

**Baker
McKenzie.**

CLINICAL TRIALS HANDBOOK Asia Pacific



SINGAPORE

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Singapore

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Introduction

Clinical trials are regulated by the Clinical Trials Branch of the Health Sciences Authority of Singapore (HSA).

Regulatory framework

In 2016, the regulations governing therapeutic products were shifted from the Medicines Act (Cap 176) (MA) to the Health Products Act (Cap 122D) (HPA), while the regulations governing medicinal products remained in the MA. Therapeutic products generally refer to pharmaceutical drugs that have biological or chemical entities as active ingredients. Conversely, medicinal products generally refer to products that are not pharmaceutical drugs, such as gene therapy products.

Additionally, the Health Products (Clinical Trials) Regulations 2016 (“**HPCT Regulations**”) were introduced to regulate clinical trials concerning therapeutic products. This introduction meant that there are now two clinical trial regimes — the HPCT Regulations and the Medicines (Clinical Trials) Regulations (“**MCT Regulations**”), which regulate therapeutic products and medicinal products, respectively.

According to the HPCT Regulations, all clinical trials for therapeutic products have to be in accordance with the principles of good clinical practice. This is similar to clinical trials for medicinal products, which, according to the MCT Regulations, have to comply with the relevant guidelines or instructions, including the Singapore Guideline for Good Clinical Practice (**GCP**). The GCP is a set of substantive guidelines that are to be adhered to in maintaining an international ethical and scientific quality standard for the conduct of clinical trials. It was adapted from the International Conference on Harmonization (**ICH**) Guideline for Good Clinical Practice, which was implemented on 1 August 1998, and first revised on 1 October 1999.

Therapeutic products

In 2016, the Clinical Trial Certificate (**CTC**) system, which used to apply to all clinical trials, was substituted by a risk-based Clinical Trial Authorisation – Clinical Trial Notification (**CTA-CTN**) system. Based on this system, the therapeutic products that will be used in a clinical trial will be risk-classified based on their local registration status, such that different requirements and degrees of pre-trial regulatory review are applied for the different classifications.

The CTA, which is akin to the CTC with regard to the regulatory review process, is meant for clinical trials that concern the unapproved use of registered therapeutic products or locally unregistered therapeutic products, which tend to be of a riskier nature.

Conversely, the CTN is meant for clinical trials that concern only therapeutic products that are used in accordance with their approved labels, which entail less risk. In such cases, since the products have already been reviewed by the HSA for product registration, any submissions through the CTN will only have to undergo a simplified regulatory screening and verification process.

Medicinal products

All clinical trials on medicinal products conducted in Singapore continue to require CTCs from the HSA.

Clinical trial agreements (CTAGs)

All clinical trials on medicinal products conducted in Singapore require the following:

- A CTC issued by the HSA
- Approval from the relevant Institutional Review Board (**IRB**) of the institution where the research is to take place

The applications to the HSA and the IRB can be done in parallel.

All clinical trials on therapeutic products that concern the unapproved use of registered therapeutic products or locally unregistered therapeutic products require the following:

- Authorization by the HSA
- Approval from the relevant IRB of the institution where the research is to take place

The applications to the HSA and the IRB can be done in parallel.

Finally, all clinical trials on therapeutic products that are used in accordance with their approved labels only require an acceptance of notification by the HSA.

The application to the HSA can only be done after IRB approval has been obtained.

As CTAGs are private agreements between the parties and are not subject to the review of the HSA, there are no requirements that the parties must fulfil before entering into CTAGs for the conduct of clinical trials in Singapore. However, it is prudent to ensure that each CTAG is reviewed for compliance with all applicable laws, regulations and guidance in Singapore, so that the parties' respective rights and obligations do not fall foul of these.

Apart from the CTAG, it is necessary to obtain a CTA, CTN or CTC (depending on the subject matter of the clinical trial) for the conduct of a clinical trial in Singapore. A local representative acting in the capacity of a local sponsor is responsible for making the application for the CTA, CTN or CTC, and for procuring the approval from the appropriate IRB before initiation of the clinical trial.

Additionally, the sponsor should also submit a Clinical Research Materials (**CRM**) notification on behalf of the importer or local manufacturer, ideally at the same time as the initial CTA/CTN/CTC application so as to streamline the process. During the drafting stage, the importer or local manufacturer will need to endorse the submission electronically to provide assurance that they are informed of their duties under the CRM regulations and that they agree to fulfil them. The sponsor can thereafter submit the endorsed CRM notification together with the CTA/CTN/CTC application. If successful, a CRM notification will be automatically generated by PRISM, which is the HSA's regulatory e-Service platform.

CRM notifications are valid for the duration of the clinical trial.

For therapeutic products, each CTA or CTN is valid throughout the length of the clinical trial.

For medicinal products, each CTC is valid for a period of two years, unless otherwise stated. It should be noted that the CTC, which the HSA issues to the principal investigator, is specific for each study protocol and for each institution or site involved in the study.

When entering into a CTAG for the conduct of a clinical trial in Singapore, there are no express requirements as to the type of insurance that must be obtained and/or maintained. However, pursuant to the HPCT Regulations, the CTA can be granted and the CTN can be given, subject to such terms and conditions as the HSA may think fit to impose,

including any condition requiring the sponsor of a clinical trial to obtain and maintain insurance to provide compensation in the event of injury or loss arising from the conduct of the clinical trial on such terms as the HSA may approve. The same applies for the issuance of a CTC, pursuant to the MCT Regulations. A local representative acting in the capacity of a local sponsor is responsible for ensuring that such insurance or other conditions imposed are complied with.

The party responsible for the costs of obtaining and/or maintaining such insurance is not prescribed by any laws or regulations and can be agreed on between the respective parties.

An indemnity or bond in order to conduct a clinical trial is not required by any laws or regulations. As noted above, however, the CTA may be granted, the CTN may be given, or the CTC may be issued subject to such terms and conditions as the HSA may think fit to impose.

In such event, the local representative acting in the capacity of local sponsor is responsible for ensuring that such conditions imposed are fulfilled and/or adhered to.

There are no specific additional requirements affecting the different trial phases.

Sponsor and contract research organizations (CROs)

There are two possible meanings of “sponsor” in the Singapore context:

- i. The ultimate sponsor located overseas
- ii. The local representative acting in the capacity of a local sponsor for the purpose of submitting the clinical trial application and therefore assuming the obligations of a sponsor as the term is referenced in the relevant regulations and the GCP (if any)

In (i), the legal functions of a sponsor are as contractually agreed between the parties, given that such a sponsor is not treated as a sponsor in the manner that the term is used in the HPCT Regulations, the MCT Regulations or the GCP for setting out the obligations, responsibilities and duties of a sponsor.

In (ii), the legal function of a sponsor (which is a local representative acting in the capacity of a local sponsor) is to ensure compliance with the GCP, all applicable laws, regulations and guidelines in Singapore with regard to the conduct of a clinical trial, as well as all matters ancillary to it. In this regard, the HPCT Regulations define a sponsor (as understood in (ii) above) as a person who takes responsibility for the initiation, management or financing of a clinical trial. Meanwhile, the MCT Regulations define a sponsor as an individual, company, institution or organization that takes responsibility for the initiation, management or financing of a clinical trial.

A sponsor that is a local representative acting in the capacity of a local sponsor is also responsible for submitting the clinical trial application form. The clinical trial application form contains a declaration that must be made by the local sponsor to the effect that it undertakes to abide by the relevant act, the relevant regulations, the GCP (where applicable) and any other conditions imposed by the HSA in the conduct of the clinical trial. The local representative also undertakes not to initiate the clinical trial until approval is obtained from the relevant IRB. Separate IRB approval may be required from each trial site, unless there is already a mutual recognition agreement in place whereby the IRB of one institution agrees to recognize the outcome of the ethics review conducted by another institution.

Regulations 13 and 14 of the HPCT Regulations provide that every person conducting a clinical trial must do so in accordance with the principles of good clinical practice, the protocol relating to the trial, and the conditions of the authorization or acceptance of notification (as the case may be) relating to the trial. Additionally, the sponsor must implement and maintain arrangements to ensure that everyone involved in conducting the clinical trial abide by the

principles of good clinical practice. Meanwhile, Regulation 21 of the MCT Regulations provides that: "[e]very sponsor, principal investigator and holder of a certificate shall comply with any guidelines or instructions relating to the conduct of clinical trials issued by the licensing authority and notified to such sponsor, principal investigator or holder of a certificate, including the Singapore Guidelines for Good Clinical Practice."

The GCP contains extensive obligations on the part of a sponsor (meaning a local representative acting in the capacity of a local sponsor).

Regulation 29 of the HPCT Regulations and Regulation 22 of the MCT Regulations expose a sponsor (which is a local representative acting in the capacity of a local sponsor) to criminal liability for offenses under the respective regulations.

As such, if there is noncompliance with any guidelines or instructions in respect of sponsor obligations, duties and responsibilities under the relevant regulations and/or the GCP, a sponsor that is a local representative acting in the capacity of a local sponsor may be exposed to criminal liability.

There is no requirement that the ultimate sponsor of a clinical trial must be located in Singapore and/or the region around Singapore. However, applications for a CTA, CTN or CTC are to be made by a local representative (in its capacity as a local sponsor), which must be a locally registered company.

Therefore, an overseas sponsor as understood in (i) above will, in any event, have to designate a local representative to act in the capacity of a local sponsor for the purpose of making the clinical trial application, as understood in (ii) above. As a result, a sponsor that is a local representative acting in the capacity of a local sponsor will assume the duties of a sponsor as defined in the relevant regulations and the GCP (where applicable) in respect of the clinical trials conducted in Singapore.

The GCP provides that a sponsor (meaning a sponsor that is a local representative acting in the capacity of a local sponsor) may transfer any or all of its clinical-trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing, and any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

CTAGs are not subject to the review of the HSA (whether in connection with the clinical trial application or otherwise), unless specifically requested. However, they may be required to be submitted in connection with obtaining approval from the relevant IRB.

Regulations relating to therapeutic products and medicinal products as CRM

Parties who are involved in supplying therapeutic products and medicinal products as CRM have certain duties and obligations under the Health Products (Therapeutic Products as Clinical Research Materials) Regulations and the Medicines (Medicinal Products as Clinical Research Materials) Regulations, respectively.

(a) Regarding all therapeutic products and medicinal products used as CRM (including locally registered products)

Firstly, all relevant parties (i.e., the local manufacturer, importer, supplier and sponsor of such CRM) are obligated to carry out the following:

1. Maintain records of receipt and supply
2. Ensure compliance with labelling requirements

3. Notify the HSA 24 hours before any recall of CRM

Secondly, the sponsor, in particular, must also report any unexpected serious adverse drug reaction to the HSA.

(b) Regarding locally manufactured or imported therapeutic products and medicinal products used as CRM

Firstly, the local manufacturer, importer, supplier and sponsor of locally manufactured or imported therapeutic products and medicinal products used as CRM have the additional obligation to ensure that the supply and use of such CRM are only for clinical research purposes.

Secondly, the local manufacturer and importer, in particular, also need to ensure that such CRM are of the correct identity and conform to the applicable standards of strength, quality and purity for the material.

Thirdly, the local manufacturer has the specific additional duty to maintain records of manufacture, assembly and testing.

Lastly, the sponsor has the additional duty to ensure that the clinical research, in which the CRM are supplied or used for, has been approved by the relevant IRB. The sponsor must also ensure that such devices are thereafter disposed or exported within six months of completion or termination of the research, and maintain records of such disposal or export. The sponsor must produce these records for inspection by the HSA as and when required by the HSA.

Principal investigator (PI)

The HPCT Regulations define “principal investigator” as a qualified practitioner or someone who is qualified by training and experience and has adequate resources to properly conduct the trial. The MCT Regulations define “principal investigator” as a doctor or dentist, as the case may be, specified in the CTC as the person responsible for the conduct and supervision of a clinical trial.

Therapeutic products

Pursuant to the HPCT Regulations, the PI is responsible for (among others): ensuring that only a PI or persons assisting him or acting under his instructions shall treat a subject or administer any test material on a subject; giving full explanation and information to subjects in clinical trials; ensuring that all test materials are properly labelled and stored; and keeping adequate records of the clinical trial.

Medicinal products

Pursuant to the MCT Regulations, the PI is responsible for (among others): informing the HSA in the event of a change in PI and providing the HSA with the particulars of the new investigator; informing the HSA in the event of the discontinuance of the clinical trial; ensuring that the applicable requirements for the use of a subject in a clinical trial are satisfied (whether under normal circumstances or in emergency situations); giving full explanation and information to subjects in clinical trials; ensuring that only a PI or persons assisting him shall treat a subject or administer any test material on a subject; furnishing the HSA with such information as may be requested; ensuring that all test materials are properly labelled and stored; keeping adequate records of the clinical trial; and complying with all other relevant provisions as set out in the GCP.

For both medicinal products and therapeutic products, a PI is responsible for reporting to the HSA in writing as soon as is practicable any serious adverse event that has arisen during the clinical trial or has come to his knowledge from reports of similar clinical trials conducted elsewhere, and which is likely to affect the safety or well-being of the subject. Further details of this responsibility as well as other applicable obligations, responsibilities and duties of PIs are set out in the respective regulations and the GCP.

Medical devices

Unlike therapeutic products and medicinal products, clinical trials of medical devices are not currently regulated by the HSA. Therefore, such clinical trials do not require a CTA, CTN or CTC.

Rather, the PI has to obtain the relevant ethics approval from the IRB of the institution where the research is to take place, as well as consider the relevant legal duties and obligations that all dealers of medical devices used as CRM have to fulfil, as governed by the Health Products (Medical Devices) Regulations 2010, incorporating the Health Products (Medical Devices) (Amendment) Regulations 2016.

(a) Regarding all medical devices used as CRM (including locally registered products)

Firstly, the importer or the local manufacturer needs to submit a CRM notification. A draft of the CRM notification should be routed to the clinical research sponsor first for endorsement, to ensure that the sponsor is informed of their duties under the CRM regulations and agrees to fulfil them. Thereafter, the importer or local manufacturer can submit the CRM notification to the HSA, and successful submission would result in an automatically generated acknowledgement by PRISM. The CRM notification is valid for one year and can be extended by application.

Secondly, all relevant parties (i.e., the local manufacturer, importer, supplier and sponsor of all medical devices used as CRM) are obligated to carry out the following:

1. Maintain records of receipt and supply
2. Ensure compliance with labelling requirements
3. Report medical device defects and adverse effects to the HSA
4. Maintain records of complaints
5. Notify the HSA concerning recall
6. Notify the HSA concerning field safety corrective actions

Thirdly, the local manufacturer and importer in particular must ensure that all medical devices used as CRM comply with the "Safety and Performance Requirements for Medical Devices" in the First Schedule of the Health Products (Medical Devices) Regulations.

Lastly, the local manufacturer has the specific duty to maintain records of manufacture, assembly and testing of all medical devices used as CRM.

(b) Regarding locally manufactured or imported medical devices used as CRM

Firstly, the local manufacturer, importer, supplier and sponsor of locally manufactured or imported medical devices used as CRM have the additional obligation to ensure that such devices in particular are only supplied or used for clinical research purposes.

Secondly, the sponsor, in particular, has a further obligation to ensure that such clinical research has been approved of by the relevant IRB. The sponsor must also ensure that such devices are thereafter disposed or exported within six months of completion or termination of the research, and maintain records of such disposal or export. The sponsor must produce these records for inspection by the HSA or an enforcement officer, as and when required.

Adverse events reporting in medical device clinical trials

Should an adverse event occur during a medical device clinical trial, the three basic criteria for it to be considered as a reportable adverse event are as follows:

- Firstly, an adverse event (or potential adverse event) has occurred.
- Secondly, the medical device product is associated with the adverse event.
- Thirdly, the adverse event led to one of the following outcomes:
 1. A serious threat to public health
 2. A serious deterioration in the state of health of the patient, user or any other person
 3. No death or serious injury but the possibility of death or serious injury to a patient, user or any other person if the event recurs
 4. Death of a patient, user or any other person

As a general rule, should an adverse event occur, a report should be made even if there might be doubt as to whether any of the above criteria have been met.

The dealers of the medical device (e.g., local sponsors of clinical trials using medical devices) should report the adverse event by using the specified form available on the HSA website within the stipulated timeframes, and submit it to the Clinical Trials Branch of the HSA.

The stipulated timeframes are as follows:

1. For events that represent a serious threat to public health, such events must be reported within 48 hours of the event.
2. For events that have led to the death, or serious deterioration in the state of health of a patient, a user of the medical device or any other person, such events must be reported within 10 days of the event.
3. For events where a recurrence of which might lead to the death, or a serious deterioration in the state of health of a patient, a user of the medical device or any other person, such events must be reported within 30 days of the event.

The initial report of an adverse event should contain as much relevant details as immediately available. The HSA specifies that even if the information available is incomplete, such a circumstance should not unduly delay reporting of the adverse event.

Sponsors of medical device clinical trials should follow up with a final report within 30 days of the initial report, which should detail the investigation into the adverse event. The HSA may request for follow-up reports if they require them.

Study drugs

Other than the abovementioned applications, licenses and approvals to administer a study drug on a person as a subject in a clinical trial, the PI must have obtained the informed consent of the subject of the clinical trial. Details on

the manner of obtaining such consent and the exceptions to this requirement in emergency situations are set out in detail in the HPCT Regulations, the MCT Regulations and the GCP.

There are no laws, regulations, or guidance identifying the party responsible for financing the supply of study drugs, governing the provision of the study drugs for free, or requiring the sponsor to otherwise finance medical procedures provided for in the protocol. However, the GCP provides that the financial aspects of the clinical trial should be documented in an agreement between the sponsor and the investigator/institution.

Liability for the study is set out in the MA, the HPA, their respective regulations and the GCP, and it is pursuant to general common law principles of liability. To the extent permitted by law, liability can also be agreed on and apportioned between parties via written contract. Therefore, it is advisable to include liability and/or indemnification clauses in CTAGs (or such other ancillary agreements) addressing the liability for obligations, responsibilities and duties of parties who may (as a result of the GCP and other applicable laws, regulations and/or guidelines) assume responsibility for matters for which they have little actual control or supervision of or knowledge about.

In this regard, we note in particular the position of a local representative (often a local CRO) who acts in the capacity of a local sponsor in respect of clinical trials conducted in Singapore. Such local representatives take on significant obligations, responsibilities and duties under the respective regulations and the GCP, even as the actual ultimate sponsor of the clinical trial is located overseas.

In such circumstances, it is important for the local representative to ensure that it is in a position to ensure compliance with the respective regulations and the GCP and/or to procure extensive indemnities from the overseas sponsor of such other relevant party, as the case may be.

A patient who wishes to use a study drug that has yet to be registered with the HSA in Singapore will require special approval from the HSA to import the drug on a "named-patient" basis. The request is made through a prescribed form by a qualified professional (i.e., a Singapore-registered doctor/pharmacist with a doctor's prescription), and the drugs must be supplied directly to the requesting doctor/pharmacist.

Intellectual property (IP) and data

Ownership of inventions and other IP rights is subject to the common law position governing the creation of IP. The MA, the HPA, their respective regulations and the GCP do not prescribe any specific rules in this regard.

Generally, issues related to IP should be addressed by the parties at the outset via suitable contractual clauses in the CTAG and ancillary agreements. Such clauses may include provisions as to the disclosure of study results (which would need to balance the need for timely disclosure of sufficient study results with the temporary secrecy needed to first make patent filings), ownership, and use of trade secrets, patient confidentiality issues and nondisclosure agreements to be entered into when providing information to third parties.

There are no laws and regulations expressly prohibiting investigator-initiated clinical trials or the support of clinical trials by pharmaceutical companies.

Innovation Office (established April 2018)

The HSA has set up an Innovation Office that aims to provide scientific and regulatory advice to researchers, academia, and biotech and pharmaceutical companies who have interest in early stage clinical product development, particularly those intending to ultimately pursue product registration in Singapore.

Guidance offered by the Innovation Office regarding technical, scientific and regulatory issues could cover matters such as non-clinical developments, clinical developments, quality developments (i.e., Chemistry, Manufacturing and Controls (**CMC**)), Manufacturing and Good Manufacturing Practice (**GMP**), as well as regulatory submissions.



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