02 MAY 2017

CLINICAL TRIALS GUIDANCE

DETERMINATION OF WHETHER A CLINICAL TRIAL REQUIRES CLINICAL TRIAL AUTHORISATION (CTA), CLINICAL TRIAL NOTIFICATION (CTN) OR CLINICAL TRIAL CERTIFICATE (CTC)

GN-CTB-2-001A-002
PREFACE
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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-2-001A-001 (01 Nov 2016)
GN-CTB-2-001A-002 (02 May 2017)

SUMMARY OF AMENDMENTS

- Administrative changes made to Revision History and Section 1.3.2.
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1. INTRODUCTION

1.1. Purpose
The purpose of this document is to provide guidance to sponsors and investigators on determining whether a clinical trial requires clinical trial authorisation (CTA), clinical trial notification (CTN) or clinical trial certificate (CTC).

1.2. Background
Clinical trials of medicinal products have been regulated under the Medicines Act and the Medicines (Clinical Trials) Regulations since 1978. Under the Medicines (Clinical Trials) Regulations, a Clinical Trial Certificate (CTC) issued by HSA is required before a clinical trial of a medicinal product can be conducted.

In 2016, the regulatory controls of therapeutic products¹ (e.g. pharmaceutical drugs and biologics) were transferred from the Medicines Act to the Health Products Act. This was part of HSA’s ongoing initiative to eventually transfer, in a step-wise manner, the regulatory controls of all health products from the Medicines Act to the Health Products Act.

Other subsets of medicinal products that had yet to be transferred to the Health Products Act, such as cellular and tissue therapy products or complementary health products, will continue to be regulated under the Medicines Act.

1.2.1. Clinical Trials of Therapeutic Products
Under the Health Products Act and the new Health Products (Clinical Trials) Regulations, the existing ‘one-size-fits-all’ Clinical Trial Certificate (CTC) system will be replaced by a risk-based Clinical Trial Authorisation-Clinical Trial Notification (CTA-CTN) system. Under the new system, the requirements and the extent of pre-trial regulatory review will be risk-stratified according to the local registration status of the investigational therapeutic product used in

¹ For the purpose of this guidance, the term therapeutic product refers to therapeutic product regulated under the Health Products (Therapeutic Product) Regulations.
the clinical trial. This has been done to improve the overall resource efficiency while ensuring participants’ safety.

The CTA will be similar to the existing CTC in regard to the regulatory review process and is intended for “higher-risk” clinical trials in that they involve locally unregistered therapeutic products or unapproved use of a registered therapeutic product. On the other hand, the new CTN submission route will be introduced for clinical trials that are considered to be of “low risk” in comparison to normal medical practice, since they involve only therapeutic products used in accordance with its approved label\(^2\) (Figure 1). As such products would already have been reviewed by HSA for product registration, CTN submissions will be subjected only to a simplified regulatory screening and verification process that leverages on review by the Institutional Review Board (IRB). In most instances, this is expected to shorten clinical trial start-up timelines as compared to clinical trials that require authorisation.

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**Figure 1. CTA or CTN for clinical trials of therapeutic products**

For regulated trial involving therapeutic product(s)  
Are all products to be administered in the trial **locally registered** products?  
   
   **YES**  
   Are all these locally registered products **used in accordance with their approved labels**?  
   **YES**  
   **Clinical Trial Notification (CTN) is required.**  
   **NO**  
   **Clinical Trial Authorisation (CTA) is required.**  

\(^2\) For details on what is considered “used in accordance with its approved label”, refer to Section 3 of this guidance.
1.2.2. Clinical Trials of Medicinal Products

Clinical trials of medicinal products (e.g. cellular and tissue therapy products or complementary health products) would continue to require a CTC issued by HSA before the trial can be conducted (Figure 2).

![Figure 2. CTC for clinical trials of medicinal products](image)

1.2.3. Exclusion of Observational Clinical Trials

Observational clinical trials will be excluded from the regulatory controls under the Health Products Act and the Medicines Act. This is in consideration that the decision to prescribe the therapeutic product or medicinal product is not dictated by the clinical trial protocol, and any risk relating to the use of the product in the observational clinical trial would be no different from the use of the product in the clinical practice setting. The exclusion of observational clinical trials from the regulatory controls reduces compliance costs and resources which, even if invested, may not necessarily result in enhanced subject safety.
1.2.4. Clinical Trial Submission Routes

Table 1 shows the differences between the three clinical trial submission routes (CTC, CTA and CTN).

Table 1. Summary of Clinical Trial Submission Routes

<table>
<thead>
<tr>
<th>Types of Clinical Trials</th>
<th>Requirement for Medicinal Products under the Medicines Act</th>
<th>Requirement for Therapeutic Products after transfer to the Health Products Act</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTC</td>
<td>60 working days for cell and tissue products</td>
<td>30 working days*</td>
</tr>
<tr>
<td></td>
<td>30 working days for other types of medicinal products</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(e.g. complementary health products)</td>
<td></td>
</tr>
<tr>
<td>CTA</td>
<td>30 working days*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Exception: 15 working days for Phase 1 clinical trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>solely to evaluate bioequivalence, bioavailability, food</td>
<td></td>
</tr>
<tr>
<td></td>
<td>effect or drug-drug interaction</td>
<td></td>
</tr>
<tr>
<td>CTN</td>
<td>5 working days</td>
<td></td>
</tr>
</tbody>
</table>

Clinical trials investigating
- Locally unregistered products
- Locally registered products not used in accordance with approved label*

Clinical trials assessing locally registered products used in accordance with approved label*

*For details on what is considered “used in accordance with its approved label”, refer to Section 3 of this guidance.
1.3. Scope

1.3.1. This guidance applies to the following types of clinical trials conducted in Singapore:

(i) Clinical trials of Therapeutic Products

(ii) Clinical trials of Medicinal Products (e.g. Cell, Tissue and Gene Therapy Products; or Complementary Health Products)

1.3.2. This guidance does not apply to the following types of clinical trials:

(i) Observational trials on registered therapeutic products, where all of the following conditions are met in respect of each product:

(a) The product is prescribed by a qualified practitioner to a patient in the usual manner in accordance with the terms of the product registration;

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

(c) The assignment of any patient involved in the trial to a particular therapeutic strategy in which the product is used is not decided in advance by a protocol but falls within the current practice of the qualified practitioner carrying out the trial.

(ii) Observational trials on approved medicinal products, where all of the following conditions are met in respect to each product:

(a) The product is prescribed by a qualified practitioner to a patient in the usual manner in accordance with the terms of the product license;

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

(c) The assignment of any patient involved in the trial to a particular therapeutic strategy in which the product is used is
not decided in advance by a protocol but falls within the current practice of the qualified practitioner carrying out the trial.

(iii) Clinical Trials on Medical Devices
Clinical trials on medical devices are not regulated by HSA.

The import and supply of medical devices used for a clinical purpose in any clinical research is regulated as a Clinical Research Material (CRM), it is thus subject to regulatory requirements under the Health Products (Medical Devices) (Amendment) Regulations 2016. Please refer to the Guidance on Clinical Research Materials.

2. STEP-BY-STEP DECISION PROCESS

To determine whether regulatory submission is required for a particular study and the applicable route of regulatory submission (i.e., CTA, CTN or CTC), it is necessary, first of all, to know, or to determine

- the product classification of the investigational product(s) (e.g. medicinal product or therapeutic product), and
- how the investigational product is to be used in the clinical trial (e.g. whether the product is used for a medicinal/therapeutic purpose; whether the use is in accordance with the approved label\(^3\))

Figure 3 provides a simplified schematic overview of the step-by-step decision making process to determine whether a clinical trial is regulated by HSA and the route of regulatory submission. Annex 1 provides the detailed step-by-step decision-making process.

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\(^3\) For details on what is considered “used in accordance with its approved label”, refer to Section 3 of this guidance.
The sponsor plans to conduct a clinical study in Singapore and would like to know if the study is regulated by HSA (i.e. whether submission to HSA is required).

**STEP 1:**
Is the product(s) used in the clinical trial a therapeutic product or medicinal product?  
(Refer to Annex Section 6.1 Determination of product classification)

Note:
- **Therapeutic products** typically refer to pharmaceutical drugs whose active ingredient is a chemical or biological entity.
- **Medicinal products** typically refer to products other than pharmaceutical drugs, such as Cell-, Tissue- and Gene Therapy Products or Complementary Products (e.g. Chinese proprietary medicine).

**STEP 2:**
Is the product the subject of investigation in the trial (i.e. purpose of using the product)?  
(Refer to Annex Section 6.2 Determination of whether the product is the subject of investigation in the trial (i.e. purpose of using the product)

**STEP 3:**
Is the trial an observational trial?  
(Refer to Annex Section 6.3 Determination of whether the trial is an observational trial)

**STEP 4:**
The trial is regulated by HSA. Which submission route (i.e. CTA, CTN or CTC) should sponsor apply?  
(Refer to Annex Section 6.4 For regulated trials, determination of route of regulatory submission (i.e. CTA, CTN or CTC))
3. WHAT IS CONSIDERED AS “USED IN ACCORDANCE WITH APPROVED LABEL”

As highlighted in previous sections, clinical trials that only involve locally registered therapeutic products used in accordance with their approved labels would be subject to the regulatory requirements for a CTN. A therapeutic product is considered to be “used in accordance with approved label” if the product is used in the usual manner in accordance with the terms of product registration in Singapore4.

The following uses are examples of off-label use (even if the use is established practice and/ or supported by published evidence and/ or guidelines), thus trials which use the therapeutic product in such manner do not qualify for the CTN submission route:

(i) Use in an indication different from the approved indication(s)
(ii) Use in a patient population different from the approved population(s)
(iii) Use of a dosing regimen that is different from the approved regimen
(iv) Use of a dosage form that is different from the approved form
(v) Any other off-label use

4. HEALTHY VOLUNTEER AND PLACEBO-CONTROLLED TRIALS

4.1. Healthy volunteer trials

All healthy volunteer trials, which involve locally unregistered therapeutic products (e.g. Phase I clinical trials), will require a CTA. The same requirement for a CTA would apply to healthy volunteer trials which involve locally registered therapeutic products, unless the products are used in accordance with approved labels and the approved population in the terms of product registration is healthy individuals (e.g. vaccine given usually to healthy individuals).

4 The list of licensed products and their current approved Package Inserts can be found on the HSA Online Information Search (Infosearch) page.
4.2. Placebo-controlled clinical trials

It is possible that a placebo control arm is included in clinical trials involving locally registered therapeutic products used in accordance with approved labels. While placebo comparator is usually an unregistered product, the inert nature of the placebo renders the use of an unregistered placebo to be of “low risk” in comparison to the use of an unregistered therapeutic product. Therefore, such trial will be subject to the regulatory requirements for a CTN (instead of a CTA).

5. REFERENCES

(i) Health Products Act
(ii) Medicines Act
(iii) Health Products (Clinical Trials) Regulations
(iv) Medicines (Clinical Trials) Regulations
(v) Medicines (Non-Medicinal Products) (Consolidation) Order
6. ANNEX – DETAILED STEP-BY-STEP DECISION CHARTS

6.1. Determination of product classification: therapeutic product or medicinal product?

6.1.1. To determine if the product is a therapeutic product

Note: Therapeutic products typically refer to pharmaceutical drugs whose active ingredient is a chemical or biological entity.

Does the product used in your study fulfill the following definition?

Is it a substance intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose, including any of the following purposes:

(a) for preventing, diagnosing, monitoring, treating, curing or alleviating any disease, disorder, ailment, injury, handicap or abnormal physical or mental state, or any symptom thereof;
(b) for investigating, modifying, or replacing any physiological process;
(c) for influencing, controlling or preventing conception;
(d) for inducing anaesthesia;

AND has as its constituent any of the following active ingredients:

(i) any chemical or botanical element, naturally-occurring chemical or botanical material or chemical product obtained by chemical change or synthesis;
(ii) any metabolite from a micro-organism;
(iii) any macromolecule extracted from an organism; or
(iv) any substance derived from a biological system,

AND exerts an inherent effect either pharmacologically, chemically or by other physiological means, leading to its use for a therapeutic, preventive, palliative or diagnostic purpose?

Is the product in your study any of the following?

(i) a medical device;
(ii) a product containing human or animal cell or tissue;
(iii) a substance administered to humans with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;
(iv) whole blood or any blood component;
(v) a Chinese proprietary medicine;
(vi) a homoeopathic medicine;
(vii) a medicated oil or balm;
(viii) a quasi-medicinal product;
(ix) a traditional medicine.

YES

NO

It is a Therapeutic Product
6.1.2. To determine if the product is a medicinal product

Note: Medicinal products typically refer to products other than pharmaceutical drugs, such as Cell-, Tissue- and Gene Therapy Products or Complementary Products (e.g. Chinese proprietary medicine).

Does the product used in your study fulfil the following definition?

Is it a substance or article which is manufactured, sold, supplied, imported or exported for use wholly or mainly by being administered to one or more human beings, or as an active ingredient in the preparation of a substance or article which is to be administered to one or more human beings, for one or more of the following purposes:
(a) treating or preventing disease;
(b) diagnosing disease or ascertaining the existence, degree or extent of a physiological condition;
(c) contraception;
(d) inducing anaesthesia;
(e) otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by way of terminating, reducing or postponing, or increasing or accelerating, the operation of that function or in any other way?

If the product used in your study is determined to be **neither a therapeutic product nor a medicinal product**, the activity is thus not a clinical trial regulated under the Health Products Act or Medicines Act.

If you are still unsure whether your product meets the definition of therapeutic product or medicinal product, please complete the **Health Product Classification Form** on HSA website.
6.2. Determination of whether the product is the subject of investigation in the trial (i.e. purpose of using the product)

Does the trial involving the therapeutic product or medicinal product fulfil at least one of the following criteria?

For therapeutic product, Is the trial intended to
(a) discover or verify the clinical, pharmacological or pharmacodynamics effects of the product;
(b) identify any adverse effect that may arise from the use of the product;
(c) study the absorption, distribution, metabolism and excretion of the product; or
(d) to ascertain the safety or efficacy of the product?

For medicinal product, Is the administration of the product in the trial for the purpose of ascertaining the effects of the product, whether beneficial or harmful?

The trial is regulated under the Health Products (Clinical Trials) Regulations, unless it fulfils the criteria of an observational trial (See Section 4.3).

The activity is not a clinical trial regulated under the Medicines Act
6.3. Determination of whether the trial is an observational trial

Does the trial involving the therapeutic product or medicinal product fulfil all the following criteria?

(a) The product is prescribed by a qualified practitioner to a patient in the usual manner in accordance with the terms of the product licence/registration;

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

(c) The assignment of any patient involved in the trial to a particular therapeutic strategy in which the product is used is not decided in advance by a protocol but falls within the current practice of the qualified practitioner carrying out the trial

YES

The trial is an observational trial, thus the activity is not a clinical trial regulated under the Health Products (Clinical Trials) Regulations or Medicines (Clinical Trials) Regulations.

NO

The trial is regulated under the Health Products (Clinical Trials) Regulations or Medicines (Clinical Trials) Regulations.
6.4. For regulated trials, determination of route of regulatory submission (i.e. CTA, CTN or CTC)

For regulated trial involving therapeutic product(s)

Are all products to be administered in the trial locally registered products?

YES

Are all these locally registered products used in accordance with their approved labels?

YES

Clinical Trial Notification (CTN) is required.

NO

Clinical Trial Authorisation (CTA) is required.

For regulated trial involving medicinal product(s)

Clinical Trial Certificate (CTC) is required.
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