HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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CLINICAL TRIALS GUIDANCE

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

GN-IOCTB-01 Rev. No. 003

HSA Health Sciences Authority

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.

CONTACT INFORMATION

For further information, please contact:

Innovation Office & Clinical Trials Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way, #11-01, Helios
Singapore 138667

Email: HSA_CT@hsa.gov.sg
Website: www.hsa.gov.sg

REVISION HISTORY

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SUMMARY OF AMENDMENTS

- Added a new category of health product, i.e., Cell, Tissue and Gene Therapy Products (CTGTPs), that is regulated under the Health Products Act
- Added a new section on trials involving imaging agents (Section 5.3)
- Amended the mode of Product Enquiry Form submission (Section 7.1)
- Amended the term “subjects” to “trial participants”

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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[1] 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 products[2] (e.g. pharmaceutical drugs and biologics) were transferred from the Medicines Act to the Health Products Act, and clinical trials of therapeutic products were regulated under the Health Products (Clinical Trials) Regulations.

In 2021, a new category of health products, i.e., cell, tissue and gene therapy products (CTGTPs)[2], was included in the First Schedule of the Health Products Act and regulated under the Act.

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

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

CTGTPs are risk-stratified into two classes as follows:

- Class 1 CTGTP[3] 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[3] means a CTGTP other than a Class 1 CTGTP.

Only clinical trials of a Class 2 CTGTP are regulated by HSA under the Health Products (Clinical Trials) Regulations. Clinical trials of a Class 1 CTGTP are not regulated by HSA. However, they are required to comply with the requirements of the Human Biomedical Research Act.

1.2.1. Clinical Trials of Therapeutic Products and Class 2 Cell, Tissue and Gene Therapy Products (CTGTPs)

The Health Products (Clinical Trials) Regulations provide a risk-based approach to the regulation of clinical trials, whereby the requirements and the extent of pre-trial regulatory review are risk-stratified according to the local registration status of the investigational product used in the clinical trial. The risk stratification of the clinical trials is intended to improve the overall resource efficiency while ensuring trial participants' safety.

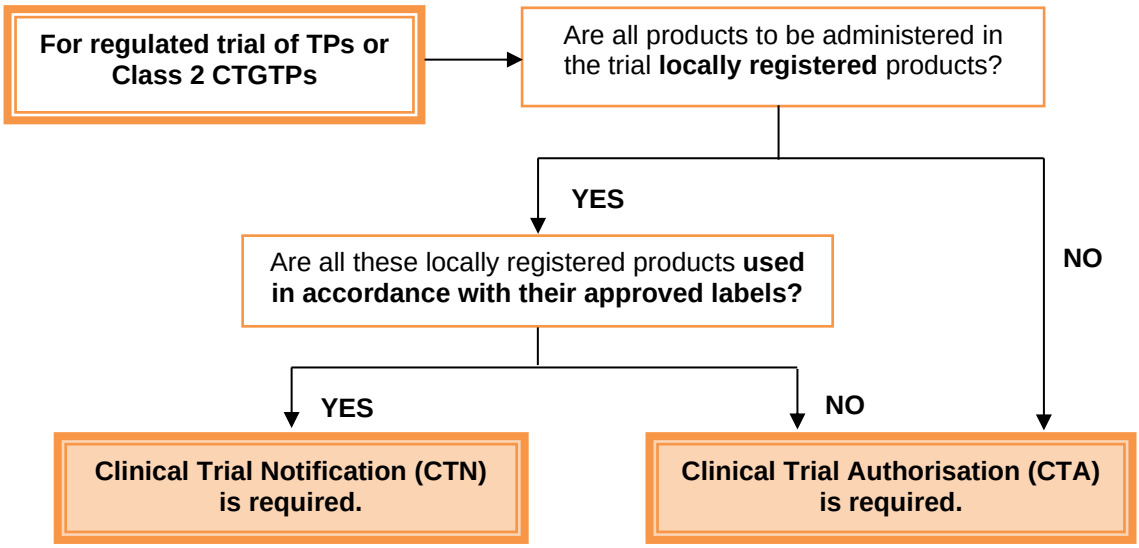
A Clinical Trial Authorisation (CTA) is required for a "higher risk" clinical trial of a locally unregistered therapeutic product or Class 2 CTGTP, or involving an unapproved use of a locally registered therapeutic product or Class 2 CTGTP. In contrast, a "lower risk" clinical trial of a locally registered product or Class 2 CTGTP that is used in accordance with its approved label[4] will only be required

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

[4] Refer to Section 4 of this guidance for further information on use in accordance with approved label.

to be notified to HSA through a Clinical Trial Notification (CTN). As locally registered 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 the 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.

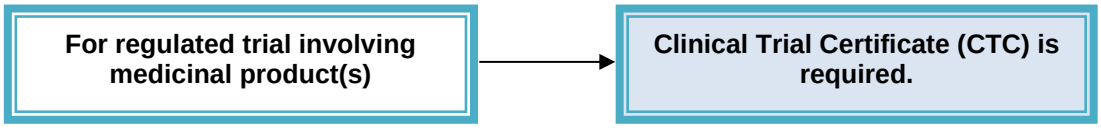
Figure 1. CTA or CTN for clinical trials of Therapeutic Products (TPs) or Class 2 CTGTPs



1.2.2. Clinical Trials of Medicinal Products

Clinical trials of medicinal products require a CTC to be issued by HSA before the trial can be conducted (Figure 2). Such clinical trials are regulated under the Medicines Act and the Medicines (Clinical Trials) Regulations.

Figure 2. CTC for clinical trials of medicinal products



1.2.3. Exclusion of Observational Clinical Trials

Observational clinical trials are 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, Class 2 CTGTP 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 trial participant safety.

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 or Class 2 CTGTPs

(ii) Clinical trials of Medicinal Products

1.3.2. This guidance <u>does not</u> apply to the following types of clinical trials. Such research will be regulated under the Human Biomedical Research Act.

(i) Observational trials of registered therapeutic products or registered Class 2 CTGTPs, 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 of 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 of 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) Regulations. Please refer to the *Guidance on Clinical Research Materials*.

(iv) Clinical trials of Class 1 CTGTPs

Clinical trials of Class 1 CTGTPs are not regulated by HSA.

2. CLINICAL TRIAL SUBMISSION ROUTES

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

Table 1. Summary of Clinical Trial Submission Routes

Types of Clinical Trials	Clinical trials of Therapeutic Products and Class 2 CTGTPs		Clinical trials of Medicinal Products
	CTA	CTN	CTC
Regulatory processing timelines	30 working days for therapeutic products 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 CTGTPs	5 working days	30 working days
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 4 of this guidance.*

3. 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:

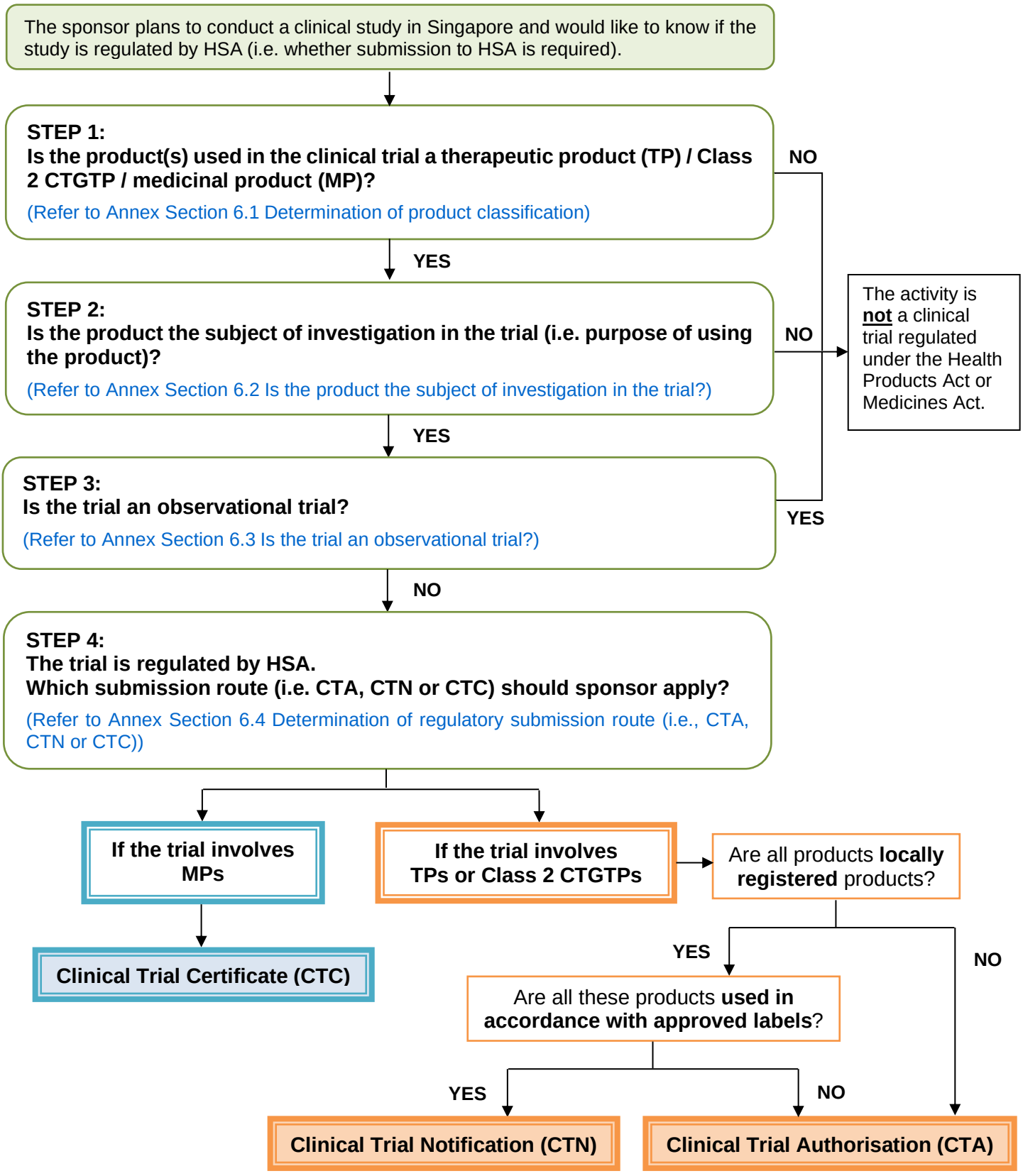
(i) the product classification of the investigational product(s) (e.g. therapeutic product, Class 2 CTGTP or medicinal product); and

(ii) 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[5]

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.

[5] Refer to Section 4 of this guidance for further information on use in accordance with approved label.

Figure 3. Simplified schematic overview of step-by-step decision-making process



4. WHAT IS CONSIDERED AS "USED IN ACCORDANCE WITH APPROVED LABEL"

As highlighted in previous sections, clinical trials that only involve locally registered therapeutic products or locally registered Class 2 CTGTPs used in accordance with their approved labels would be subject to the regulatory requirements for a CTN.

A 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 Singapore[6].**

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 or Class 2 CTGTP 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

5. HEALTHY VOLUNTEER, PLACEBO-CONTROLLED, AND IMAGING AGENT TRIALS

5.1. 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).

[6] The list of licensed products and their current approved Package Inserts can be found on the HSA Infosearch available on the HSA website.

5.2. Placebo-controlled clinical trials

It is possible that a placebo control arm is included in clinical trials involving locally registered therapeutic products or locally registered Class 2 CTGTPs 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 or unregistered Class 2 CTGTP. Therefore, such trials will be subject to the regulatory requirements for a CTN (instead of a CTA).

5.3. Imaging agent trials

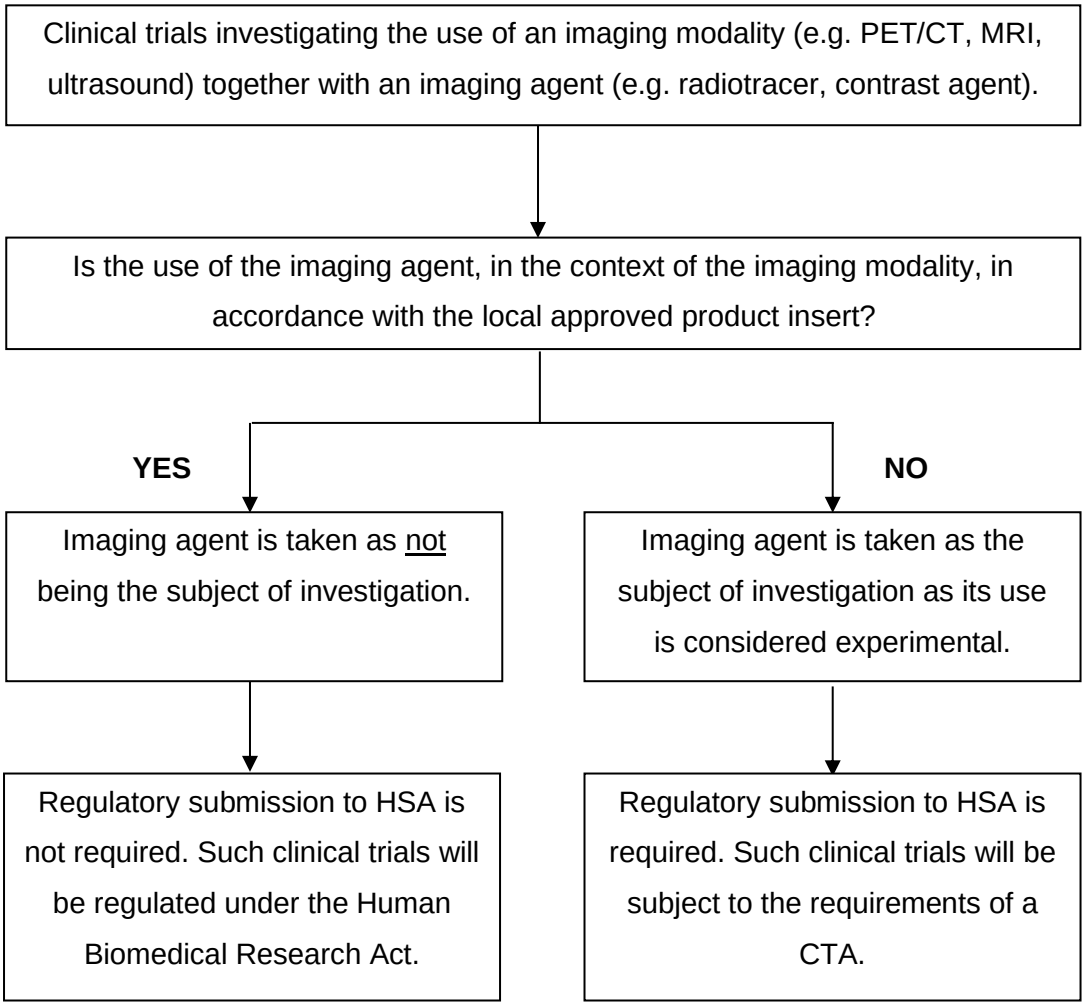
Clinical trials investigating the use of an imaging modality (e.g. PET / CT, MRI, ultrasound) together with an imaging agent (e.g. radiotracer, contrast agent) will be subject to the regulatory requirements for a CTA, if the imaging agent, in the context of the imaging modality, is not used in accordance with its local approved product label, and is therefore taken as the subject of investigation (as its use is considered experimental).

Regulatory submission is not required for clinical trials investigating the use of an imaging modality together with an imaging agent, if the imaging agent, in the context of the imaging modality, is used in accordance with its local approved product label, and therefore taken as not being the subject of investigation.

Such clinical trials will be regulated under the Human Biomedical Research Act.

Refer to Figure 4 for further details.

Figure 4. Clinical trials investigating the use of an imaging modality together with an imaging agent



6. REFERENCES

(i) Health Products Act

(ii) Medicines Act

(iii) Health Products (Clinical Trials) Regulations

(iv) Medicines (Clinical Trials) Regulations

(v) Health Products (Cell, Tissue and Gene Therapy Products) Regulations

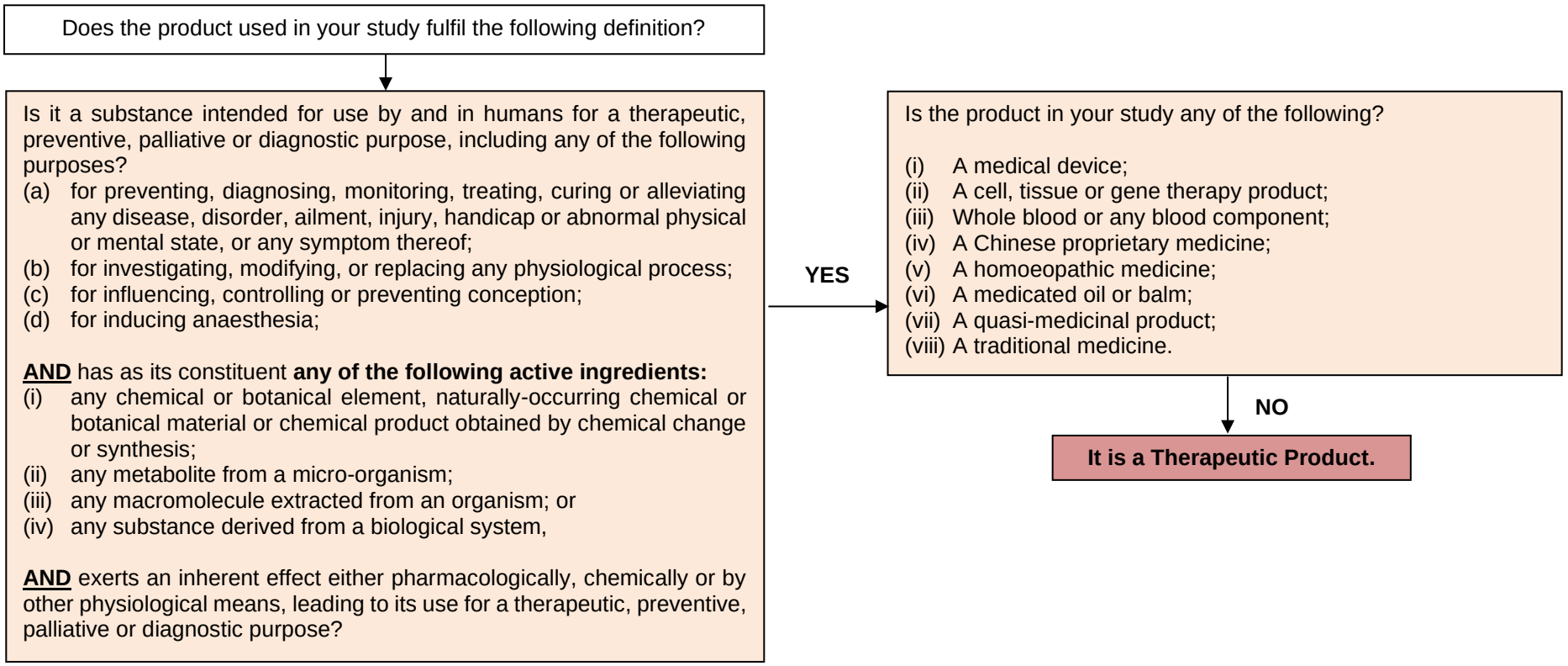
(vi) Medicines (Non-Medicinal Products) (Consolidation) Order

7. ANNEX – DETAILED STEP-BY-STEP DECISION CHARTS

7.1. Determination of product classification

7.1.1. Is the product a <u>therapeutic product</u>?

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



7.1.2. Is the product a <u>cell, tissue or gene therapy product?</u>

Does the product used in your study fulfil 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?
(i) for preventing, diagnosing, treating, curing or alleviating any disease, disorder, injury, ailment, handicap or abnormal physical or mental state, or any symptom thereof;
(ii) for replacing, repairing, regenerating or reconstructing any anatomy, or for modifying or replacing any physiological processes;
(iii) for regulating, repairing, replacing, adding or deleting a genetic sequence or modifying genetic material; or
(iv) for supporting or sustaining life.

<u>AND</u> has as a constituent **any of the following substances or combination of substances:**
(i) Viable or non-viable human cells or tissues;
(ii) Viable animal cells or tissues;
(iii) Recombinant nucleic acids, where the effect of the recombinant nucleic acid relates directly to the recombinant nucleic acid sequence that it contains or to the product of the genetic expression of its sequence

<u>AND</u> achieves its primary intended action by pharmacological, immunological, physiological, metabolic or physical means, leading to its use for a therapeutic, palliative or diagnostic purpose?

YES

Is the product in your study any of the following?
(a) A recombinant vaccine for a preventive purpose;
(b) In-vitro diagnostic product;
(c) Bone marrow, peripheral blood or umbilical or placental cord blood from a human that is minimally manipulated[7] and intended for homologous use[8];
(d) Cells & tissues obtained from a patient that are minimally manipulated and re-implanted for homologous use into the same patient during the same surgical procedure;
(e) Organs and tissues that are minimally manipulated and intended for transplant;
(f) Reproductive cells (sperm, eggs) and embryos intended for assisted reproduction;
(g) Whole blood and any blood component that is minimally manipulated and intended for treating blood loss or blood disorders.

NO

It is a Cell, Tissue or Gene Therapy Product.

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.

NB: Clinical trials of Class 1 CTGTP will be regulated under the Human Biomedical Research Act.

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

NB: Clinical trials of Class 2 CTGTP will be regulated under the Health Products (Clinical Trials) Regulations.

[7] "Minimally manipulated" means processing the cell or tissue by way of any process so that the biological characteristics or functions of the cell or the structural properties of the tissue (as the case may be) are not altered.

[8] "Homolgous use" means the use of a CTGTP to repair, reconstruct, replace or supplement the cells or tissue of an individual if the CTGTP perform the same basic function or functions in the recipient as the original cells or tissue in the donor in the same anatomical or histological environment.

7.1.3. Is the product a medicinal product?

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?

YES

Is the product in your study any of the following?

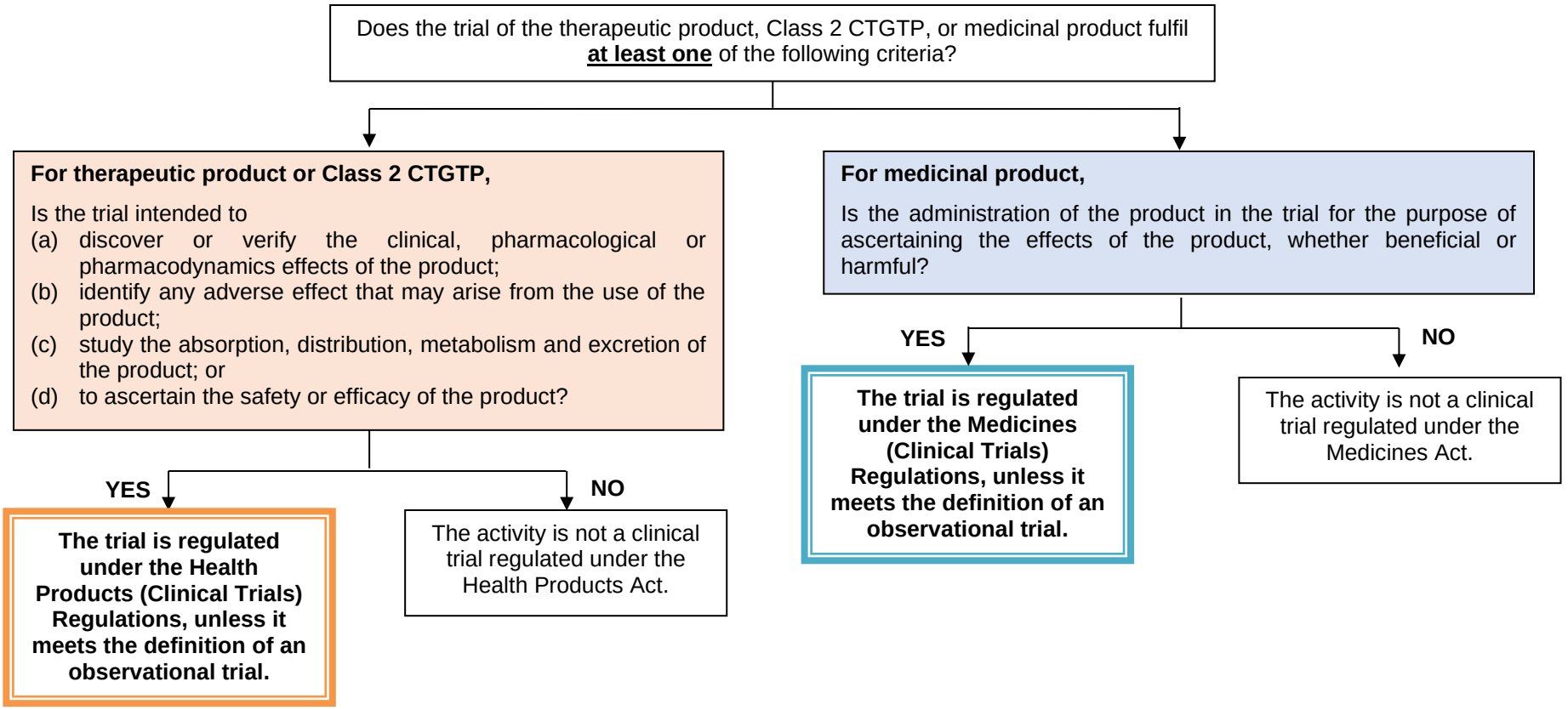
(a) Phisoderm (oily and normal formulations);
(b) anti-wrinkle or rejuvenation substances which do not contain any ingredient specified in the Poisons Act (Cap. 234);
(c) substances used for the treatment of freckles and age-spots which do not contain any ingredient specified in the Poisons Act;
(d) sunscreen substances which do not contain any ingredient specified in the Poisons Act;
(e) face cleansers which help to prevent pimples and acne (excluding those for the treatment of pimples) which do not contain any ingredient specified in the Poisons Act;
(f) substances used for the treatment of nappy rash and prickly heat which do not contain any ingredient specified in the Poisons Act;
(g) ginseng tea;
(h) garlic pills;
(i) high protein preparations or substances used for slimming;
(j) oyster, yeast or mushroom extracts;
(k) herbal tea drinks;
(l) anti-dandruff preparations which do not contain any ingredient specified in the Poisons Act;
(m) health foods with vague or general medicinal claims;
(n) sweets for relieving cough and throat irritations;
(o) staminade powder;
(p) mouthwashes and gargles for bad breath and for general oral hygiene; and
(q) substances used for bleaching and to reduce pigmentation which do not contain any ingredient specified in the Poisons Act (Cap. 234).

NO

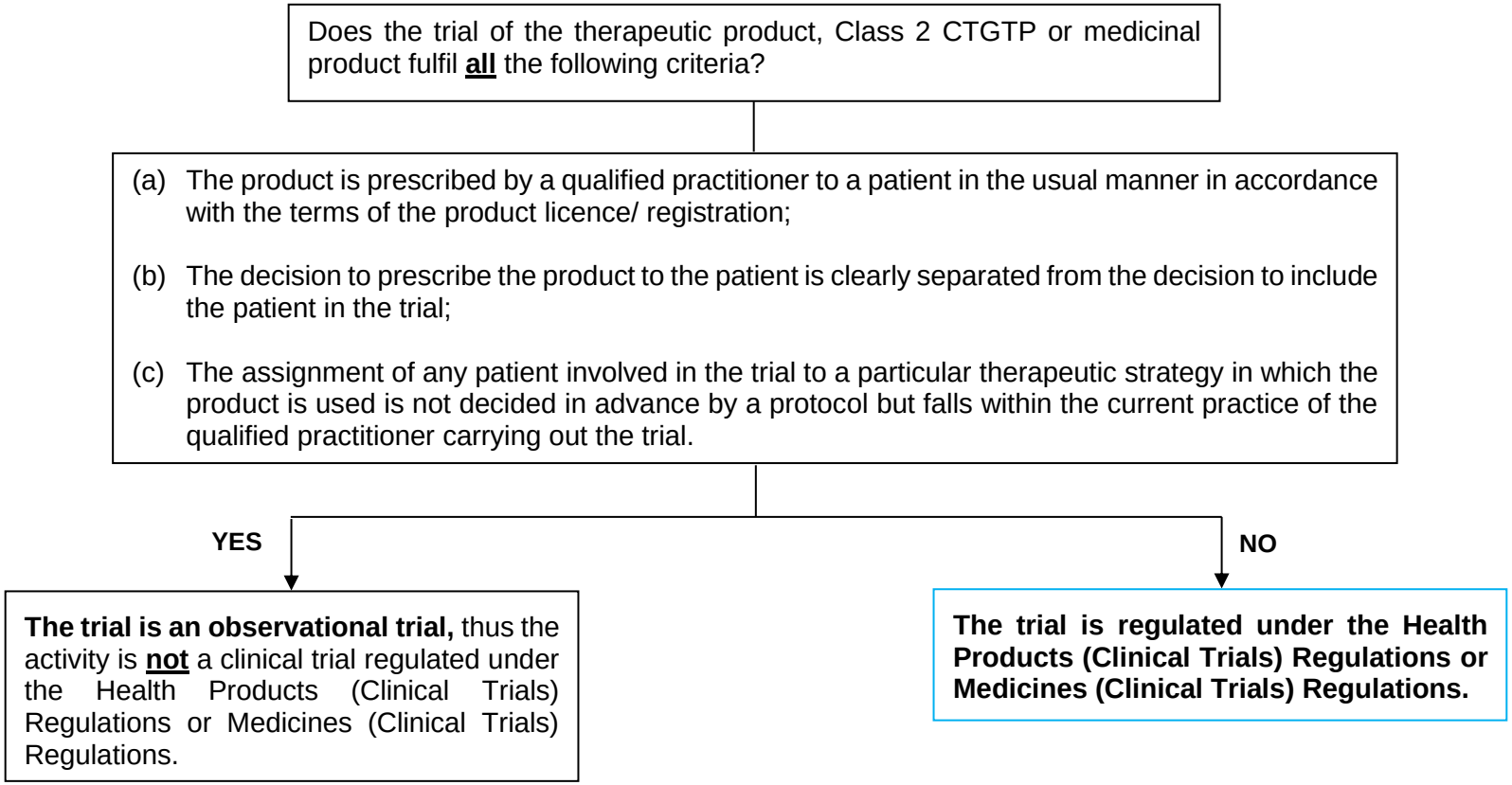
It is a Medicinal Product.

If you are still unsure whether your product meets the definition of therapeutic product / cell, tissue or gene therapy product / medicinal product, please submit a Health Product Classification Enquiry through the HSA website (https://www.hsa.gov.sg/).

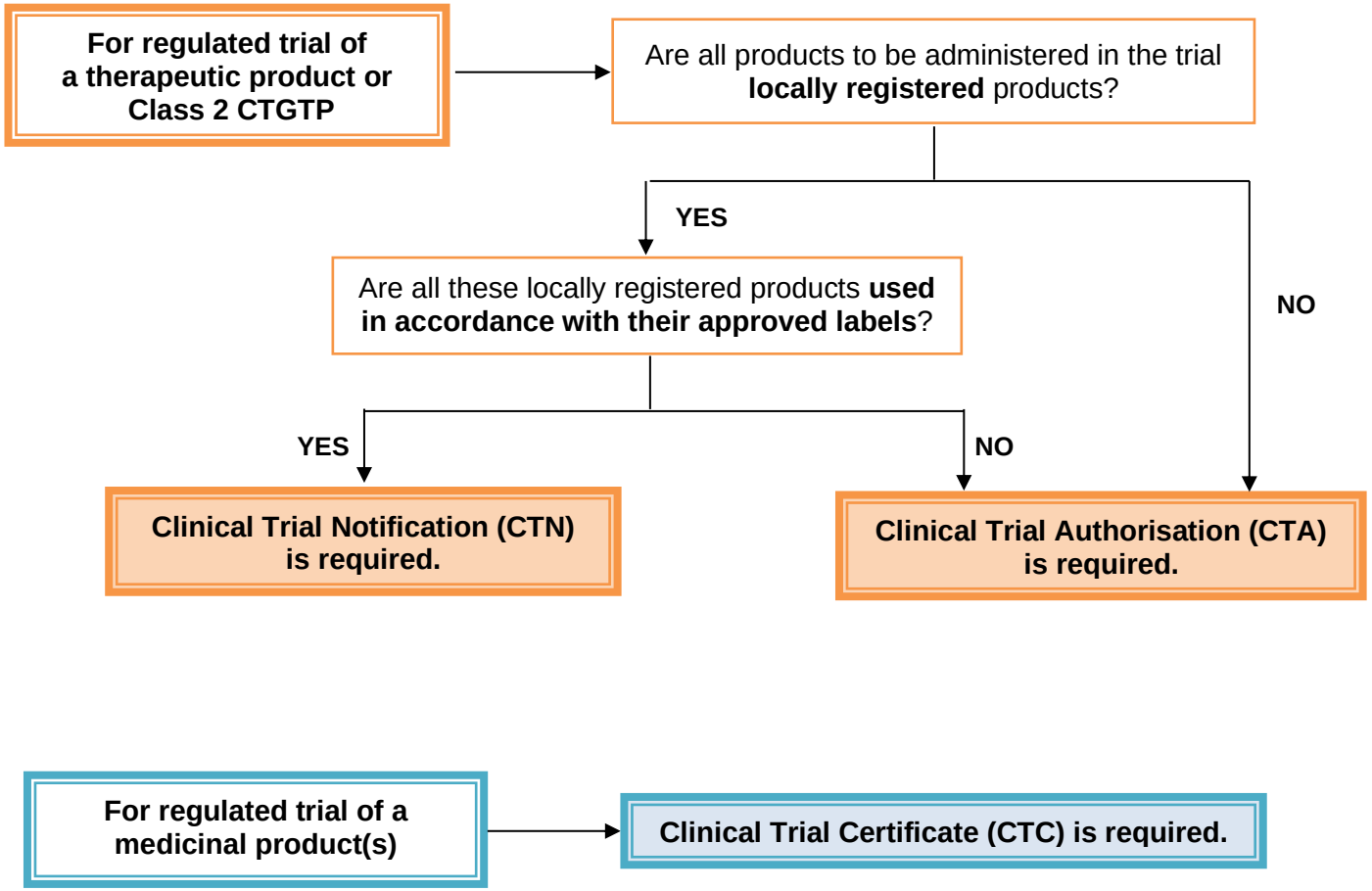
7.2. Is the product the subject of investigation in the trial?



7.3. Is the trial an observational trial?



7.4. Determination of regulatory submission route (i.e., CTA, CTN or CTC)



HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
Blood Services Group
Applied Sciences Group

www.hsa.gov.sg

CONTACT INFORMATION:

Innovation Office & Clinical Trials Branch

Health Products Regulation Group

Health Sciences Authority

11 Biopolis Way, #11-03, Helios

Singapore 138667

Email: HSA_CT@hsa.gov.sg

Website: www.hsa.gov.sg

HSA
Health Sciences Authority