Research & Innovation Office

Standard Operating Procedure

St Luke's Hospice

Reporting Protocol & GCP Deviations & Violations

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Date Effective	23/06/2025	**Author**	Clare Pye Research & Innovation Manager
Related SOP's: Research Policies & procedures. V3. Dated 21/01/2025 SLHSOP001. Informed Consent Process. V1 dated 23/06/2025 SLHSOP003. Documenting Source data. V1 dated 23/06/2025 SLHSOP004 – Maintaining a study site file. V1 dated 23/06/2025		**Document Summary:** Describes the processes for reporting and recording protocol deviations & violations.	
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Standard Operating Procedure: Research & Innovation Office

Reporting Protocol & GCP Deviations & Violations

Contents

Acronyms

CI – Chief Investigator
PI- Principal Investigator
CTIMP - Clinical Trial of an Investigational Medicinal Product
GCP- Good Clinical Practice
SOP – Standard Operating Procedure
R&IO – Research & Innovation Office
SLH – St Luke's Hospice
TMF - Trial Master File
CRFs - Case Report Forms
ISF - Investigator Site File
HRA - Health Research Authority
REC - Research Ethics Committee
MHRA - Medicines for Human Use

1. Introduction

The UK Policy Framework for Health and Social Care Research requires that the principles of Good Clinical Practice (GCP) are applied to all NHS research studies involving patients and that the safety of research participants is prioritised at all times. While St Luke's Hospice is not an NHS organisation our policies and procedures align with this framework.

The Medicines for Human Use (Clinical Trials) Regulations (2004 [Statutory Instrument 2004/1031]) and subsequent amendment (2006 [Statutory Instrument 2006/1928]), require that serious breaches of Good Clinical Practice (GCP) or the clinical trial protocol are notified in writing to the licensing authority.

In the UK, this is the Medicines and Healthcare Products Regulatory Agency (MHRA). Regulation 29A of the Regulations states: "(1)The Sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of – (a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.(2) For the purpose of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree – (a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial." Reporting serious breaches to regulatory authorities in a timely manner is a crucial aspect of research governance.

MHRA regulations and requirements for regulatory reporting apply to Clinical Trials of Investigational Medicinal Products (CTIMPs) and device trials. St Luke's Hospice currently does not sponsor any trials but will participate as a recruiting site.

As such, it is essential that local study team are aware of their responsibilities when recording deviations and violations, and reporting breaches to the study

Sponsor. Studies which do not involve an investigational medicinal product or device do not require MHRA approval and therefore are only subject to HRA/REC Approvals. For these studies, notification of any serious breaches should be sent by the Sponsor to the REC which issued the favourable opinion for the study.

2. Purpose

To define and distinguish between deviations, violations, and breaches; to describe the process for identifying deviations, violations, and breaches; to describe the process for reporting serious breaches to the study Sponsor; and the procedures Sponsor representatives must follow to assess, report, and manage any such occurrences which are classified as serious breaches.

This document describes the process for identifying and reporting a serious breach of GCP or the approved clinical trial protocol to the R&I Office, Sponsor, Health Research Authority (HRA)/Research Ethics Committee (REC), and the MHRA

3. Roles and responsibilities

All SOPs can be accessed on the Hospice website.

The R&I Office is responsible for managing Hospice R&I SOPs including their approval, dissemination and archiving. All Hospice R&I SOPs are available and published on the Hospice website.

4. Specifics of this SOP

Definition

A **deviation** is a relatively minor non-compliance, which does not have a significant detrimental effect on either the patient or the trial.

A **violation** is when a member of the study team intentionally and deliberately fails to comply with the protocol or the requirements of GCP.

A **breach** is a more serious non-compliance, which has a significant negative effect on either the patient or the trial. Only serious breaches must be reported to the HRA and MHRA as appropriate

5. Serious breaches

REC SOPs define serious breaches as 'a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards for conduct of non CTIMPs) which is likely to affect, to a significant degree, the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

The Sponsor should notify the REC and relevant regulatory bodies of a serious breach in any study within ***7 days*** of the matter coming to their attention.' (REC SOP p. 151) The judgement on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors, including the design of the trial, the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, or the impact of excluding the data from the analysis. Therefore, it is the local PI's responsibility to inform the sponsor as soon as they become aware of the breech locally/

It is the responsibility of the Trial Steering Committee (TSC) and/or Data Monitoring Committee (DMC/DMEC) to assess the impact of the breach on the scientific value of the trial. The above definition of a serious breach is applicable to all types of clinical research studies run at the Hospice.

Serious Breaches of the Protocol or GCP in Clinical Trials of Investigational Medicinal Products

SLH does not sponsor CTIMPs. However, it is essential that any serious breaches occurring in studies taking place at SLH are reported to the Sponsor in a timely manner for onward reporting. Sponsors must notify the MHRA within ***7 days*** of becoming aware of the breach.

Study Deviations in Clinical Investigations of Medical Devices

SLH does not sponsor device trials. However, it is essential that any serious breaches occurring in studies taking place at SLH are reported to the Sponsor in a timely manner for onward reporting.

MHRA no objection letters for Clinical Investigations of Medical Devices include the following requirement for all deviations to be reported: 'You must notify the Competent Authority (the MHRA) of all deviations to the study as soon as you have been made aware of them. Please provide details about the nature of the deviation, when it occurred, where it occurred, and any proposed corrective actions.'

6. Roles and Responsibilities

Duties within the Organisation

It is the responsibility of the R&I Office to make Hospice R&I SOPs available to all research active staff working on Hospice approved research studies. It is the responsibility of the study Chief Investigator (CI) or local Principal Investigator (PI) to ensure that up-to-date copies of Hospice R&I SOPs are available to research staff.

It is the responsibility of the study CI or local PI to inform the R&I Office of the names of all research staff involved on a study so that copies of SOPs can be distributed appropriately.

It is the responsibility of the study CI or PI to indicate if the SOPs of another organisation are to be followed for a study. For example, those of a Clinical Research Network or commercial Sponsor. If there is significant conflict between the external SOP and the Hospice R&I SOP it is the responsibility of the CI or PI to resolve these with the R&I Office prior to starting the study. It is the personal responsibility of all staff to follow Hospice (or the designated alternative organisations) procedural documents.

Specific to this SOP

It is the responsibility of the Sponsor, or a person legally authorised by the Sponsor if this function has been delegated by the Sponsor to another party, to notify the MHRA within 7 days of becoming aware of a serious breach. SLH will facilitate this process by ensuring the timely reporting of any breech to the sponsor.

In accordance with Statutory Instrument 2004/1031 as amended by Statutory Instrument 2006/1928, the Sponsor retains legal responsibility even if the function is delegated. For non-CTIMPs, the Chief Investigator (if a hospice staff member) must report serious breaches to the Research Ethics Committee (REC) which granted the study favourable opinion, within 7 days of the Sponsor becoming aware of the breach. Chief Investigators should copy in the Sponsor when notifying the REC.

For Hospice hosted trials and other studies, it is the responsibility of the PI and the research team to report any issues and incidents to the Sponsor and R&I Office as soon as possible, ideally within ***ten working*** days.

7. Procedure

Deviations and Violations

Identifying Deviations and Violations

Deviations and violations from the study protocol or GCP may be identified in several ways, for example:

- By the research team themselves
- At monitoring visits or audits.
- During data checking
- At Trial Management Group or Trial Steering Committee
- Following a deviation or violation in another study
- Via an incident.

Recording Protocol/GCP Deviations and Violations

Most instances are technical deviations or errors that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. Deviations should be discussed with the CI/PI and documented in a Case Report Form (CRF) and in the study's protocol deviation log.

This record should explain concisely what happened, the Investigator's assessment of the event and details of any corrective and preventative actions taken. Template deviation logs are available from the sponsor. Deviations should also be included and considered when the clinical study report is produced, as cumulatively they may have an impact on the analysis of the data.

Sponsor and CI/PI Review of Protocol/GCP Deviations and Violations

The Sponsor and CI will review the study deviation log periodically. This will usually be performed by the Sponsor during scheduled monitoring visits (where a monitoring plan is in place) or via routine audits. The purpose of this is:

- To identify protocol or GCP deviations
- To identify any 'patterns' of deviations which may collectively constitute a serious breach. For each deviation or violation, the Sponsor and Investigator should consider:
- Is the event likely to affect the safety or physical or mental integrity of the trial participants?
- Is it likely to affect the scientific value of the trial?

If a deviation or violation is considered to have a significant effect on either of the above, it is likely to constitute a serious breach and should be assessed by the Sponsor as such. It is important to be aware that while a deviation in isolation does not constitute a serious breach, it may become a serious breach if repeated systematically.

Action Required for Protocol and GCP Deviations and Violations

Reporting to the Sponsor is not required for individual deviations (which are reviewed through monitoring and audit). For protocol and GCP deviations, the Investigator and research team can typically decide on the appropriate corrective and preventative actions and implement these. For protocol and GCP violations, the Sponsor is likely to want to make, or to be involved in, the decision on what action to take. The Sponsor may also wish to assess the violation as a potential serious breach.

Planned Deviations

SLH will not approve 'future planned deviations' (i.e. protocol waivers) in any circumstances. Research teams must not plan to deviate from the approved protocol for any study. If a research team finds that the requirements of a protocol are such that they are unable to comply in practice, this should be addressed in other ways, e.g. by discussing a potential amendment to the protocol with their Sponsor representative, or by closing the study but this should be discussed with the Sponsor.

8. Serious Breaches

Identifying Serious Breaches

Potential serious breaches are usually discovered in the same way as protocol and GCP deviations or violations

Notifying the CI/PI, R&I Office, and the Sponsor of a Serious Breach

It is expected that notification of all events is sent by a member of the study team, with no delay and in parallel, to SLH R&I Office and the study CI (for Sponsored studies) or the PI (for hosted studies). This is to ensure prompt clinical follow up on any potential safety issues. For any breaches taking place at SLH, the person reporting the event should also consider whether the breach should be reported as

an incident on the hospice incident reporting system (Vantage). The hospice defines incidents as follows:

> *An event or circumstance that could have resulted or did result in unnecessary damage, loss, or injury such as physical or mental injury to an individual.*

If the person reporting the breach is unsure, the R&I Office can advise as to whether an incident report needs to be submitted. All serious breaches must be reported to the study Sponsor within ***24 hours*** of the breach being identified. If the R&I Office identify, or are alerted to, a potential serious breach during a monitoring visit for a hosted study, the Sponsor organisation will be notified as soon as possible by the R&I Office.

A potential serious breach occurring in a trial hosted by the hospice should be reported to the R&I Office who will review the incident. The initial report should contain the name of the CI/PI, the full title of the study, the R&I Office project reference, details of the potential serious breach, and details of any corrective actions implemented.

The R&I office will contact the Chief Investigator who may consult with the Trial Steering Committee (TSC) and/or Data Management Committee (DMC) for further guidance on whether the breach should be classified as serious. If it is determined that a serious breach has occurred, the Chief Investigator or appropriately delegated member of the study team must report the breach to the HRA within ***7 days*** of them being notified.

Researchers should retain details of the serious breach and notification to the Sponsor within the trial site file so that an audit trail is available.

9. Blind Breaks

Blinding is a procedure used commonly in clinical trials, whereby the treatment allocation of participants is withheld from one or more of the study team members. Blinding helps reduce the possibility of bias undermining the rigour of a study.

Unblinding takes place when a member of the study team becomes aware of the treatment assignment of a trial participant. However, there will often be procedures outlined in the protocol designed to mitigate the impact of a blind break. The blind may be broken for a study for any number of reasons.

Where the blind is broken because of a participant enquiring with a blinded study team member about their treatment or accidental disclosure from the clinical team, this should not be considered a protocol deviation, unless the study team member in question does not take action to resolve the blind break to re-establish protocol compliance.

The study team should record the blind break and corrective actions taken and be prepared for these records to be reviewed as part of an audit or monitoring visit. Where the blind is broken, as a result of a study team member's actions, but does not have a significant impact on the participant or the conduct/rigour of the study, a record should be kept by the study team internally, including details of the investigation and corrective actions. This may be a in the form of a log of blind breaks, or in a GCP/protocol deviations log. Staff members linked to the blind break should receive training as appropriate to ensure further blind breaks are avoided.

Blind breaks do need to be immediately reported to the R&I Office. The blind break or GCP/protocol deviation log should be made available to staff conducting auditing or monitoring visits for the study.

Blind breaks may be classified as serious protocol or GCP breaches where:

- The scientific rigour of the trial is called into question
- There is evidence of systematic blind breaks (e.g. repeated blind breaks by a single member of staff)

- Where corrective action is not taken on multiple occasions.

A serious protocol and/or GCP breach should be reported to the R&I Office and the Sponsor. It is expected that study teams will have systems in place for review and analysis of trends arising from recorded blind breaks. Trend analysis of serious breaches may also alert the study team to systematic failures of compliance with trial procedures and GCP that are designed to protect the blind. This usually involves independent review by the Trial Steering Committee (TSC) and the Data Management Committee (DMEC).

10. Corrective and Preventative Action Plan (CAPA)

When reporting the serious breaches to the MHRA, the Sponsor and Investigator team should produce a formal plan of action to address the breach. Where the identified issue stems from SLH local practices, relates to hospice facilities, or is a direct result of a failure in study management locally, the R&I Office will work with the sponsor to support the PI and the research team.

11. References

RES_Standard_Operating_Procedures_Version_7.5.1_August_2021_Final_Accessible_07lVkXt.pdf

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