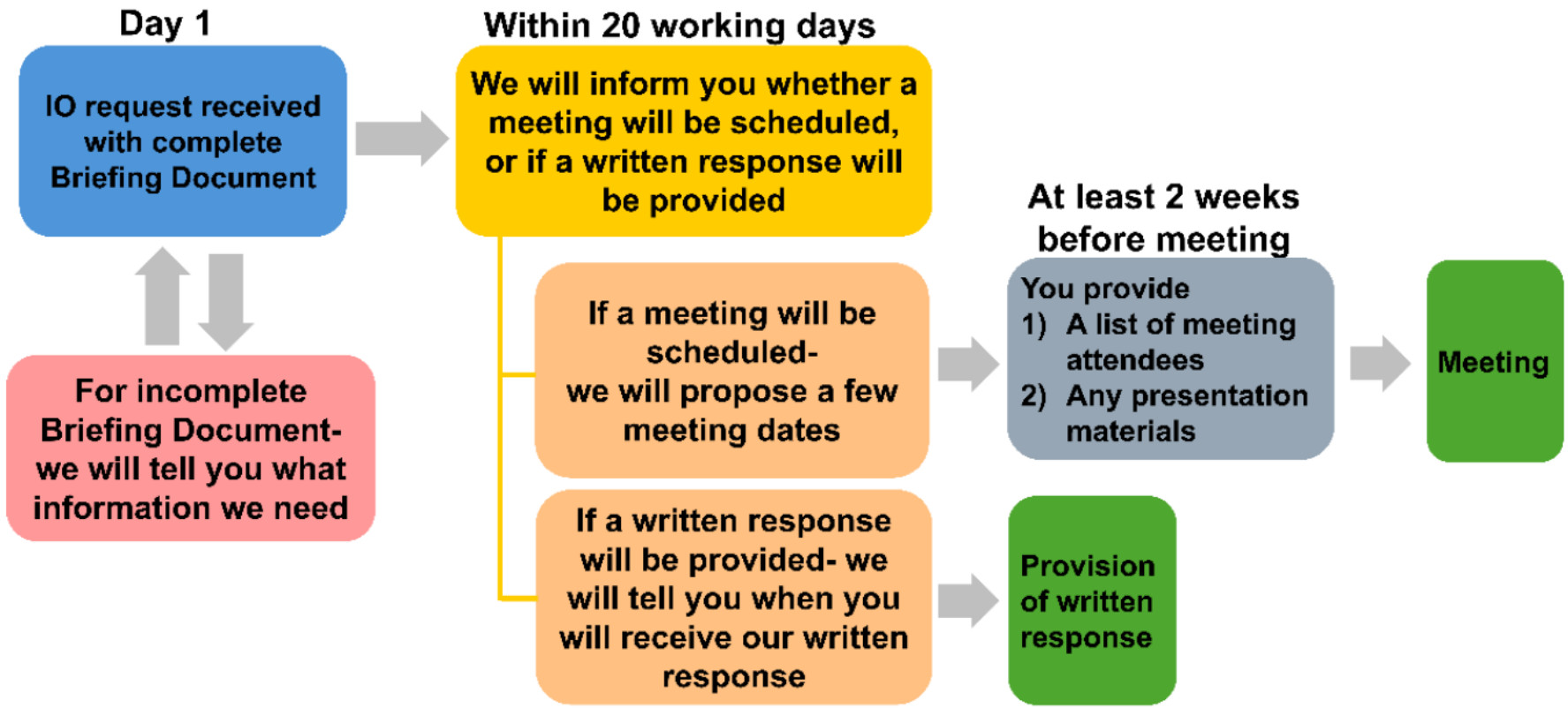
Innovation Office (IO) Requests

Process and Timelines

Submit IO request form and briefing document to:
HSA_InnovationOffice@hsa.gov.sg

Briefing document:

- **Clear overview** of your product and its development stage.
- **Specific regulatory or scientific questions** you're seeking feedback on, e.g., *"Are these comparability data sufficient to support a manufacturing change?"*
- **Supporting information** such as development plans, key study data, and relevant literature.



HSA Regulatory Guidance (GN-IOCTB-17): *Submission of Innovation Office Requests*

SPONSOR AND PRINCIPAL INVESTIGATOR RESPONSIBILITIES

Sponsor and Investigator Responsibilities

- Every clinical trial must have a sponsor.
- For multi-site investigator-initiated trials (IITs)
  - More than one sponsor may be allowed if a lead sponsor is appointed among the sponsors.
- Sponsor must fulfil sponsor responsibilities in accordance with the Clinical Trials Regulations and Good Clinical Practice (GCP).
- The Principal Investigator must also ensure that the clinical trial is conducted in accordance with the Clinical Trials Regulations and GCP.

Legal Duties

Sponsors and Principal Investigators

Sponsors	Principal Investigators
1. Obtain CTC/CTA/CTN 2. Obtain approval for substantial trial amendments 3. Notify HSA of trial status, suspension, termination and/or conclusion, and submit final report within stipulated timelines 4. Ensure info in IB is concise, objective and kept up to date 5. Ensure trial conducted under supervision of qualified principal investigator 6. Ensure trial conducted at specified place(s) 7. Carry out functions of the sponsor in accordance with principles of GCP 8. Put and keep in place arrangements to ensure compliance with principles of GCP 9. In the case of a trial involving an applicable CTGTP, ensure that a system of traceability (from donor/source to patient and vice-versa) is established and maintained, in accordance with the regulations 10. Notify HSA of serious breach of GCP/protocol and urgent safety measures taken to protect subjects against immediate hazard within stipulated timelines 11. Keep adequate trial-related documents, which, in the case of a CTGTP, also include records that would allow traceability of the product 12. Ensure appropriate investigational health product labelling 13. Report unexpected serious adverse drug reactions (USADRs) to HSA within stipulated timelines	1. Conduct trial in accordance with protocol, regulatory conditions, the Regulations and principles of GCP 2. Conduct trial at specified place(s) 3. Ensure medical care/decisions relating to trial participants by qualified investigators 4. Ensure proper consent and provision of information 5. In the case of a trial involving an applicable CTGTP, ensure that a system of traceability is established and maintained at the trial site such that the product may be linked to the trial participant who received it and vice-versa 6. Keep adequate trial-related documents, which, in the case of a CTGTP, also include records that would allow traceability of the product 7. Declare financial interest to IRB 8. Report serious breach of GCP/protocol to IRB, if required 9. Report serious adverse events (SAEs) to sponsor, and IRB if required, within stipulated timelines

Additional Legal Duties

Lead Sponsor and Other Sponsor(s)

Lead Sponsor	Other Sponsor(s)*
1. Regulatory submissions and notifications to HSA (e.g., CTA/CTN applications, amendments, serious breaches, trial status reports, final trial reports, etc.) 2. Ongoing safety evaluation of investigational product(s) administered to trial participants 3. Prompt notification to all participating site investigators/ institutions of findings that could adversely affect trial participant safety or impact conduct of trial 4. Notification of unexpected serious adverse drug reactions, and serious breaches of GCP/protocol/regulations, to HSA	1. Report immediately to lead sponsor on any SAE at participating site, or any finding that could adversely affect trial participant safety or impact conduct of trial 2. Provide all relevant information to lead sponsor that is necessary for the lead sponsor to perform trial-related regulatory submissions and notifications to HSA ** Other sponsor(s), e.g., other participating site sponsors*

This slide is applicable only to multi-site investigator-initiated trials, for which all participating institutions have chosen to adopt the "multi-sponsor" model. Otherwise, the clinical trial should have a single sponsor.

HSA Regulatory Guidance (GN-IOCTB-02): *Multi-Sponsor Investigator-Initiated Trials*

CLINICAL TRIALS REGISTER

Clinical Trials Register

- HSA may publish particulars of clinical trial (marked with ^ in PRISM application form) in a publicly available clinical trials register.
- The enhanced CT Register is in development.

Current Data Set in CT Register (PRISM)

- Protocol Title/ No.
- Phase
- Therapeutic Area
- Intervention [Name of Study Drug]
- Sponsor
- Trial Site
- Principal Investigator
- Trial Status

In the meantime, please register your trial at any ICMJE-accepted public clinical trial register to meet requirements for publication.

WHO Trial Registration Data Set	
Primary Registry & Trial Identification Number	Intervention(s)
Date of Registration in Primary Registry	Key Inclusion & Exclusion Criteria
Secondary Identifying Numbers	Study Type
Source of Monetary or Material Support	Primary & Secondary Outcomes
Primary & Secondary Sponsor	Date of First Enrolment Recruitment Status
Contact for Public & Scientific Queries	Completion Date
Public & Scientific Title	Ethics Review
Countries of Recruitment	Summary Results
Health Condition Studied	IPD sharing statement

Clinical Trials Register

Clinical Trials Register

Get the latest information on active clinical trials.

Overview

Our Clinical Trials Register currently lists only ongoing clinical trials in our applications database. The aim of this register is to help increase transparency and accountability to the researchers, industry, healthcare professionals and patients.

All information in our Clinical Trials Register is maintained and updated by the local sponsors at least once every six months.

Disclaimer: Please note that this register does not include the full 24-item trial registration dataset required for the purpose of journal publication. Sponsors are reminded to ensure that their clinical trial is prospectively registered in an International Committee of Medical Journal Editors (ICMJE)-acceptable clinical trial register for the purpose of journal publication.

ACCESS THE HSA CLINICAL TRIALS REGISTER

https://www.hsa.gov.sg/clinical-trials/clinical-trials-register

Summary

- Clinical trials of therapeutic products and Class 2 CTGTPs, except observational clinical trials, are regulated by HSA to uphold participant safety and ensure clinical trial data credibility.
- HSA adopts a risk-based approach, applying oversight that is proportionate to the level of risk involved. Depending on product type and registration status:
  - A CTA is required for locally-unregistered products or off-label use.
  - A CTN is required for locally-registered products used as approved.
- Sponsors and principal investigators are entrusted with clear responsibilities under the Health Products (Clinical Trials) Regulations and Good Clinical Practice.
- The Innovation Office provides early scientific and regulatory advice to facilitate the development of novel therapeutics.
- The Clinical Trials Register enhances transparency by publishing key trial information, reinforcing public awareness and accountability in clinical trials.

References

- Health Products (Clinical Trials) Regulations
- ICH E6(R3) Good Clinical Practice (GCP) Guideline
- HSA Regulatory Guidance
  - GN-IOCTB-01: Determination of Whether a Clinical Trial Requires a Clinical Trial Authorisation, Clinical Trial Notification or Clinical Trial Certificate
  - GN-IOCTB-02: Multi-sponsor investigator-initiated trials
  - GN-IOCTB-04: Regulatory Requirements for New Applications and Subsequent Submissions
  - GN-IOCTB-05: Guidance on Determining Whether an Amendment to a Clinical Trial is a Substantial Amendment
  - GN-IOCTB-17: Submission of Innovation Office Requests

We welcome your enquiries and feedback!

HSA_CT@hsa.gov.sg

THANK YOU!