REGULATORY GUIDANCE

02 MAY 2017

CLINICAL TRIALS GUIDANCE

REGULATORY REQUIREMENTS FOR
NEW APPLICATIONS AND SUBSEQUENT SUBMISSIONS

GN-CTB-2-003A-002
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)

SUMMARY OF AMENDMENTS

- Administrative changes made to Revision History, Section 1.1, Section 2.3, Section 3.1.2, Section 4.1, Section 4.2, Section 4.5 and Section 5.
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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 medicinal products under the Health Products (Clinical Trials) Regulations and the Medicines (Clinical Trials) Regulations respectively. 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 therapeutic products)
• clinical trial notification (CTN - for clinical trials of therapeutic products used in accordance with approved label),
• clinical trial certificate (CTC - for clinical trials of medicinal products)

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).

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 reports, where applicable.
1.2. Scope

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

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

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

Once it has been determined that a clinical trial on therapeutic product/s 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 on therapeutic products is summarised in Figure 1.
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. 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 on medicinal products

Once it has been determined that a clinical trial on 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.
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

<table>
<thead>
<tr>
<th></th>
<th>Clinical Trial Authorisation (CTA)</th>
<th>Clinical Trial Notification (CTN)</th>
<th>Clinical Trial Certificate (CTC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Processing Timeline</td>
<td>30 working days¹</td>
<td>5 working days</td>
<td>30 working days</td>
</tr>
<tr>
<td>(excluding stop-clock time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submission Dossier</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Informed Consent Form (English)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Investigator's Brochure</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Principal Investigator's CV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>List of overseas trial sites</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>(if applicable)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good Manufacturing Practice</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>(GMP) certificate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certificate of Analysis (COA)</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>for study batches of Investigational Products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry, Manufacturing and</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Control (CMC) documents, if</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>requested</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approved Product Label</td>
<td>x</td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td>IRB Approval Letter</td>
<td>x</td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td>Substantial Amendments²</td>
<td>Authorisation</td>
<td>Notification</td>
<td>Approval</td>
</tr>
<tr>
<td>Regulatory Outcome</td>
<td>Authorisation</td>
<td>Acceptance of Notification</td>
<td>Issuance of Clinical Trial Certificate</td>
</tr>
<tr>
<td>Validity Period</td>
<td>Duration of trial</td>
<td>Duration of trial</td>
<td>Duration of trial</td>
</tr>
</tbody>
</table>

¹ Phase 1 clinical trials solely to evaluate bioequivalence, bioavailability, food effect or drug-drug interaction: 15 days

² 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 subject 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 on the sponsor company’s behalf, the sponsor should apply for a Client Registration and Identification Service (CRIS) account to access PRISM.

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

<table>
<thead>
<tr>
<th>Supporting Document</th>
<th>Clinical Trial Authorisation (CTA)</th>
<th>Clinical Trial Notification (CTN)</th>
<th>Clinical Trial Certificate (CTC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Trial Protocol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Informed Consent Form (English)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Investigator’s Brochure</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>List of Overseas Trial Site, where applicable</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Principal Investigator’s CV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Good Manufacturing Practice (GMP) Certificate(^1)</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Certificate of Analysis (COA) for study batches of Investigational Products</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Chemistry. Manufacturing and Control (CMC) information, if requested by HSA</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Approved Product Label</td>
<td>×</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>IRB Approval Letter</td>
<td>×</td>
<td>✓</td>
<td>×</td>
</tr>
</tbody>
</table>

\(^1\) **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 Biological and Biotechnology Products,** 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 sponsor declaration to declare, that the manufacture of the product(s) is in compliance with current GMP standards and, for the sponsor declaration, that the product is sourced from an authorised manufacturer in the source country.
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 subject’s partner
(d) Diary Cards
(e) Data Collection Forms
(f) Case Report Forms
(g) Clinical Trial Advertisements

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
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
The sponsor must report urgent safety measures relating to a subject 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.

4.4. 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 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

<table>
<thead>
<tr>
<th>Field</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRIAL STATUS [for local trial site(s)]</strong></td>
<td></td>
</tr>
<tr>
<td>Not yet recruiting</td>
<td>The local trial site(s) has/have not commenced recruiting subjects into the clinical trial.</td>
</tr>
<tr>
<td>Ongoing, recruiting</td>
<td>The local trial site(s) has/have commenced recruiting subjects into the clinical trial.</td>
</tr>
<tr>
<td>Ongoing, recruitment suspended</td>
<td>The recruitment at the local trial site(s) has been suspended. However, the enrolled subjects are still continuing with the study procedures.</td>
</tr>
<tr>
<td>Ongoing, recruitment closed</td>
<td>The recruitment at the local trial site(s) has been closed. However, the enrolled subjects are still continuing with the study procedures.</td>
</tr>
<tr>
<td>Premature Closure</td>
<td>The local trial site(s) was/were closed prematurely as no subjects were screened into the clinical trial.</td>
</tr>
<tr>
<td>Suspended</td>
<td>The clinical trial has been suspended. All screening and enrollment activities should be suspended. Please notify the IRB and HSA if existing subjects are to continue with the study procedures.</td>
</tr>
<tr>
<td>Terminated</td>
<td>The clinical trial has been terminated. All screening and enrollment activities should be terminated; and existing subjects should not continue with the study procedures.</td>
</tr>
<tr>
<td>Completed</td>
<td>Study completion is defined as ‘Last Patient Last Visit (LPLV)’ for the clinical trial. For clinical trials where subjects are followed up remotely after LPLV (e.g. survival follow-up via telephone calls or safety follow-up etc.), study completion is defined as the end of remote follow-up.</td>
</tr>
<tr>
<td><strong>RECRUITMENT STATUS [for each local trial site]</strong></td>
<td></td>
</tr>
<tr>
<td>No. of subjects screened</td>
<td>Number of subjects screened for the clinical trial.</td>
</tr>
<tr>
<td>No. of screened failures</td>
<td>Number of subjects who failed any of the screening procedures for the clinical trial.</td>
</tr>
<tr>
<td>No. of subjects pending screening outcome</td>
<td>Number of subjects whose screening results are still pending.</td>
</tr>
<tr>
<td>No. of subjects enrolled</td>
<td>Number of subjects enrolled into the clinical trial</td>
</tr>
<tr>
<td>No. of subjects withdrawn or prematurely terminated</td>
<td>Number of subjects who did not complete all the study procedures and had to be withdrawn or prematurely terminated.</td>
</tr>
<tr>
<td>No. of subjects ongoing</td>
<td>Number of subjects who are undergoing the study procedures.</td>
</tr>
<tr>
<td>No. of subjects completed</td>
<td>Number of subjects who have completed the study procedures.</td>
</tr>
<tr>
<td>No. of SAEs experienced by local subjects</td>
<td>Number of Serious Adverse Events (SAEs) experienced by the subjects.</td>
</tr>
</tbody>
</table>
4.5. Unexpected Serious Adverse Drug Reactions (USADRS)
Refer to the Guidance on Expedited Safety Reporting Requirements for Therapeutic Products and Medicinal Products Used in Clinical Trials for further details.

4.6. Updates to the Investigator’s Brochure or New Safety Information
The sponsor must notify HSA of all updates to the Investigator's Brochure or new safety information.

4.7. Suspension / Termination / Completion of a clinical trial
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. Notification for trial suspension / termination must be done within 15 days of the trial suspension / termination, while notification of trial completion must be done within 30 days of study completion.

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

4.9. Other submissions
The sponsor should notify HSA of any changes to the following:
(a) Clinical Research Material Notification
(b) Information in the Clinical Trial Register
(c) Regulatory status of the trial in other countries (e.g. clinical hold or non-approval by regulatory authority)
5. 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 (CTA), Clinical Trial Notification (CTN) or a Clinical Trial Certificate (CTC)
(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 Therapeutic Products and Medicinal Products Used in Clinical Trials
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