UNIVERSITY OF LEEDS / NHS The Leeds Teaching Hospitals NHS Trust Standard Operating Procedure	Title	**Researchers Guide to Protocol Deviations, Violations and Potential GCP Breaches**				
	Scope	Describes the process that the research team will follow when identifying and reporting potential serious breaches reported from CTIMPs being sponsored by the LTHT / UoL				
	Version	**3.0**	Date	**04/06/2020**	SOP ID	**QCRES_02**

Details:

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Version no. of replaced SOP:	2.0
Effective date of replaced SOP:	26/03/2018

Approval:

Version no. of SOP	Name of person approving this SOP	Date	Signature of the person approving this SOP
3.0	Clare Skinner Head of Research Integrity and Governance Secretariat University of Leeds	01.07.2020	
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Distribution & Storage:

Distribution to:

Investigators and all members of research teams conducting or assisting with a CTIMP trial sponsored by the University of Leeds or Leeds Teaching Hospital NHS Trust.

Location of document:

Paper: QA Department, Room 5, Research and Innovation Centre, St James' University Hospital

Electronic: http://www.leedsth.nhs.uk/research/information-for-researchers/key-documents
http://lthweb.leedsth.nhs.uk/sites/research-and-development/resources/Sponsored%20CTIMPs%20%28Quality%20Assurance%29

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Please note: *This SOP should be used and followed in conjunction with other UoL / LTHT SOPs developed for researchers to support study set up and management. These can be found on the LTHT website or by contacting R&I / QA directly. For clinical trials where Leeds is not the trial Sponsor, please refer to any Sponsor SOPs for further information.*

Section A: Introduction

1.1 This Standard Operating Procedure (SOP) defines the procedure for the identification and onward reporting of protocol deviations, violations and potential Good Clinical Practice (GCP) breaches by the research team.

1.2 This SOP aims to ensure standardisation and continuity in the reporting procedure between all members of research staff working on a Clinical Trial of an Investigational Medicinal Product (CTIMP) sponsored by the Leeds Teaching Hospitals NHS Trust (LTHT) / University of Leeds (UoL).

1.3 This SOP will outline the necessary steps and requirements to allow for the appropriate identification, capture, assessment and reporting of protocol and GCP non-compliance.

1.4 For the sponsor to meet the pre-determined timelines for the reporting of serious breaches to the authorities, **all** staff involved in trial procedures must be aware of the reporting timelines and procedures outlined in this SOP.

Section B: Applicability

1.1 This SOP is applicable to all members of staff working on non-Clinical Trials Unit (CTU) / non-Clinical Research Organisation (CRO) Managed CTIMPs sponsored by the University of Leeds (UoL) or Leeds Teaching Hospitals NHS Trust (LTHT).

Section C: Researchers Guide to Protocol Deviations, Violations and Potential GCP Breaches

1.0 Protocol Non-Compliances

1.1. **Protocol non-compliances** can be defined as any departure from the approved trial protocol that has been identified after it has occurred.

1.2. **Protocol non-compliance** refers to any **deviation** or **violation** of the trial protocol.

1.3. Some non-compliances lie out of the control of the research team (such as a patient not arriving for a scheduled visit), and as a result cannot always be avoided despite the team's best efforts. However, such non-compliances **must still be documented and reported to the Sponsor within the required timelines.**

1.4. Examples of protocol non-compliances that may occur in a clinical trial include (but are not restricted to):

- A patient missing an appointment/visit required by the protocol
- Laboratory testing carried outside of the designated time window
- Incorrect consenting of a patient
- Incorrect handling and processing of samples
- Malfunctioning equipment

2.0 Serious Breaches of GCP and the Protocol

2.1 A serious breach of GCP or the protocol is a breach that is likely to significantly affect:

- the safety, physical or mental integrity of the trial subject(s); or
- the scientific value of the clinical trial.

2.2 A protocol deviation or violation that is suspected or known to have the **potential** to seriously impact on a patient's safety, physical or mental integrity or scientific value will be classified as a **serious breach**.

2.3 Examples of serious breaches that may occur in a clinical trial include (but are not restricted to):

- Administering the IMP via the incorrect administration route
- Dosing a subject with the IMP from the incorrect treatment arm
- Failure to carry out safety testing (e.g. ECG, blood tests) required by the protocol
- Failure to code break in an appropriate and timely manner
- Destroying a Trial Master File (TMF) earlier than agreed
- No reduction of dose or halting of trial medication in response to laboratory testing parameters
- Failure to report Serious Adverse Events (SAEs) or Suspected Unexpected Serious Adverse Reactions (SUSARs) to the Sponsor in the agreed process stated in the trial protocol

3.0 Identification of Protocol Non-compliances and Suspected Serious Breaches and Reporting Requirements

3.1 Deviations from trial protocols and GCP are a frequent occurrence in clinical trials and are usually minor deviations that do not have a significant impact on the trial subject's safety or the trial's scientific value. However, systematic or major deviations **may** constitute a serious

breach, and may require subsequent reporting to the Medicines and Healthcare Product Regulatory Agency (MHRA) and the Research Ethics Committee and (REC).

3.2 All protocol non compliances / deviations and suspected breaches must be appropriately recorded and reported to the Sponsor, regardless of Investigator opinion (e.g. even if the investigator does not consider the deviation to be a reportable breach).

3.3 Breaches of the protocol or GCP can be identified in several ways such as routine daily trial activities, monitoring visits or audits / inspections.

3.4 Although minor non-compliances from the protocol do not need to be reported to the MHRA as a serious breach, **only** the Sponsor QA Office are permitted to make this assessment.

3.5 Once a non-compliance or suspected serious breach of GCP, the trial protocol, the REC Favourable Opinion or the MHRA Clinical Trial Authorisation has been identified, it **must be reported to the Sponsor QA office immediately** if possible, and **no later than three working days** of the research team becoming aware.

3.6 A member of the research team must complete the form ***CTT20: UoL / LTHT CTIMP Protocol Deviations, Violations and Potential GCP Breaches*** and send this via email (leedsth-tr.sponsorqa@nhs.net) to Sponsor QA for review (please see section 4.0).

3.7 It is acceptable for the research team to make the initial notification of the suspected serious breach verbally providing this is followed up with a written notice using ***CTT20*** within **3 days**.

3.8 When a suspected breach has been identified, the Chief Investigator (CI) should be notified as soon as possible, however this should not hold up the reporting of the breach to Sponsor QA.

3.9 If the research team have any doubt or uncertainty if what they have identified is a suspected serious breach, it must be discussed with the Sponsor QA Office **without delay**.

3.10 Please note that protocol waivers are **not permitted** as they constitute a deliberate breach of Regulation 29 of SI 2004/1031.

4.0 Reporting to the Sponsor - Completing the CTT20 Form

4.1 ***CTT20: LTHT / UoL CTIMP Protocol Deviations, Violations and Potential GCP Breaches*** must **always** be completed by the research team for any protocol non-compliance or suspected serious breach.

4.2 Only one deviation / suspected serious breach can be reported per ***CTT20*** form unless previously agreed with Sponsor QA.

4.3 The research team must complete Part 1 (comprising sections A-C) in **full**.

4.4 The ***CTT20*** form must be fully legible and provide enough detail and information relating to the reported deviation to allow for accurate and timely Sponsor assessment.

4.5 The CI / Principle Investigators (PI's) assessment of the deviation and the rationale to support this **must be included.** However, if the CI / PI is not available at the time of submission **this must not delay reporting to the Sponsor**. In this instance, the CI / PI can provide comment when they return.

4.6 If during the review process the Sponsor believes there is a lack of detail or information, the form will be returned to the initial sender for expansion and clarification.

4.7 Please ensure that any changes / corrections to the form are neatly struck through and initialled and dated in line with GCP Guidelines.

4.8 **Section A** requests key information relating to the trial. Please ensure this is fully completed to allow the Sponsor to clearly identify which trial it relates to.

4.9 **Section B** requires the specific details of the deviation being reported.

4.9.1 **Date of deviation:** This is the date that the incident being reported occurred.

4.9.2 **Date deviation identified:** This date may differ to the 'Date of deviation' as this refers to when the team became aware of the incident.

4.9.3 **Description of deviation:** Please provide as much detail as possible relating to the incident to allow the Sponsor to make an accurate assessment. Ensure that if appropriate, the number of patients and how they were / could potentially be affected is included.

4.9.4 **How was the deviation identified?:** Please describe the process by which the deviation was discovered. This could be from a wide range of activities such as during a routine monitoring visit, in the laboratory or by a member of the research team.

4.9.5 **Potential impact of deviation:** Please select all that apply as in some instances more than one category may be applicable.

4.10 **Section C** asks for details of any corrective actions undertaken to date / actions planned to be implemented prior to Sponsor review. It is essential to complete this section to allow the Sponsor to accurately review any corrective action to date and to use this to make an informed decision as how best to proceed. If corrective action has yet to be taken, please note this and do not leave blank.

4.11 Please email the form when sections A-C are complete to Sponsor QA (leedsth-tr.sponsorqa@nhs.net).

4.12 The Sponsor will complete the remainder of the form during the review process and will contact the research team should any additional information be required.

4.13 QA will acknowledge receipt of the ***CTT20*** form within three working days. If a confirmation of receipt is not received within this timeline, please chase Sponsor QA.

5.0 Sponsor Review of a Serious Breach

5.1 The ***CTT20*** form will be reviewed by the Sponsor in accordance with the process detailed in ***LTU_QM_15: LTHT / UoL Sponsored CTIMP Suspected Serious Breaches***.

5.2 The Sponsor may request additional information / clarification from the research team at any time to aid with Sponsor assessment. The research team must comply in a timely manner to allow the Sponsor to meet onward reporting timelines.

5.3 If Sponsor assessment confirms a serious breach has occurred, this must be reported to the MHRA and REC within 7 days of Sponsor notification. Please note, it is the **Sponsor QA office who will be responsible for onward reporting to the relevant authorities**.

5.4 If the Sponsor assesses the protocol deviation / serious breach to not be reportable to the regulator, confirmation of this will be given to the initial sender of the ***CTT20*** within seven working days of receipt of the form.

5.5 The Sponsor will return the completed ***CTT20*** to the research team. Please ensure this is filed in the Trial Master File (TMF) alongside any other related documentation and **all** correspondence.

6.0 Planning and Implementing Corrective Action

6.1 If further corrective or preventative actions are required, the Sponsor will detail this in the **Sponsor Review** section of the ***CTT20*** form.

6.2 Any corrective and / or preventative actions **must be followed to resolution** to avoid deviations of the same nature in future.

6.3 If an immediate corrective action is unclear, the Sponsor may request a meeting with the research team to discuss the next steps.

6.4 Occasionally, an amendment to temporarily halt the trial or to amend the trial protocol to prevent further deviations may be required. If applicable, this will be clearly documented on the Sponsor's assessment section and the research team must follow the procedures outlined in ***QCRES_03_Notification of Amendments for Researchers for UoL / LTHT Sponsored CTIMPs***.

6.5 Any actions required by the authorities after submission of the breach will be Sponsor led and discussed with the CI / research team as necessary.

6.6 If the research team has any issue or problems in the undertaking of any required corrective actions **this must be discussed with Sponsor QA immediately**.

6.7 Details of all non-compliances and serious breaches and any related documentation and correspondence should be retained by the research team in the Trial Master File (TMF).

6.8 Please note that all significant protocol non-compliances should be listed in the Clinical Study Report (CSR) or publication. The Sponsor review section (Section D) of the ***CTT20*** form will indicate if this is required or whether the research team should liaise with the Sponsor prior to publication.

Section D: References

1. **MHRA Good Clinical Practice Guide** (2012)
2. MHRA guidance for the notification of serious breaches of GCP or the trial protocol (Version 5 06/11/2014)

Section E: Acronyms

CI	Chief Investigator
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
LTHT	Leeds Teaching Hospitals NHS Trust
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
QA	Quality Assurance
R&I	Research and Innovation
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operation Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UoL	University of Leeds

Section F: Previous versions of Document

Version no.	Valid from	Approved by	Date approved
1.0	28/04/2016	Clare Skinner, Louise Brook	03/05/2016
2.0	26/03/2018	Clare Skinner, Louise Brook	27/04/2018