02 MAY 2017

CLINICAL TRIALS GUIDANCE

NOTIFICATION OF SERIOUS BREACH

GN-CTB-3-005A-001
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)

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GN-CTB-3-005A-001 (02 May 2017)

SUMMARY OF AMENDMENTS

- Administrative and formatting changes.
- Updated regulatory terms following the port-over to Therapeutic Products (Clinical Trials) Regulations (e.g., Clinical Trial Notification (CTN), Clinical Trial Authorisation (CTA)).
- **Section 1:** Content has been revised.
- **Section 3.4:** Amended reporting process to reflect reporting via the online PRISM system.
- **Section 5.2 (Appendix B):** Added further examples of cases that could qualify as serious breaches.
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1. INTRODUCTION

1.1. Purpose
The purpose of this document is to provide guidance to the industry on the notification of serious breaches occurring in all phases of regulated clinical drug trials to the Clinical Trials Branch, Health Products Regulation Group (HPRG), Health Sciences Authority (HSA).

1.2. Background
Regulation 11(1) of the Health Products (Clinical Trials) Regulations 2016 and Medicines (Clinical Trials) Regulations 2016 requires that the trial sponsor notifies HSA in writing of any serious breach during the clinical trial of any of the following, as soon as possible but no later than 7 days after becoming aware of the breach:

(a) the principles of good clinical practice (GCP);
(b) the clinical trial protocol;
(c) clinical trials regulations

Any serious breach during the clinical trial should also be reported to the relevant institutional review board (IRB), in accordance with the IRB requirements.

This requirement was implemented to ensure that the trial sponsor promptly informs HSA and IRB (if required) of serious breaches and that appropriate action in response to the breach is taken, so as to enhance the safety and wellbeing of trial subjects and assure the reliability of trial data.
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).

2. DEFINITIONS

2.1. Breach
A breach is any change, divergence, or departure from:

(a) the principles of GCP; or

(b) the trial protocol agreed to by the sponsor, and approved by the IRB and HSA (as required).

(c) the clinical trial regulations

2.2. Serious Breach
A serious breach is a breach during a clinical trial which is likely to affect to a significant degree:

(a) the safety, or physical or mental integrity, of any subject of a clinical trial; or

(b) the scientific value of the clinical trial
3. STANDARDS FOR EXPEDITED REPORTING

3.1. What should be notified to HSA

Any serious breach* of the principles of GCP, trial protocol or the clinical trials regulations must be reported to HSA.

* A serious breach is a deviation which is likely to affect to a significant degree:
  (a) the safety or physical or mental integrity of any subjects in a clinical trial; or
  (b) the scientific value of the clinical trial

The decision on whether a breach is likely to have a significant impact on the safety, physical or mental integrity of subjects should be assessed by both the sponsor and investigator.

As the scientific value of the clinical trial depends on a variety of factors (such as the study design, type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, the impact of excluding the data from analysis etc.), it is the responsibility of the sponsor to assess the impact of the breach on the scientific value of the clinical trial.

The serious breach assessment should be documented, as the appropriateness of the decisions taken by the sponsor may be examined by HSA, when applicable.

It is, ultimately, the sponsor’s responsibility to assess the breach, report the serious breach to the IRB and HSA (if required) and take appropriate corrective and preventive actions in response to the serious breach, and to document these actions.

Refer to Appendix A for other considerations in the reporting of serious breaches and Appendix B for examples of situations that may be considered serious breaches depending on the context of the situation.
3.2. Who should notify
The local sponsor of a clinical trial must notify HSA in writing of any serious breaches. The sponsor still retains the legal responsibility for notifying serious breaches even if this responsibility is delegated to a third party (e.g. Contract Research Organisation). The sponsor/ Principal Investigator should also comply with the IRB reporting requirements.

3.3. When to notify
Serious breaches must be notified to HSA, as soon as possible and in any event not later 7 calendar days after the sponsor becoming aware of the serious breach.

- If the sponsor has delegated the notification responsibility to a third party (e.g. Contract Research Organisation), the 7-day timeline applies to the third party.

- If the sponsor retains the notification responsibility, it is recommended that agreements between the sponsor and other parties involved in the clinical trial state that the other parties will promptly notify the sponsor of a serious breach, in order for the sponsor to comply with the reporting timelines. In this case, the clock starts when the sponsor becomes aware of the serious breach.

If there is clear and unequivocal evidence that a serious breach has occurred, the sponsor should notify HSA first, within 7 calendar days, and investigate and take action concurrently or after notification. In this case, the sponsor should not wait to obtain all of the details of the breach prior to notification.

3.4. How to notify
The sponsor should complete the Serious Breaches module in the online PRISM system, and ensure that all appropriate information is submitted to HSA. The sponsor should inform the Principal Investigators of the serious breach (where
applicable), so as to facilitate the implementation of corrective and preventive action(s).

The sponsor may initially contact HSA to discuss the serious breach and follow-up with the online submission of the serious breach within 7 calendar days of becoming aware of the serious breach.

The sponsor does not have to wait for all the information to be available before notifying the serious breach to HSA. If investigations or corrective and preventive actions are ongoing at the time of notification, the expected timelines for resolution of the corrective and preventive actions should be included in the initial notification. Follow-up notifications, once available, should be submitted through the online PRISM system.
3.5. Reporting Workflow

Figure 1. Flow Chart of Serious Breach Notification Process for Clinical Drug Trials

Deviation occurs

Does the deviation fulfil the definition of serious breach?

No

Not for reporting to HSA
- Document the deviation in study files
- Report to IRB, as per IRB requirements

Yes

Notification of Serious Breaches to HSA
- Complete the Serious Breaches module in PRISM
- Initial report within 7 calendar days

Follow-up notifications, once available, should be submitted through the online PRISM system.

HSA will review and follow up till corrective and preventive action (CAPA) plan is satisfactorily completed.
4. REFERENCES

(i) Medicines (Clinical Trials) Regulations
(ii) Health Products (Clinical Trials) Regulations
(iii) ICH E6 (R2) Good Clinical Practice (GCP) Guidelines
(iv) MHRA Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol (Version 5 dated 6 Jan 2014)
5. APPENDICES

5.1. Appendix A – Other Considerations

(a) Should a breach of the GCP principles, trial protocol or clinical trial regulations leading to the occurrence of a Serious Adverse Event (SAE) be reported as a serious breach?
An SAE or unexpected serious adverse drug reaction (USADR) resulting from a breach of GCP principles, trial protocol or clinical trial regulations will constitute a serious breach. However, it should be noted that not every SAE or USADR would routinely be classified as a serious breach.

Submission of a serious breach notification does not obviate the requirement for safety reporting to HSA. Please refer to the Guidance on Expedited Safety Reporting Requirements for Therapeutic Products and Medicinal Products Used in Clinical Trials for more information on safety reporting to HSA.

(b) Should serious breaches that occur at overseas sites be reported for local regulated clinical trials?
If a serious breach, which is identified at an overseas site, has a significant impact on the scientific value of the clinical trial, or safety, physical or mental integrity of trial subjects at that site and is likely to have a significant impact on the trial subjects in Singapore, it will require notification to HSA.

For example:
- Death of a subject in an overseas site occurred due to incorrect administration of IP which resulted from erroneous reconstitution instructions in the protocol. This would likely have a significant impact on the safety of trial subjects in Singapore, thus this breach will require reporting to HSA. In addition, if urgent safety measure (e.g. protocol amendment) is implemented to address the cause of this breach, the sponsor should also notify HSA of the urgent safety measure.
• If a serious breach that occurs at an overseas site is likely to affect to a significant degree the overall scientific value of the trial and the result will impact on patients in Singapore or the public (e.g. data will be used in a marketing authorisation application that affects Singapore), then this breach should be notified to HSA.

It is the sponsor’s responsibility to assess the information and ensure appropriate reporting. The sponsor is also responsible for taking appropriate measures in response to the serious breach.
### 5.2. Appendix B – Examples of Serious Breaches

Table 1 illustrates examples of situations that may be considered serious breaches depending on the context of the situation. The list serves as an aid to guide whether notification to HSA is required. **This is not an exhaustive list.**

**Table 1. Examples of Serious Breaches**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details of Breach Reported</th>
<th>Is this a Serious Breach?</th>
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</thead>
<tbody>
<tr>
<td><strong>Study Procedures</strong></td>
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<tr>
<td><strong>Scheduling Issues</strong></td>
<td>1) Subject’s visit was not within the window period. Visit was supposed to be on day 28 (+/- 2 days), but subject had returned on day 24.</td>
<td>1) <strong>No</strong>, if there was no impact on the safety or integrity of trial subjects or on the scientific value of the trial.</td>
</tr>
<tr>
<td></td>
<td>2) Sampling for Pharmacokinetics (PK) parameter was collected five minutes out of permitted window period.</td>
<td>2) <strong>No</strong>, if there was no impact on the safety or integrity of trial subjects or on the scientific value of the trial.</td>
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<td></td>
<td><strong>Yes</strong>, if the issue was systematic and persistent leading to a significant impact on the safety or integrity of subjects or scientific value of the trial.</td>
</tr>
<tr>
<td><strong>Omitted Procedures</strong></td>
<td>1) Subjects did not complete the end-of-study questionnaires.</td>
<td>1) <strong>No</strong>, if there was no impact on the safety or integrity of trial subjects or on the scientific value of the trial.</td>
</tr>
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<td></td>
<td>2) Instead of triplicate electrocardiogram (ECGs), duplicate ECGs were performed for two subjects</td>
<td>2) <strong>No</strong>, if there was no impact on the safety or integrity of trial subjects or on the scientific value of the trial.</td>
</tr>
<tr>
<td>Category</td>
<td>Details of Breach Reported</td>
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<tr>
<td></td>
<td>during one of the study visits.</td>
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<tr>
<td></td>
<td>3) ECGs were not performed, resulting in compromise of subject safety as dose adjustments could not be made accordingly.</td>
<td>3) <strong>Yes</strong>, there was significant potential to impact the safety or integrity of trial subjects and scientific value of the trial.</td>
</tr>
</tbody>
</table>
| Investigational Product (IP) | **Treatment Allocation Issues**  
The Interactive Voice Response System (IVRS) was used to randomize subjects and assign treatment kits to subjects. Some treatment kits shipped to the sites had misallocated treatment type in IVRS. As a result, subjects may have received misallocated treatment for some cycles. | **Yes**, there was significant potential to impact the safety or integrity of trial subjects and scientific value of the trial. |
|                          | **Dosing Issues**  
1) The label on the IP did not reflect the correct concentration of IP in the vial, resulting in subject receiving more than the required amount of IP. | 1) **Yes**, there was significant potential to impact the safety or integrity of trial subjects. |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>2)</td>
<td>The IP was administered to the subject via an incorrect route (e.g. IP was administered via the intravenous route instead of intramuscular route).</td>
<td>2) Yes, there was significant potential to impact the safety or integrity of trial subjects.</td>
</tr>
<tr>
<td>3)</td>
<td>The study site failed to reduce or stop IP dosing, in response to certain laboratory parameters or criteria, as required by the protocol. As a result, subject was exposed to an increased risk of adverse events.</td>
<td>3) Yes, there was significant potential to impact the safety or integrity of trial subjects.</td>
</tr>
<tr>
<td>4)</td>
<td>The subject was to take the IP daily for 30 days but instead took the IP for 21 days; subject informed that he had forgotten to take the IP for a week.</td>
<td>4) No, if there was no impact on the safety or integrity of trial subjects or on the scientific value of the trial. In addition, the assessment of the breach identified this as a single episode and a detailed corrective and preventive action plan was implemented.</td>
</tr>
</tbody>
</table>

**Temperature Excursions**

IP temperature excursions occurred over the weekend.

Yes, if the situation was not managed and subjects were dosed with IP assessed as unstable, which resulted in harm/potential to harm subjects.

No, if the excursions were managed appropriately and timely. There was also an assessment by qualified
### Category: Informed Consent

#### Details of Breach Reported

<table>
<thead>
<tr>
<th>Consent Issues</th>
<th>Is this a Serious Breach?</th>
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</thead>
<tbody>
<tr>
<td>1) Consent was not obtained from subject. ([Note: There is no legal provision for short consent form. Subject should provide consent on the full consent form.])</td>
<td>1) Yes, there was significant potential to impact the safety or integrity of trial subjects.</td>
</tr>
<tr>
<td>2) Consent was not obtained from the appropriate legal representative (for subject lacking capacity to give consent to being a subject, or minor lacking sufficient understanding and intelligence to give consent).</td>
<td>2) Yes, there was significant potential to impact the safety or integrity of trial subjects.</td>
</tr>
<tr>
<td>3) Subject was enrolled into the clinical trial, despite subject’s (or his/her legal representative’s, as applicable) refusal (or objection) to participate in the trial.</td>
<td>3) Yes, there was significant potential to impact the safety or integrity of trial subjects.</td>
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<tr>
<td>4) Subject had consented on an Informed Consent Form (ICF) or substantial amendment to an ICF, which had never been reviewed nor approved by HSA.</td>
<td>4) Yes, there was significant potential to impact the safety or integrity of trial subjects.</td>
</tr>
<tr>
<td>5) Subject had not been re-consented with the ICF amendment, and the amendment has the</td>
<td>5) Yes, there was significant potential to impact the safety or integrity of trial subjects.</td>
</tr>
<tr>
<td>Category</td>
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<td>potential to affect his or her willingness to continue participation in the trial.</td>
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<td></td>
<td>6) A substantial amendment to the ICF was approved by HSA and IRB. However, re-consent was not obtained from subjects in a timely manner.</td>
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<td>7) The informed consent process had been inadequate to ensure that the subject fully understands the ICF or has ample time and opportunity to enquire about/ consider participation.</td>
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<td>8) No impartial witness or inappropriate impartial witness had been present during the ICF process, for situation where subject was illiterate.</td>
</tr>
</tbody>
</table>
| Study Conduct | *Repeated non-compliance*  
Persistent or systematic non-compliance with GCP or trial protocol was discovered at the trial site. | **Yes**, if the systematic or persistent non-compliance has significant impact on integrity of subjects or scientific value of the trial. |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject eligibility</strong></td>
<td>The study investigator failed to ensure that the subject was eligible for the trial, prior to subject dosing. This resulted in an ineligible subject being exposed to the IP and risk of adverse event.</td>
<td><strong>Yes</strong>, there was significant potential to impact the safety or integrity of trial subjects.</td>
</tr>
</tbody>
</table>
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