02 MAY 2017

CLINICAL TRIALS GUIDANCE

MULTI-SPONSOR INVESTIGATOR-INITIATED CLINICAL TRIALS

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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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1. INTRODUCTION

1.1. Purpose
The purpose of this document is to provide guidance to institutions on sponsor responsibilities for multi-sponsor investigator initiated clinical trials (i.e. multi-sponsor IITs), where an investigator-initiated clinical trial (IITs) is conducted at more than one local trial site involving a single protocol.

1.2. Background
The sponsor of a clinical trial is responsible for the initiation, management or financing of the clinical trial. Clinical trials may either be initiated by industries or investigators. For clinical trials initiated by investigators, the institution is the sponsor for investigator-initiated clinical trials (i.e. IITs).

Some investigators from various local institutions may decide to collaborate to conduct an IIT involving a single protocol. For such multi-sponsor IITs involving a single protocol, each institution has traditionally been the sponsor for each local trial site. Figure 1 summarises the previous workflow for multi-sponsor IITs involving a single protocol.

Figure 1. Previous Workflow for Multi-sponsor IITs involving a single protocol (prior to 2015)

HEALTH SCIENCES AUTHORITY (HSA)

Multiple clinical trial applications to HSA for an IIT

Institution A  Institution B  Institution C
The Health Products (Clinical Trials) Regulations and the Medicines (Clinical Trials) Regulations (henceforth referred to as “the Regulations”) require that every clinical trial must have a single sponsor. The concept of a single sponsor for multi-sponsor IITs involving a single protocol was discussed with institutions in 2015 in order to streamline the management of safety information across the trial sites. However, feedback from the institutions indicated that such a change would pose difficulties in indemnity and insurance coverage across institutions.

As such, for multi-sponsor IITs involving a single protocol, HSA will continue to allow multiple sponsors (i.e. each institution sponsoring their own trial site) for a single protocol, however with a lead sponsor nominated amongst the sponsors.

1.3. Scope
This guidance applies to clinical trials regulated by HSA, namely:
(i) Clinical trials of Therapeutic Products that are subject to the requirements for 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).

1.4. Definitions

1.4.1. Sponsor
A sponsor, in relation to a clinical trial, means a person who takes responsibility for the initiation, management or financing of a clinical trial.

1.4.2. Investigator-initiated clinical trial (IIT)
An investigator-initiated clinical trial (IIT) is a clinical trial that is sponsored by the institution where the clinical trial is being conducted.
1.4.3. Multi-sponsor Investigator-initiated clinical trial (Multi-sponsor IIT)
A multi-sponsor investigator-initiated clinical trial (multi-sponsor IIT) is an investigator-initiated clinical trial (i.e. IIT) conducted at more than one local institution, involving a single protocol.

1.4.4. Lead sponsor
A lead sponsor is a sponsor appointed by all the sponsors of the multi-sponsor IIT involving a single protocol.

1.4.5. Other sponsor(s)
Other sponsor(s) means all other sponsors (excluding the lead sponsor) of a multi-sponsor IIT involving a single protocol. Such a sponsor may also be referred to as a ‘participating site sponsor’.

2. GUIDANCE

2.1. Workflow for multi-sponsor IITs
For multi-sponsor IITs involving a single protocol, each institution will remain as the sponsor of the multi-sponsor IIT conducted at the respective trial sites. However, the sponsors must nominate a ‘lead sponsor’ amongst themselves to liaise with HSA, whilst all other sponsors will be referred to as ‘other sponsors’. Figure 2 summarises the revised workflow for multi-sponsor IITs.
2.2. Objectives of the revised workflow for multi-sponsor IITs involving a single protocol

The objectives of the revised workflow for multi-sponsor IITs involving a single protocol include the following:

(a) To ensure a coordinated and effective management of safety information and trial updates between all the trial sites through the lead sponsor;

(b) To have a single point of contact through the lead sponsor for regulatory submissions for a more effective and streamlined communication with HSA.

2.3. Responsibilities for Lead Sponsor and other sponsor(s)

2.3.1. It is important to note that both the lead sponsor and other sponsor(s) remain the sponsor for their respective trial sites for multi-sponsor IITs involving a single protocol; and must comply with the sponsor
responsibilities outlined in the clinical trials regulations and Good Clinical Practice.

2.3.2. Additionally, the lead sponsor and the other sponsor(s) must comply with the following additional sponsor responsibilities for multi-sponsor IITs involving a single protocol. Refer to Table 1 for further details.

**Table 1. Additional responsibilities for the lead sponsor and other sponsor for multi-sponsor IITs involving a single protocol**

<table>
<thead>
<tr>
<th>Additional Sponsor Responsibilities for multi-sponsor IITs involving a single protocol</th>
<th>Lead Sponsor</th>
<th>Other sponsor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REGULATORY SUBMISSIONS / NOTIFICATIONS TO HSA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTA / CTN / CTC applications</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Substantial amendments</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Investigator’s Brochure and updates</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Clinical Research Material (CRM)</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Change of Principal Investigator (PI)</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Addition of Trial Site(s)</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Serious Breaches</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Urgent Safety Measures</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Unexpected Serious Adverse Drug Reactions</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Trial Status Reports</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Final Report</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td><strong>MANAGEMENT OF SAFETY INFORMATION AND STUDY CONDUCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing safety evaluation of the study drug(s) administered to the subject</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Prompt notification to all participating site investigators/institutions of findings that could adversely affect subject safety or impact conduct of trial.</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Report immediately to lead sponsor any Serious Adverse Events (SAEs) at the participating site, or any finding that could adversely affect subject safety or impact conduct of trial.</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Provide all relevant information to lead sponsor that is necessary for the lead sponsor to perform trial-related regulatory submissions and notifications to HSA.</td>
<td>×</td>
<td>✓</td>
</tr>
</tbody>
</table>
2.4. Submission of multi-sponsor IITs to HSA

Figure 3 summarises clinical trial application process for multi-sponsor IITs.

**Figure 3. Clinical trial application process for multi-sponsor IITs**

![Flowchart diagram of the clinical trial application process for multi-sponsor IITs.]

- **Determine if the investigator-initiated clinical trial (IIT) involves other local trial sites.**
  - **YES**
    - Identify a lead sponsor amongst the local trial sites. The other local trial sites will become participating site sponsors.
    - Lead sponsor should draft CTC/CTA/CTN application on PRISM.
    - The draft CTC/CTA/CTN application will be routed to the participating site sponsors and the principal investigators for endorsement via PRISM.
    - After endorsement, the lead sponsor should submit the CTC/CTA/CTN application to HSA via PRISM.
    - HSA will issue the CTC/CTA/CTN acceptance to the lead sponsor.
  - **NO**
    - Proceed with clinical trial application to HSA.
    - **Addition of Sponsor (at a later date)**
      - **Single sponsor:** If the existing sponsor is willing to insure and indemnify the additional local trial sites, the existing sponsor should submit an application for Addition of Trial Site via PRISM to HSA; or
      - **Multiple sponsors:** If the existing sponsor is not willing to insure and indemnify the additional local trial sites, the existing sponsor should submit applications for Addition of Trial Site and Addition of Sponsor via PRISM to HSA.

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**Addition of Sponsor**

**Multiple sponsors:** If the lead sponsor is not willing to insure and indemnify the additional local trial sites, the lead sponsor should submit applications for Addition of Trial Site and Addition of Sponsor via PRISM to HSA.
2.4.1. Once it has been determined that the IIT involves more than one local trial site,
(a) The local trial sites should identify a lead sponsor to submit all clinical trial applications to HSA; whilst all other local trial sites will become other sponsors.
(b) The lead sponsor should draft CTC/CTA/CTN application on PRISM.
(c) The CTC/CTA/CTN application will then be routed to the other sponsors and the principal investigators for endorsement via PRISM.
(d) After endorsement by the other sponsors and the principal investigators, the lead sponsor should submit the CTC/CTA/CTN application to HSA via PRISM.
(e) HSA will issue the CTC/CTA/CTN acceptance to the lead sponsor.

2.4.1.1. If additional local trial sites are to be involved in conducting the clinical trial at a later date and the lead sponsor is not willing to insure and indemnify the additional local trial sites, the lead sponsor should submit applications for Addition of Trial Site and Addition of Sponsor via PRISM to HSA.

2.4.2. If initially there was one sponsor involved in conducting the IIT, and additional local trial sites were to be included at a later date, the additional local trial sites should decide on either of the following:
(a) Single sponsor: If the existing sponsor is willing to insure and indemnify the additional local trial sites, the existing sponsor should submit an application for Addition of Trial Site via PRISM to HSA; or
(b) Multiple sponsors: If the existing sponsor is not willing to insure and indemnify the additional local trial sites, the existing sponsor should submit applications for Addition of Trial Site and Addition of Sponsor via PRISM to HSA.
3. REFERENCES

(i) Health Products (Clinical Trials) Regulations
(ii) Medicines (Clinical Trials) Regulations
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