HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

28 APR 2021

CLINICAL TRIALS GUIDANCE

REGULATORY REQUIREMENTS FOR NEW APPLICATIONS AND SUBSEQUENT SUBMISSIONS

GN-IOCTB-04 Rev. No. 004

HSA Health Sciences Authority

PREFACE

This document is intended to provide general guidance. Although we have tried to ensure that the information contained here is accurate, we do not, however, warrant its accuracy or completeness. The Health Sciences Authority (HSA) accepts no liability for any errors or omissions in this document, or for any action / decision taken or not taken as a result of using this document. If you need specific legal or professional advice, you should consult your own legal or other relevant professional advisers.

In the event of any contradiction between the contents of this document and any written law, the latter should take precedence.

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REVISION HISTORY

Guidance Version (Version Date)

GN-CTB-2-003A-001 (01 Nov 2016)

GN-CTB-2-003A-002 (02 May 2017)

GN-IOCTB-04 Rev. No. 003 (01 Mar 2021)

GN-IOCTB-04 Rev. No. 004 (28 Apr 2021)

SUMMARY OF AMENDMENTS

Version (Version Date)	Amendments
Rev. No. 003 (01 Mar 2021)	• Added a new category of health products, i.e., Cell, Tissue and Gene Therapy Products (CTGTPs), that is regulated under the Health Products Act • Added a new section on satellite sites (Section 3.4) • Clarified on updates to urgent safety measures previously notified to HSA (Section 4.3) • Clarified on trial status report submission when there is a change in trial status (Section 4.4) • Added a summary table of timelines for subsequent submissions to HSA (Section 4.10) • Added a new section on Frequently Asked Questions (Section 5) • Amended the term “subjects” to “trial participants”
Rev. No. 004 (28 Apr 2021)	• Clarified on regulatory requirements for clinical trials of controlled drugs or psychotropic substances (Section 5.6)

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1. INTRODUCTION

1.1. Purpose

The purpose of this document is to provide guidance to sponsors and investigators on the regulatory requirements for new applications and subsequent submissions to the Health Sciences Authority (HSA).

The Health Sciences Authority regulates the conduct of clinical trials of therapeutic products and Class 2 cell, tissue, and gene therapy products[1] (CTGTPs) under the Health Products (Clinical Trials) Regulations, and the conduct of clinical trials of medicinal products under the Medicines (Clinical Trials) Regulations.

The Regulations require trial sponsors to submit clinical trial applications to HSA under one of 3 submission routes:

(i) Clinical Trial Authorisation (CTA) - for clinical trials of therapeutic products or Class 2 CTGTPs;
(ii) Clinical Trial Notification (CTN) - for clinical trials of locally registered therapeutic products or Class 2 CTGTPs used in accordance with the approved label; and
(iii) Clinical Trial Certificate (CTC) - for clinical trials of medicinal products.

For determination of whether a clinical trial is regulated by HSA, please refer to the *Guidance on Determination of Whether a Clinical Trial Requires a Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or a Clinical Trial Certificate (CTC)*.

[1] 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.

After CTA, acceptance of CTN or a CTC has been granted by HSA, the sponsor of the clinical trial has obligations relating to the conduct and follow-up of the clinical trial. These obligations include subsequent submissions of substantial amendments, notification of serious breaches and urgent safety measures, submission of trial status reports, reporting of unexpected serious adverse drug reactions, updates to the Investigator's Brochure or new safety information, notification of trial suspension / termination / completion, and submission of final clinical study reports, where applicable.

1.2. Scope

This guidance applies to clinical trials regulated by HSA, namely:

(i) Clinical trials of Therapeutic Products or Class 2 CTGTPs that are subject to the requirements of a Clinical Trial Authorisation (CTA) or a Clinical Trial Notification (CTN);

(ii) Clinical trials of Medicinal Products that are subject to the requirements of a Clinical Trial Certificate (CTC).

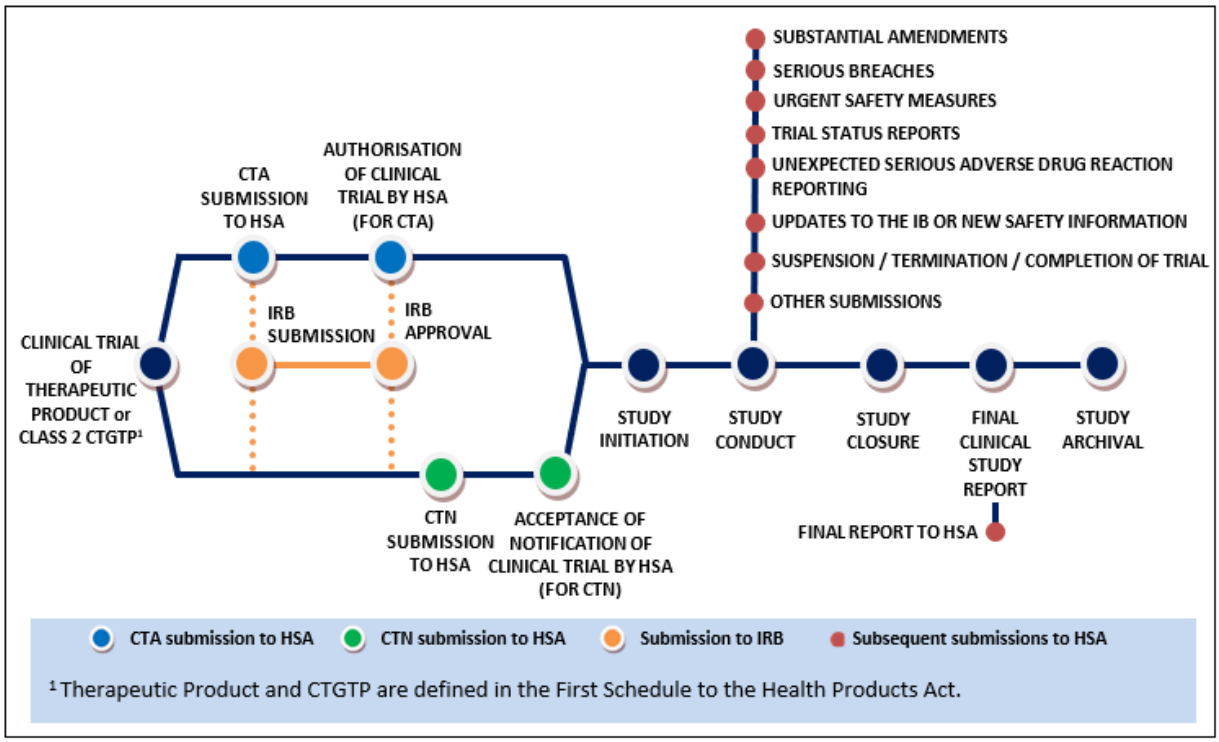
2. REGULATORY ROAD MAPS FOR CLINICAL TRIALS

2.1. Regulatory road map for clinical trials on therapeutic products and Class 2 CTGTPs

Once it has been determined that a clinical trial of a therapeutic product or class 2 CTGTP is subject to the requirements of a Clinical Trial Authorisation (CTA) or Clinical Trial Notification (CTN), the sponsor should submit the clinical trial application to HSA.

The regulatory road map for clinical trials of therapeutic products or Class 2 CTGTPs is summarised in Figure 1.

Figure 1. Regulatory roadmap for clinical trials of therapeutic products or Class 2 CTGTPs



2.1.1. The sponsor may submit the clinical trial application to HSA and the relevant IRB as follows:

- **For clinical trials that are subject to the requirements for a Clinical Trial Authorisation (CTA),** the sponsor may submit the clinical trial application to HSA and the IRB in parallel (Figure 1).
- **For clinical trials that are subject to the requirements for a Clinical Trial Notification (CTN),** the sponsor should submit the clinical trial application to HSA only after receipt of IRB approval of the clinical trial (Figure 1).

2.1.2. The sponsor must not initiate the clinical trial without authorisation (for CTA) or acceptance of notification (for CTN) by HSA and IRB approval.

2.1.3. The authorisation (for CTA), or acceptance of notification (for CTN), of the clinical trial by HSA is valid for the duration of the clinical trial. The duration of the clinical trial refers from study initiation to study completion/closure. Refer to section 4.4 on trial status reporting.

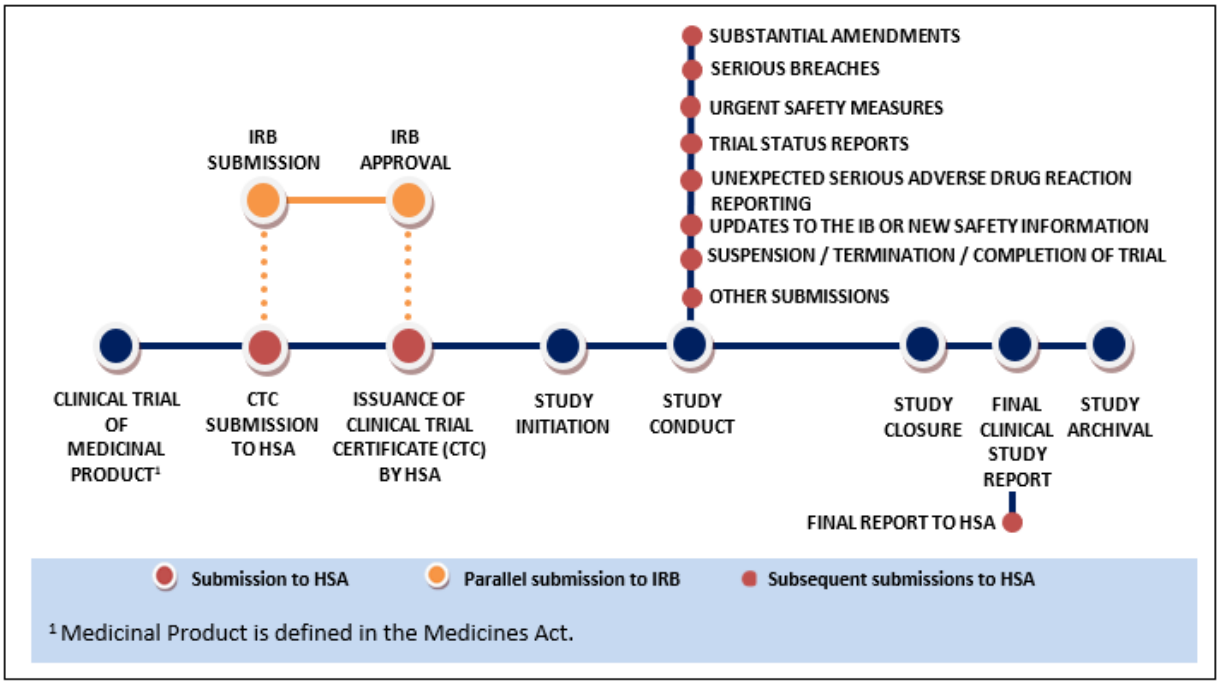
2.1.4. Refer to section 4 for subsequent submissions to be submitted to HSA following authorisation (for CTA), or acceptance of notification (for CTN), of the clinical trial by HSA.

2.2. Regulatory road map for clinical trials of medicinal products

Once it has been determined that a clinical trial of medicinal product(s) is subject to the requirements for a Clinical Trial Certificate (CTC), the sponsor should submit the clinical trial application to HSA.

The regulatory road map for clinical trials on medicinal products is summarised in Figure 2.

Figure 2. Regulatory roadmap for clinical trials of medicinal products



2.2.1. For clinical trials that are subject to the requirements for a CTC, the sponsor may submit the clinical trial application to HSA and the IRB in parallel (Figure 2).

2.2.2. The sponsor must not initiate the clinical trial without a CTC from HSA and IRB approval.

2.2.3. The CTC is valid for the duration of the clinical trial. The duration of the clinical trial refers from study initiation to study completion. Refer to section 4.4 on trial status reporting.

2.2.4. Refer to section 4 for subsequent submissions to be submitted to HSA following issuance of the CTC by HSA.

2.3. Differences between CTA, CTN and CTC

Table 1 summarises the key differences between the CTA, CTN and CTC.

Table 1. Key differences between CTA, CTN and CTC

	Clinical Trial Authorisation (CTA)	Clinical Trial Notification (CTN)	Clinical Trial Certificate (CTC)
Target Processing Timeline (excluding stop-clock time)	30 working days[1]	5 working days	30 working days
Submission Dossier			
Protocol	✓	✓	✓
Informed Consent Form (English)	✓	✓	✓
Investigator's Brochure	✓[2]	✗	✓
Local Approved Product Label	✗[2]	✓	✗
Principal Investigator's CV	✓	✓	✓
List of overseas trial sites (if applicable)	✓	✓	✓
Good Manufacturing Practice (GMP) certificate (if applicable)[3]	✓	✗	✓
Certificate of Analysis (COA) for study batches of Investigational Products	✓	✗	✓
Chemistry, Manufacturing and Control (CMC) documents, if requested	✓	✗	✓
IRB Approval Letter	✗	✓	✗
Substantial Amendments[4]	Authorisation	Notification	Approval
Regulatory Outcome	Authorisation	Acceptance of Notification	Issuance of Clinical Trial Certificate
Validity Period	Duration of trial	Duration of trial	Duration of trial

[1] Other Target Processing Timelines:
- 15 working days for Phase 1 clinical trials solely to evaluate bioequivalence, bioavailability, food effect or drug-drug interaction
- 60 working days for Class 2 CTGTP trials

[2] The local approved product label may be submitted in place of an Investigator's Brochure for locally registered therapeutic products or locally registered Class 2 CTGTPs.

[3] Refer to Table 2 for further details on requirements for GMP certificate.

[4] Substantial amendments include:
(i) changes to the local sponsor or principal investigator(s) of the trial
(ii) addition of trial site(s); or
(iii) amendments to any particulars or documents accompanying the clinical trial application which is likely to affect to a significant degree
  (a) the safety, or physical or mental integrity, of any trial participant of a clinical trial;
  (b) the scientific value of a clinical trial;
  (c) the conduct or management of a clinical trial; or
  (d) the quality or safety of any investigational therapeutic/medicinal product used in a clinical trial.

Refer to the *Guidance on Determining Whether an Amendment to a Clinical Trial is a Substantial Amendment* for further details.

3. NEW CLINICAL TRIAL APPLICATIONS TO HSA

3.1. Application requirements

The sponsor is responsible for submitting the clinical trial application to HSA.

3.1.1. The sponsor should submit the clinical trial application to HSA online via the Pharmaceutical Regulatory Information System (PRISM). PRISM uses an electronic authentication system with Corppass.

3.1.2. The sponsor should be a locally registered business entity registered with the Accounting and Corporate Regulatory Authority (ACRA) in Singapore. In order for the sponsor to carry out electronic transactions with HSA via PRISM, the sponsor should apply for a Corppass account and a Client Registration and Identification Service (CRIS) account.

3.2. Supporting documents required to be submitted to HSA

The sponsor should submit the supporting documents (listed in Table 2) to HSA for CTA, CTN and CTC applications.

Table 2. Supporting documents for CTA, CTN and CTC applications to HSA

Supporting Document	Clinical Trial Authorisation (CTA)	Clinical Trial Notification (CTN)	Clinical Trial Certificate (CTC)
Clinical Trial Protocol	✓	✓	✓
Informed Consent Form (English)	✓	✓	✓
Investigator's Brochure	✓[1]	✗	✓
Local Approved Product Label	✗[1]	✓	✗
List of Overseas Trial Site, where applicable	✓	✓	✓
Principal Investigator's CV	✓	✓	✓
Good Manufacturing Practice (GMP) Certificate[2]	✓	✗	✓
Certificate of Analysis (COA) for study batches of Investigational Products[3]	✓	✗	✓
Chemistry, Manufacturing and Control (CMC) information, if requested	✓	✗	✓
IRB Approval Letter	✗	✓	✗

[1] Local Approved Product Label
The local approved product label may be submitted in place of an Investigator's Brochure for locally registered therapeutic products and Class 2 CTGTPs.

[2] GMP Certificate:

(a) **For all Investigational and Auxiliary Products that are not locally registered,** the sponsor should submit GMP certificate(s) to HSA that certifies that the manufacture of the finished product is in compliance with current GMP standards. For products that are registered overseas for which a GMP certificate is not available, the sponsor may submit a declaration to declare that the product is manufactured in compliance with current GMP standards and sourced from an authorised manufacturer in the source country (i.e. a manufacturer approved by the regulatory authority of the country of manufacture).

(b) **For Biologics and Class 2 CTGTPs that are substantially manipulated,** the sponsor should additionally submit GMP certificate(s) to HSA that certifies that the manufacture of the drug substance is in compliance with current GMP standards. For products that are registered overseas for which a GMP certificate is not available, the sponsor may submit a declaration to declare that the drug substance is manufactured in compliance with current GMP standards and sourced from an authorised manufacturer in the source country (i.e. a manufacturer approved by the regulatory authority of the country of manufacture).

(c) **For Investigational and Auxiliary Products that are locally registered but not sourced from the same manufacturer as the locally registered product,** the sponsor should submit GMP certificate(s) that certifies, or a declaration to declare, that the manufacture of the product(s) is in compliance with current GMP standards and, for the declaration, that the product is sourced from an authorised manufacturer in the source country.

(d) **For Investigational and Auxiliary Products that are locally registered and sourced from the same manufacturer as the locally registered product,** a GMP certificate is not required to be submitted.

[3] Certificate of Analysis (CoA):
For Investigational and Auxiliary Products that are locally registered and sourced from the same manufacturer as the locally registered product, a CoA is not required to be submitted.

3.3. Documents not required to be submitted to HSA

The sponsor is not required to submit the following documents to HSA, where applicable:

(a) IRB Application Form
(b) Translated informed consent forms
(c) Informed consent forms for the trial participant's partner
(d) Diary Cards
(e) Data Collection Forms
(f) Case Report Forms
(g) Clinical Trial Advertisements

3.4. Satellite Sites

3.4.1. All clinical trials should be conducted by or under the supervision of a principal investigator at each trial site, and should only be conducted at the trial sites that have been specified in the clinical trial application.

3.4.2. Satellite sites are location(s), other than the trial site(s), where trial participants have to visit for some trial-related procedures. These satellite sites may include other healthcare institutions that offer specialised clinical services or a dedicated early phase clinical trial units where certain aspects of the trial are conducted. Examples of such trial-related procedures may include investigational product administration, pharmacokinetic sampling, radio-diagnostic scans, cardiac monitoring procedures, ophthalmological safety assessments, biopsies etc.

3.4.3. All satellite sites, and the trial-related procedures that are conducted at these sites, should be included in the clinical trial application to HSA. The principal investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions, including at satellite sites, and should ensure that this individual or party is qualified to perform those trial-related duties and functions. The principal investigator should also ensure that procedures are implemented to

ensure the integrity of the trial-related duties and functions performed and any data generated, including at any satellite site.

4. SUBSEQUENT SUBMISSIONS TO HSA

Subsequent submissions to HSA may be required during a clinical trial. All subsequent submissions to HSA should be submitted via PRISM, unless otherwise specified.

4.1. Substantial Amendments

Substantial amendments may include the following, where applicable:

(a) Amendments to Protocol
(b) Amendments to Informed Consent Form
(c) Change of Local Sponsor
(d) Change of Principal Investigator
(e) Addition of Trial Site
(f) Change of Manufacturer
(g) Change of Chemistry, Manufacturing and Controls (CMC) information (if CMC information had been submitted in the initial clinical trial application)

Refer to the *Guidance on Determining Whether an Amendment to a Clinical Trial is a Substantial Amendment* for further details.

4.2. Serious Breaches

4.2.1. A Serious Breach is defined as a breach of the protocol, the principles of GCP, or the Regulations, during a clinical trial which is likely to affect to a significant degree —

(a) the safety, or physical or mental integrity, of any participant of the trial; or
(b) the scientific value of the trial.

The sponsor must notify HSA of any serious breach to HSA as soon as possible and no later than within 7 days of becoming aware of the serious breach. Refer to the *Guidance on Notification of Serious Breach* for further details.

4.3. Urgent Safety Measures

4.3.1. Urgent Safety Measures are defined as measures implemented by the sponsor and/or investigator to avoid an immediate hazard to the health or safety of trial participants.

4.3.2. The sponsor must report urgent safety measures relating to a trial participant in the clinical trial to HSA as soon as possible and no later than 7 days of the urgent safety measure. The sponsor must also provide details of the circumstances giving rise to the urgent safety measure.

4.3.3. The sponsor must notify HSA (via email) of any updates to the urgent safety measures previously notified to HSA.

4.4. Trial Status Reports

4.4.1. The sponsor must submit Trial Status Reports to HSA on a 6-monthly basis from authorisation (for CTA), acceptance of notification (for CTN) or approval (for CTC) of clinical trial till study completion, or termination. The sponsor must submit the Trial Status Report to HSA within 14 days of each 6-monthly reporting period.

4.4.2. The sponsor must also immediately report on the status of the clinical trial at any time when requested by HSA.

4.4.3. The sponsor should submit a Trial Status Report to HSA whenever there is a change of study status (e.g. trial initiation, temporary suspension of recruitment, resumption of recruitment etc.).

4.4.4. An acknowledgement of receipt is not issued for submission of Trial Status Reports. If required, the message displayed on screen upon successful submission in PRISM may be retained as an acknowledgement of receipt by HSA.

4.4.5. The definitions of the trial status and recruitment status fields of the Trial Status Report are detailed in Table 3:

Table 3. Definitions of trial status and recruitment status fields of the Trial Status Report

Field	Definition
TRIAL STATUS	
Not yet recruiting	The local trial site(s) has/have not commenced recruiting trial participants into the clinical trial.
Ongoing, recruiting	The local trial site(s) has/have commenced recruiting trial participants into the clinical trial.
Ongoing, recruitment suspended	The recruitment at the local trial site(s) has been suspended. However, the enrolled trial participants are still continuing with the study procedures*.
Ongoing, recruitment closed	The recruitment at the local trial site(s) has been closed. However, the enrolled trial participants are still continuing with the study procedures*.
Premature Closure	The local trial site(s) was/were closed prematurely as no trial participants were screened for the clinical trial.
Suspended	The clinical trial has been suspended. All screening and enrollment activities should be suspended. Please notify the IRB and HSA if existing trial participants are to continue with the study procedures*.
Terminated	The clinical trial has been terminated. All screening and enrollment activities should be terminated, and existing trial participants should not continue with the study procedures*.
Completed	Study completion is defined as 'Last Patient Last Visit (LPLV)' for the clinical trial. For clinical trials with remote follow-up after LPLV, trial completion is defined as the end of remote follow-up (i.e., Last Patient Last Contact).
RECRUITMENT STATUS [for each local trial site]	
No. of trial participants screened	Number of trial participants screened for the clinical trial.
No. of screened failures	Number of trial participants who failed any of the screening procedures for the clinical trial.
No. of trial participants pending screening outcome	Number of trial participants whose screening results are still pending.
No. of trial participants enrolled	Number of trial participants enrolled into the clinical trial
No. of trial participants withdrawn or prematurely terminated	Number of trial participants who did not complete all the study procedures* and had to be withdrawn or prematurely terminated from the clinical trial.
No. of trial participants ongoing	Number of trial participants who are undergoing the study procedures*.
No. of trial participants completed	Number of trial participants who have completed the study procedures*.
No. of SAEs experienced by local trial participants	Number of Serious Adverse Events (SAEs) experienced by the trial participants.

*Note: Study procedures include remote follow-up activities (e.g. remote study visits, survival follow-up).

4.5. Unexpected Serious Adverse Drug Reactions (USADRS)

Refer to the *Guidance on Expedited Safety Reporting Requirements for Clinical Trials* for further details.

4.6. Updates to the Investigator's Brochure or New Safety Information

4.6.1. The sponsor must notify HSA of all updates to the Investigator's Brochure or new safety information.

4.6.2. An acknowledgement of receipt is not issued for submission of updates to the Investigator's Brochure or New Safety Information. If required, the message displayed on screen upon successful submission in PRISM may be retained as an acknowledgement of receipt by HSA.

4.7. Suspension / Termination / Completion of a clinical trial

4.7.1. The sponsor must notify HSA (via a Trial Status Report through PRISM) about the trial suspension / termination / completion and the reason(s) for such a decision.

4.7.2. Notification for trial suspension / termination must be done within 15 days of the trial suspension / termination. The sponsor should notify HSA (via a Trial Status Report through PRISM) once the suspension has been lifted.

4.7.3. Notification of trial completion must be done within 30 days of the study completion.

4.8. Final Clinical Study Report

4.8.1. The sponsor must submit the Final Clinical Study Report of the clinical trial to HSA within 1 year of study completion, unless otherwise agreed by HSA.

4.8.2. For more information, you may refer to *ICH Guideline E3: Structure and Content of Clinical Study Reports* that elaborates on the note for guidance

on structure. For investigator-initiated clinical trials, a publication of the clinical trial may be submitted to HSA in place of a Final Clinical Study Report.

4.9. Other submissions

4.9.1. The sponsor should notify HSA of the following:

(a) Changes to the Clinical Research Material (CRM) Notification

(b) Changes to the trial application information

(c) Changes to the regulatory status of the trial in other countries (e.g. clinical hold or non-approval by regulatory authority)

(d) CRM Non-compliances (refer to the *Guidance on Clinical Research Materials* for details)

4.10. Summary of Timelines for Subsequent Submissions to HSA

The regulatory timelines for subsequent submissions include:

Subsequent Submission to HSA	**Submission Timeline**
Substantial amendments	Prior to implementation
Serious Breaches	As soon as possible, but no later than 7 calendar days
Urgent Safety Measures	As soon as possible, but no later than 7 calendar days
Trial Status Reports	6 monthly (+ 14 calendar days), and whenever there is a change of study status (e.g. trial initiation, temporary suspension of recruitment, resumption of recruitment etc.)
Unexpected Serious Adverse Drug Reactions (USADR) - Fatal or life threatening events	Initial report As soon as possible, and not later than 7 calendar days from sponsor's first awareness of the USADR Follow-up report As soon as possible, and not later than 8 calendar days following the initial report.
Unexpected Serious Adverse Drug Reactions (USADR) - Non-fatal or non-life threatening events	Initial report As soon as possible, and not later than 15 calendar days from sponsor's first awareness of the USADR Follow-up report As soon as available
Updates to the Investigator's Brochure or new safety information	As soon as available
Suspension of clinical trial	15 calendar days of the trial suspension
Termination of clinical trial	15 calendar days of the trial termination
Completion of clinical trial	30 calendar days of the trial completion
Final Clinical Study Report	1 year from date of trial completion, unless otherwise agreed by HSA

If the sponsor is unable to comply with the above regulatory timelines, the sponsor should notify HSA in writing of the reason(s) for the delay and corrective and preventive actions implemented to prevent a recurrence.

5. FREQUENTLY ASKED QUESTIONS

5.1. What are the regulatory requirements for First-in-Human (FIH) trials of therapeutic products and Class 2 CTGTPs?

In general, the regulatory requirements for FIH applications are not significantly different from that for later phase studies. The therapeutic product and Class 2 CTGTP need not be approved in other countries before the FIH trial can be conducted in Singapore. As with all clinical trials, the sponsor applicant must be a locally registered company.

Companies may refer to applicable ICH guidelines and other relevant guidelines, including:

- ICH M3(R2) Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals
- FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers
- EMA Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical and Early Clinical Trials with Investigational Medicinal Products (EMA/CHMP/SWP/28367/07 Rev.1)

If the investigational product is of a novel therapeutic class or mechanism of action, we would encourage the sponsor to request for a pre-submission meeting with HSA through the Innovation Office (HSA_InnovationOffice@hsa.gov.sg).

5.2. Are non-clinical safety/toxicology studies required to be conducted in compliance to GLP standards?

Non-clinical safety/toxicology should be conducted in compliance with Good Laboratory Practice (GLP). GLP is a quality system on the organisation process and conditions under which the non-clinical studies are planned, recorded, archived and reported. Compliance with GLP helps to assure regulatory agencies that the non-clinical safety results are reliable and credible for the purpose of risk evaluation. Any noncompliance to GLP should be justified and the potential impact on the reliability of the study results should be addressed. For more information on GLP, please refer to the GLP Compliance Programme administered by Singapore Accreditation Council.

5.3. What kind of preclinical data is required to support clinical trials of Class 2 cell, tissue and gene therapy products (CTGTPs)?

Relevant preclinical data include:

(i) Non-clinical proof of concept to provide the scientific basis for conducting clinical trial:
- Potential mechanism of action
- Establish pharmacologically effective doses
- Optimize route of administration and dosing regimen
- Rationale for species/model selection

(ii) Biodistribution/Toxicity studies in relevant animal species to provide useful information about the safety of the product
- Identify, characterize, quantify potential local and systemic toxicities
- Safety data to support safe initial dose and dose escalation scheme in humans, and to guide clinical safety monitoring and duration of follow up
- Biodistribution, migration, persistence, differentiation, integration and tumorigenicity, where applicable

The investigational CTGTP that will be used in the clinical trial should be used in the pivotal preclinical studies conducted to support the trial. Any differences between

the product intended for preclinical use and for clinical use should be highlighted and discussed in the clinical trial submission.

Relevant guidelines include:

- FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products
- FDA Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products
- FDA Guidance for Industry: Long Term Follow-up After Administration of Human Gene Therapy Products
- EMA Guideline on the Non-Clinical Studies Required Before First Clinical Use of Gene Therapy Medicinal Products
- EMA Guideline on Quality, Non-Clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials
- EMA Guideline on Safety and Efficacy Follow-up and Risk Management of Advanced Therapy Medicinal Products
- Guideline on Human Cell-Based Medicinal Products

5.4. Are there any additional dossier requirements for submission of Class 2 cell, tissue and gene therapy products (CTGTPs) clinical trials?

In addition to the standard supporting documentation required of all clinical trial applications (refer to Section 3.2), the submission dossier for a Class 2 CTGTP clinical trial should also include Chemistry, Manufacturing, and Control (CMC) Information. Please refer to *Appendix 8 of the CTGTP product registration guide, "Chemistry, Manufacturing and Controls Requirements for Cell, Tissue or Gene Therapy Products for Clinical Trials and Product Registration"* at HSA website.

Other relevant guidelines include:

- FDA Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)

- FDA Guidance for Industry: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- FDA Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products
- EMA Guideline on Quality, Non-Clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials
- EMA Guideline on Potency Testing of Cell Based Immunotherapy Medicinal Products for the Treatment of Cancer

5.5. Are there any regulatory requirements for clinical trials involving the use of radiopharmaceuticals?

The regulation of radiopharmaceutical clinical trials is similar to that for the conventional therapeutic products.

The import, export, possession, use, transport, disposal etc. of radioactive material is subject to control under the Radiation Protection Act, which is regulated by the National Environment Agency (NEA). Please refer to Radiation Safety on NEA's website for more information.

5.6. What are the additional regulatory requirements for clinical trials of controlled drugs or psychotropic substances?

Additional import and export controls under the Health Products (Therapeutic Products) Regulations 2016 and the Misuse of Drugs Regulations are applicable to clinical trials using clinical research materials containing psychotropic substances and/or controlled drugs.

The sponsor and investigators must comply with the duties and obligations relating to the handling and storage of controlled drugs and psychotropic substances

stipulated in the Misuse of Drugs Regulations, including prescription use, record keeping and destruction.

If the clinical research material containing controlled drugs or psychotropic substances are to be exported out of Singapore, a corresponding export licence shall be applied and issued before the export is made.

General information on regulatory requirements for controlled drugs or psychotropic substances can be found at HSA website.

Additional requirements for controlled drugs

In addition to submitting the clinical trial application to HSA for review and approval, approval from the Central Narcotics Bureau (CNB) will also be required for the clinical trial. HSA will coordinate with the applicant on the submission to CNB after the clinical trial application is considered approvable by HSA. The clinical trial may only be initiated after written approvals have been obtained from both HSA and CNB.

In addition to dealers' licences or Clinical Research Material (CRM) Notification (where applicable), additional import and wholesale licences for the controlled drug are required from the HSA Licensing and Certification Branch (LCB). Following receipt of the authorisation (CTA) / acceptance of notification (CTN) / approval (CTC) for the clinical trial and acknowledgement of CRM notification by HSA, copies of the CTA / CTN / CTC and the CRM-notification should be submitted to the HSA LCB as supporting documents for the application of import and wholesale licences for controlled drug. HSA LCB will then process the application and issue the Import Licence and Wholesale Licence for the controlled drug.

The Controlled Drug Wholesale Licence can only be issued to a registered pharmacist within the company. The applicant for the import licence for Controlled Drugs should also be the Controlled Drug Wholesale Licence holder to whom the import licence may be issued. The company making the application for Controlled Drug Wholesale Licence would be subject to an audit by the HSA Licensing and Certification Branch and the licence would be issued 10 days after close-out of the

audit. The consignment of imported drugs can only be used for its designated purpose and must not be distributed or sold outside of the trial.

5.7. Are licences required for the import and export of biological samples?

An import licence is not required from HSA for import of biological samples into Singapore. Please be informed that the Ministry of Health (MOH) regulates the import of infectious biological samples used in research. Hence, if the biological samples are infectious in nature, please refer to the Biological Agents and Toxins Act (BATA) and consult MOH for further advice.

An export licence is not required from HSA for shipping of biological samples for testing overseas.

6. REFERENCES

(i) Health Products (Clinical Trials) Regulations
(ii) Medicines (Clinical Trials) Regulations
(iii) ICH E6 (R2) Good Clinical Practice Guidelines
(iv) Guidance on Determination of Whether a Clinical Trial Requires a Clinical Trial Authorisation, Clinical Trial Notification or Clinical Trial Certificate
(v) Guidance on Determining Whether an Amendment to a Clinical Trial is a Substantial Amendment
(vi) Guidance on Notification of Serious Breach
(vii) Guidance on Expedited Safety Reporting Requirements for Clinical Trials
(viii) Appendix 8 of the CTGTP Product Registration Guide, “Chemistry, Manufacturing and Controls Requirements for Cell, Tissue or Gene Therapy Products for Clinical Trials and Product Registration”

HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
Blood Services Group
Applied Sciences Group

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