HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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CLINICAL TRIALS GUIDANCE

NOTIFICATION OF SERIOUS BREACH

GN-CT-13 Rev. No. 003

HSA
Health Sciences Authority

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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SUMMARY OF AMENDMENTS

- Administrative changes due to HSA re-organisation

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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 clinical trials requiring a Clinical Trial Authorisation, Clinical Trial Notification or Clinical Trial Certificate.

1.2. Background

Regulation 11(1) of the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations 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 participants and assure the reliability of trial data.

1.3. Scope

This guidance applies to following clinical trials:

(i) Clinical trials of Therapeutic Products[1] and Class 2 Cell, Tissue and Gene Therapy Products (CTGTPs)[1,2] that are subject to the requirements for a Clinical Trial Authorisation (CTA) or a Clinical Trial Notification (CTN);

(ii) Clinical trials of Medicinal Products[3] 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 trial participant of a clinical trial; or

(b) the scientific value of the clinical trial

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

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

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

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

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 trial participants 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 trial participants 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

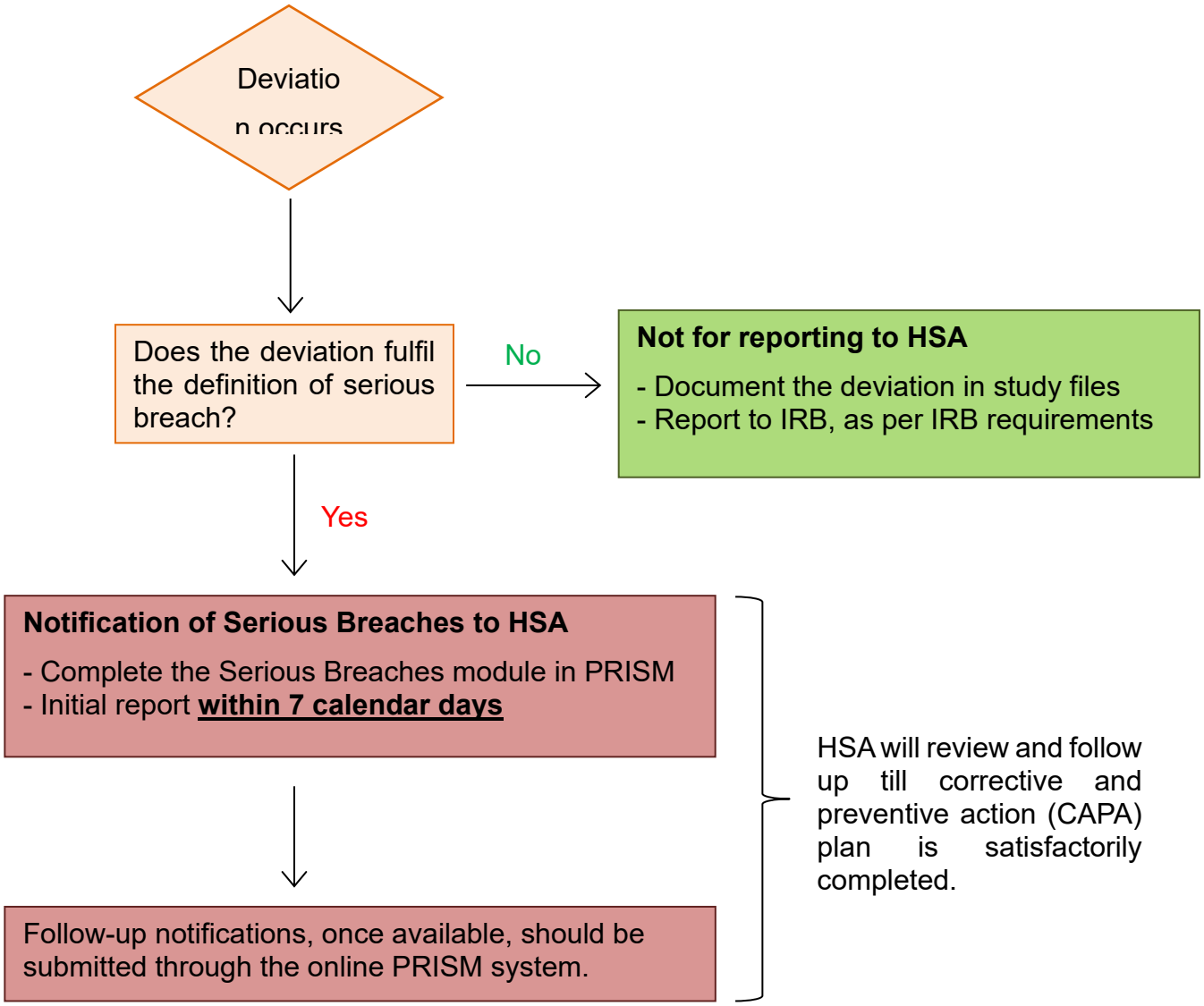
The sponsor should complete the Serious Breaches module in the online PRISM system, and ensure that all appropriate information is submitted to HSA. The sponsor should inform the Principal Investigators of the serious breach (where applicable), so as to facilitate the implementation of corrective and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



4. REFERENCES

(i) Medicines (Clinical Trials) Regulations

(ii) Health Products (Clinical Trials) Regulations

(iii) ICH E6 (R3) 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 Clinical Trials* for more information.

(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 participants at that site and is likely to have a significant impact on the trial participants in Singapore, it will require notification to HSA.

For example:

- Death of a trial participant 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 participants 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 occur 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

Category	Details of Breach Reported	Is this a Serious Breach?
Study Procedures	*Scheduling Issues* 1) Trial participant's visit was not within the window period. Visit was supposed to be on day 28 (+/- 2 days), but trial participant had returned on day 24. 2) Sampling for Pharmacokinetics (PK) parameter was collected five minutes out of permitted window period.	1) **No**, if there was no impact on the safety or integrity of trial participants or on the scientific value of the trial. 2) **No**, if there was no impact on the safety or integrity of trial participants or on the scientific value of the trial. **Yes**, if the issue was systematic and persistent leading to a significant impact on the safety or integrity of trial participants or scientific value of the trial.
	Omitted Procedures 1) Trial participants did not complete the end-of-study questionnaires.	1) **No**, if there was no impact on the safety or integrity of trial participants or on the scientific value of the trial.

Category	Details of Breach Reported	Is this a Serious Breach?
	Omitted Procedures (continued) 2) Instead of triplicate electrocardiogram (ECGs), duplicate ECGs were performed for two trial participants during one of the study visits. 3) ECGs were not performed, resulting in compromise of trial participant safety as dose adjustments could not be made accordingly.	2) **No**, if there was no impact on the safety or integrity of trial participants or on the scientific value of the trial. 3) **Yes**, there was significant potential to impact the safety or integrity of trial participants and scientific value of the trial.
Investigational Product (IP)	*Treatment Allocation Issues* The Interactive Voice Response System (IVRS) was used to randomize trial participants and assign treatment kits to trial participants. Some treatment kits shipped to the sites had misallocated treatment type in IVRS. As a result, trial participants may have received misallocated treatment for some cycles.	**Yes**, there was significant potential to impact the safety or integrity of trial participants 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 trial participant receiving more than the required amount of IP.	1) **Yes**, there was significant potential to impact the safety or integrity of trial participants.

Category	Details of Breach Reported	Is this a Serious Breach?
	Dosing Issues (continued) 2) The IP was administered to the trial participant via an incorrect route (e.g. IP was administered via the intravenous route instead of intramuscular route). 3) 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, trial participant was exposed to an increased risk of adverse events. 4) The trial participant was to take the IP daily for 30 days but instead took the IP for 21 days; trial participant informed that he had forgotten to take the IP for a week.	2) **Yes**, there was significant potential to impact the safety or integrity of trial participants. 3) **Yes**, there was significant potential to impact the safety or integrity of trial participants. 4) **No**, if there was no impact on the safety or integrity of trial participants 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.
	Temperature Excursions IP temperature excursions occurred over the weekend.	**Yes**, if the situation was not managed and trial participants were dosed with IP assessed as unstable, which resulted in harm/ potential to harm trial participants. **No**, if the excursions were managed appropriately and timely. There was also an assessment by qualified personnel to show that the quality of IP was still intact.

Category	Details of Breach Reported	Is this a Serious Breach?
Informed Consent	*Consent Issues* 1) Consent was not obtained from trial participant. *[Note: There is no legal provision for short consent form. Trial participant should provide consent on the full consent form.]* 2) Consent was not obtained from the appropriate legal representative (for trial participant lacking capacity to give consent to being a trial participant, or minor lacking sufficient understanding and intelligence to give consent). 3) Trial participant was enrolled into the clinical trial, despite trial participant's (or his/ her legal representative's, as applicable) refusal (or objection) to participate in the trial. 4) Trial participant had consented on an Informed Consent Form (ICF) or substantial amendment to an ICF, which had never been reviewed nor approved by HSA.	1) **Yes**, there was significant potential to impact the safety or integrity of trial participants. 2) **Yes**, there was significant potential to impact the safety or integrity of trial participants. 3) **Yes**, there was significant potential to impact the safety or integrity of trial participants. 4) **Yes**, there was significant potential to impact the safety or integrity of trial participants.

Category	Details of Breach Reported	Is this a Serious Breach?
	Consent Issues (continued)	
	5) Trial participant had not been re-consented with the ICF amendment, and the amendment has the potential to affect his or her willingness to continue participation in the trial.	5) **Yes**, there was significant potential to impact the safety or integrity of trial participants.
	6) A substantial amendment to the ICF was approved by HSA and IRB. However, re-consent was not obtained from trial participants in a timely manner.	6) **Yes**, if there was significant impact on the integrity of trial participants (e.g. there was key safety information or important information that could affect trial participant's willingness to continue participation in the trial).
	7) The informed consent process had been inadequate to ensure that the trial participant fully understands the ICF or has ample time and opportunity to enquire about/ consider participation.	7) **Yes**, there was significant potential to impact the safety or integrity of trial participants.
	8) No impartial witness or inappropriate impartial witness had been present during the ICF process, for situation where trial participant was illiterate.	8) **Yes**, there was significant potential to impact the safety or integrity of trial participants.
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 trial participants or scientific value of the trial.

Category	Details of Breach Reported	Is this a Serious Breach?
	Trial participant eligibility The study investigator failed to ensure that the trial participant was eligible for the trial, prior to trial participant dosing. This resulted in an ineligible trial participant being exposed to the IP and risk of adverse event.	**Yes**, there was significant potential to impact the safety or integrity of trial participants.

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