HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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CLINICAL TRIALS GUIDANCE

GUIDANCE ON DETERMINING WHETHER AN AMENDMENT TO A CLINICAL TRIAL IS A SUBSTANTIAL AMENDMENT

GN-CT-05 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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SUMMARY OF AMENDMENTS

- Administrative changes due to HSA re-organisation

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1. INTRODUCTION

1.1. Purpose

The purpose of this document is to provide guidance to clinical trial sponsors on determining whether an amendment to a clinical trial is a substantial amendment, and the supporting documents required for regulatory submission of a substantial amendment.

1.2. Background

The Health Sciences Authority regulates the conduct of clinical trials of therapeutic products (TPs)[1] and Class 2 cell, tissue and gene therapy products (CTGTPs)[1,2] under the Health Products (Clinical Trials) Regulations, and clinical trials of medicinal products (MPs)[3] under the Medicines (Clinical Trials) Regulations. The Regulations require sponsors of clinical trials to submit details of the clinical trials to HSA under one of 3 submission routes:

- Clinical Trial Authorisation (CTA - for clinical trials of TPs and Class 2 CTGTPs)
- Clinical Trial Notification (CTN - for clinical trials of TPs and Class 2 CTGTPs used in accordance with approved label),
- Clinical Trial Certificate (CTC - for clinical trials of MPs)

For determination of the requirements, 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)*.

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[1] Therapeutic Product and CTGTP are defined in the First Schedule to the Health Products Act.

[2] Class 1 and Class 2 CTGTP are defined in the Health Products (Cell, Tissue and Gene Therapy Products) Regulations.

- 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.
- Class 2 CTGTP means a CTGTP other than a Class 1 CTGTP.

[3] Medicinal Product is defined in the Medicines Act.

After CTA, acceptance of CTN or a CTC has been granted by HSA, the sponsor of the trial may make amendments to the clinical trial as needed for various reasons, including, but not limited to, ensuring the continued safety of trial participants, clarifying study procedures or patient eligibility criteria and/or accommodating changing development strategies.

Trial amendments may be substantial or non-substantial. The Health Products (Clinical Trials) Regulations and the Medicines (Clinical Trials) Regulations (henceforth referred to as "the Regulations") define a substantial amendment as an amendment –

(a) Which changes a sponsor or principal investigator of the trial; or

(b) Which is likely to affect to a significant degree –

(i) The safety, or physical or mental integrity, of any subject of the trial;

(ii) The scientific value of the trial;

(iii) The conduct or management of the trial; or

(iv) The quality or safety of any investigational product used in the trial.

Sponsors are required to submit all substantial amendments of the trial to Health Sciences Authority (HSA) for approval or acceptance of notification. The sponsor must not implement any substantial amendment before HSA approval (for authorised clinical trials or trials issued with a Clinical Trial Certificate) or HSA acceptance of notification of the substantial amendment (for notified clinical trials), unless the amendment is to protect any subject of a clinical trial against any immediate hazard to the health or safety of the subject (i.e. urgent safety measure).

In addition, the sponsor is required to keep records of all substantial and non-substantial amendments to the trial, and provide such records to HSA if requested.

1.3. Scope

This guidance applies to substantial amendments to the following clinical trials:

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

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

2. DEFINITIONS

- **"amendment"** means an amendment to —

(a) any term of an application for certification to conduct a clinical trial; or

(b) any particulars or documents (including a protocol) accompanying that application;

- **"substantial amendment",** in relation to a clinical trial, means an amendment —

(a) which changes a sponsor or principal investigator of the trial; or

(b) which is likely to affect to a significant degree —

(i) the safety, or physical or mental integrity, of any subject of the trial;

(ii) the scientific value of the trial;

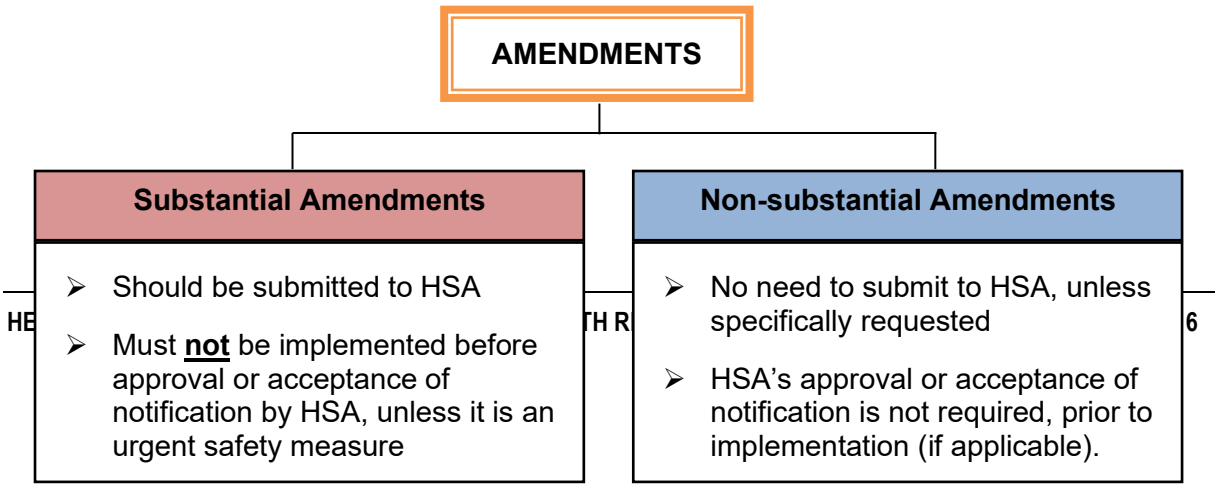
(iii) the conduct or management of the trial; or

(iv) the quality or safety of any investigational therapeutic product used in the trial

3. WHY MUST SUBSTANTIAL AMENDMENTS BE SUBMITTED TO HSA?

As substantial amendments to a clinical trial have the potential to affect the benefit-risk assessment of the trial, they should be subjected to a review process similar to the initial clinical trial application and must not be implemented before approval (for authorised clinical trials or trials issued with CTC) or acceptance of notification (for notified trials) by HSA, unless it is an urgent safety measure. Conversely, non-substantial amendments need not be submitted to HSA unless specifically requested by HSA. HSA's approval or acceptance of notification is not required prior to implementation, if applicable, of non-substantial amendments (Figure 1).

Figure 1. Types of amendments



Appendix A provides examples of amendments that may be considered as substantial. These examples may help the sponsor to determine whether the amendment should be approved or accepted by HSA before implementation.

4. WHO SHOULD DETERMINE WHETHER AN AMENDMENT IS A SUBSTANTIAL AMENDMENT?

It is the sponsor's responsibility to assess whether an amendment is regarded as substantial and to comply with the submission requirements. This assessment should be documented, as the appropriateness of the determination by the sponsor may be reviewed by HSA. The sponsor should consult HSA for advice when in doubt.

The sponsor is required to keep records of all substantial and non-substantial amendments to the trial, and provide such records to HSA if requested.

5. WHAT ARE THE SUPPORTING DOCUMENTS REQUIREMENTS?

The sponsor of the clinical trial should ensure that the details and rationale for the amendment(s) are clearly described in the submission. This can take the form of a summary table and/ or tracked change version of the original/ approved document. Table 1 illustrates the supporting documents that should be attached in the PRISM submission.

Table 1. Supporting documents for substantial amendments

Type of substantial amendments	Supporting documents
Amendment to Protocol	• Clinical Trial Protocol Amendment • Summary of Protocol Amendment • IRB Approval Letter [Mandatory for CTN]
Amendment to Informed Consent Form	• Revised Informed Consent Form • Track Change Version for Informed Consent Form

Type of substantial amendments	Supporting documents
	• IRB Approval Letter [Mandatory for CTN]
Change of Local Sponsor	• Letter from the current local sponsor indicating transfer of local sponsorship to the new local sponsor. This letter should be copied to the new local sponsor and the respective trial site PI(s) and IRB(s). • IRB Approval Letter [Mandatory for CTN]
Change of Principal Investigator	• Curriculum Vitae of Principal Investigator • Informed Consent Form, if revised • IRB Approval Letter [Mandatory for CTN]
Addition of Trial Site	• Curriculum Vitae of Principal Investigator • Informed Consent Form (for new trial site) • IRB Approval Letter [Mandatory for CTN]
Change of Manufacturer	• For change/ addition of a manufacturer, o Good Manufacturing Practice (GMP) certificate; or o Where the GMP certificate is not available, a declaration by the manufacturer of its compliance with cGMP, and the Certificate of Analysis of the product manufactured by the new manufacturer
Change of Chemistry, Manufacturing, Controls (CMC) Information [if CMC had been submitted in the initial clinical trial application]	• Supporting CMC information, where relevant

6. FREQUENTLY ASKED QUESTIONS (FAQs)

6.1. What should the sponsor do when there is a change in the contact person?

The contact person of the local sponsor is deemed to be the applicant who had submitted the most recent PRISM application for that clinical trial (excluding safety reports). E-mail reminders for submission of Trial Status Report are sent to this contact person. Hence, it is essential to inform HSA when there is a change in the contact person.

The change of local sponsor contact person can be effected through the submission of a Trial Status Report or any other application (excluding safety reports). Subsequent regulatory correspondences would thereafter be directed to the new local sponsor contact person after the submission has been processed by HSA.

6.2. What should the local sponsor do when there is a change in company address?

The local sponsor should inform HSA via e-mail at HSA_CT@hsa.gov.sg.

In addition, the local sponsor should update the company address in PRISM. To update the company address in PRISM, please go to PRISM e-Services for Clinical Trials > Amend Company Information on HSA website.

6.3. What should be done when the Principal Investigator (PI) is on extended leave?

The PI should have sufficient time to properly conduct and supervise the clinical trial. It is recommended that an amendment application for Change of PI be submitted to HSA if the PI is away on extended leave for more than 4 months.

6.4. If there is a change of Principal Investigator (PI) for a clinical trial, how can this change be documented on the Signature Sheet?

It would be recommended to complete an end date for all study staff on the current Signature Sheet; and complete a new Signature Sheet for all study staff to be authorised by the new PI.

6.5. If the Principal Investigator (PI) of a suspended / terminated / completed clinical trial has resigned, is there a need to submit an amendment application for Change of PI to HSA?

An amendment application for Change of PI must be submitted if the PI of a suspended clinical trial has resigned. However, this is not required if the PI of a terminated / completed clinical trial has resigned.

7. REFERENCES

(i) Health Products (Clinical Trials) Regulations

(ii) Medicines (Clinical Trials) Regulations

(iii) European Commission - Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)

(iv) Guidance on Determination of Whether a Clinical Trial Requires a Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or a Clinical Trial Certificate (CTC)

8. APPENDIX

8.1. Appendix A – Examples of Amendments

The following table illustrates examples of amendments that may be considered as substantial or non-substantial amendments. The list serves as an aid to guide whether submission to HSA is required. **This is not an exhaustive list.**

Type of amendment	Scope of amendments	Substantial amendments requiring submission?
Protocol/ Informed Consent Form	• Change of main study objective • Change of primary or secondary endpoint which is likely to have a significant impact to *(i) the safety, or physical or mental integrity, of any subject of the trial;* *(ii) the scientific value of the trial;* *(iii) the conduct or management of the trial* • Use of a new measurement for primary endpoint • New toxicological or pharmacological data or new interpretation of these data which is likely to impact the risk/benefit assessment • Change in the definition of the end of the trial, even if the trial has in practice already ended • Changes to inclusion/ exclusion criteria such as changes to age range, if these changes are likely to have a significant impact on the safety or scientific value of the clinical trial or the conduct or management of the trial • Addition of treatment arm (including placebo) • Changes relating to the Investigational Product (e.g. change of Investigational Product, doses, mode of administration) • Reduction of number of subject monitoring visits • Change of a diagnostic or medical monitoring procedure which is likely to have a significant impact on the safety or scientific value of the trial	**Yes.** Such amendment is typically considered as a substantial amendment.

Type of amendment	Scope of amendments	Substantial amendments requiring submission?
	• Change in the **overall** sample size for the trial • Withdrawal of an independent data monitoring board • Change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit assessment • Any change in study design that fulfils the criteria for 'substantial amendment'	
Protocol/ Informed Consent Form	• Changes to identification of trial (e.g. change of protocol title, protocol number) • Change in (competitive) enrolment target in Singapore site, but overall sample size for the trial remains unchanged • Change to overall trial duration, provided that: *(i) the subject's exposure to treatment with Investigational Product is not extended;* *(ii) the definition of end of the trial in protocol is unchanged* *(iii) subject monitoring frequency and procedures are unchanged* • Addition or deletion of overseas sites (not as a result of safety concerns) • Correction of typographical errors	**No.** Such amendment is typically not considered as a substantial amendment.
Change of Local Sponsor/ Principal Investigator/ Addition of Trial Site	• Change of local trial sponsor • Change of principal investigator • Addition of **local** trial site and principal investigator • Change of address of **local** trial site	**Yes.** Such amendment is typically considered as a substantial amendment.

Type of amendment	Scope of amendments	Substantial amendments requiring submission?
Change of Chemistry, Manufacturing, Controls (CMC) Information [if the CMC information had been submitted in the initial clinical trial application]	• Importation of the medicinal product • Change of name or code of IMPs • Immediate packaging material • Manufacturer(s) of drug substance • Manufacturing process of the drug substance • Specifications of active substance • Manufacture of the medicinal product • Specification (release or shelf-life) of the medicinal product • Specification of excipients where these may affect product performance • Shelf-life including after first opening and reconstitution • Major change to the formulation • Storage conditions • Test procedures of active substance • Test procedures of the medicinal product • Test procedures of non-pharmacopoeial excipients	**Yes, if the CMC information had been submitted in the initial clinical trial application.**
Contact information for local sponsor	• Change in contact person • Change in email, phone number, fax or postal address of contact person • Change of monitor • Change of Contract Research Organisation (CRO), provided the CRO is not a local sponsor	**No**. This is not considered as an amendment, if the local sponsor remains the same. *NB: Change in contact person or change in contact details of contact person should be notified to HSA via Trial Status Report or*

Type of amendment	Scope of amendments	Substantial amendments requiring submission?
		any other application (excluding safety reports).
Contact information for Principal Investigator	• Change in email, phone number or fax of principal investigator	**No.** This is not considered as an amendment, if the principal investigator and site address remains the same.

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