STANDARD OPERATING PROCEDURE

S05 – NOTIFICATION OF SERIOUS BREACHES OF GOOD CLINICAL PRACTICE OR STUDY PROTOCOL

Version	5
Effective Date	23rd March 2021
Review Date	22nd March 2024
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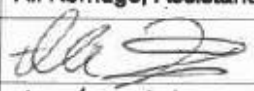
Signature	
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DISCLAIMER

This generic R&D Standard Operating Procedure (SOP) must be followed unless a study specific SOP exists.

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Full History			
Version	**Date**	**Author**	**Reason**
1.0	04/03/2011	Assistant R&D Manager	New Policy to meet standards for reporting breaches
2.0	11/04/2014	Research Management & Governance Manager	Revised to incorporate reporting requirement to NRES and inclusion of R&D reporting form
3.0	27/11/2014	Assistant R&D Manager	Updated following MHRA Inspection. Clarification of reporting process and nominated leads. Inclusion of HRA and removal of NRES. Update to R&D reporting form to reflect MHRA document.
4.0	16/10/2017	Assistant R&D Manager	Adapted into new format based on Trust standard template
5	21/12/2020	Assistant R&D Manager	Adapted into new format based on Trust standard template. Minor changes to reference the updated R&D governance structure

Associated Trust Policies/ Procedural documents:	S22 Safety Reporting S52 Urgent Safety Measures
Key Words:	Good Clinical Practice Serious breach MHRA
In consultation with: QA Group (Dec 2020)	

Contents

1 INTRODUCTION

This standard operating procedure (SOP) describes the procedures for identifying and reporting serious breaches of Good Clinical Practice (GCP) or study protocol. The Medicines for Human Use (Clinical Trials) Regulations 2004 have transposed the EU Directive 2001/20/EC of the European Parliament into UK law. The EU GCP Directive 2005/28/EC was transposed into UK law as the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, and regulates in tandem with the Medicines for Human Use (Clinical Trials) Regulations 2004.

It is a requirement that serious breaches of Good Clinical Practice (GCP) or the trial Protocol are reported to the Medicines and Healthcare products Regulatory Agency (MHRA), the sponsor and the Research Ethics Committee (REC)) as applicable.

2. PURPOSE

The purpose of this SOP is to outline the procedures for identifying, notifying and ensuring appropriate assessments are carried out and documented when a serious breach of GCP or Protocol violation occurs. This SOP also outlines the roles of the Chief Investigator (CI), Principal Investigator (PI), Sponsor and Research & Development (R&D) when a serious breach occurs.

3. SCOPE

This SOP is relevant to all those involved Research undertaken within the Royal Devon & Exeter NHS Foundation Trust (RDEFT), hereafter referred to as the Trust.

The notification procedure described in this SOP should be followed when a breach of GCP or Protocol is identified in any clinical trial sponsored by the Trust. For co-sponsored trials the Sponsorship Agreement or research Protocol should clearly state which co-sponsoring organisation's SOP will be followed.

For research which is hosted but not sponsored by the Trust, notification of breaches of GCP or Protocol should be directed to the Sponsor's contact person designated in the Clinical Trials Agreement or research Protocol within specified timescales. If no specific sponsor instructions exist then this SOP must be used in default and all breaches of GCP or trial Protocol must be clearly documented as described in 6.2.

4. DEFINITIONS

AE	Adverse Event
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
EU	European Union
GCP	Good Clinical Practice
GOG	Governance Oversight Group
HRA	Health Research Authority
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
R&D	Research & Development
RDEFT	Royal Devon & Exeter NHS Foundation Trust
REC	Research Ethics Committee
RG&Q	Research Governance & Quality (Manager)
SOG	Sponsorship Oversight Group
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

5. DUTIES AND RESPONSIBILITIES OF STAFF

It is the responsibility of the CI and PI to continually monitor the conduct of the research study.

It is the responsibility of any person involved in the research study (includes investigators, research team, monitors or auditors) to report a potentially serious breach.

It is the responsibility of the Sponsor (or a person authorised by the Sponsor) to carry out the notification procedure within 7 days of becoming aware of the serious breach. For studies sponsored or co-sponsored by the Trust then responsibility for carrying out the notification procedure within this SOP is that of the R&D Office unless specified otherwise in the protocol or in writing.

6. PROCEDURES

Protocol and GCP breaches may occur in research. These can be serious or non-serious in nature. Not every deviation from the Protocol represents a serious breach that must be reported to the MHRA – the majority are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. Breaches of this type, while they must be documented, are not serious breaches or reportable.

6.1 Identification of GCP or Protocol Breaches

6.1.1 What is a Serious breach?

A breach is defined as serious when it is likely to affect to a significant degree:

- The safety, physical or mental integrity of the subjects in the trial
- The scientific value of the trial

6.1.2 Examples of Serious Breach

- Proof of fraud relating to clinical trial records or data
- Persistent or systematic non-compliance with GCP or Protocol that has a significant impact on the integrity of trial subjects or the scientific value of the trial
- Failure to control investigational medicinal product(s) such that trial subjects or the public are put at significant risk or the scientific value of the trial is compromised
- Failure to report adverse events (AEs), serious adverse events (SAEs) or Suspected Unexpected Serious Adverse Reactions (SUSARs) in accordance with the legislation such that trial subjects or the public are put at significant risk.

6.1.3 Identification of a Serious Breach

Not all breaches from Protocols are considered to be serious. However all deviations from the approved Protocol should be documented by researchers in the Trial Master File/Investigator Site File (TMF/ISF) for affected sites.

Breaches can be identified by anyone who is conducting, managing or monitoring a trial.
In a Trust sponsored study, it is the responsibility of the person who identifies a suspected serious breach to notify the CI and the R&D Department of any SUSPECTED serious breaches of GCP. The R&D Department must be notified of any suspected serious breaches within 24 hours of the breach being identified. For a hosted study, in addition, this notification must be made to the sponsor.

6.2 Documentation of ALL breaches

When identified, ALL breaches in GCP or Protocol must be clearly documented e.g. in the Case Report Form for the trial or TMF/ISF, in order for appropriate corrective and preventative actions to be taken.

Documentation of the breach will include as a minimum:
(i) full details of the breach
(ii) the date and time of its occurrence
(iii) any remedial action and further actions to be undertaken
(iv) any information given to participants
(v) assessment by the CI or PI (or delegated individual) as to whether the breach is serious in nature
(vi) signature from the CI or PI (or delegated individual) with date and time to confirm they have made an assessment of the severity of the breach.

Breaches must be included and considered when the clinical study report is written as they may have an impact on the analysis or interpretation of the data.

6.3 Notifying the Sponsor of a Serious Breach

A serious breach in a Trust sponsored study that is detected by a member of the research team or by the trial monitor during a monitoring visit and assessed as above MUST be reported by the individual identifying the breach to the CI and the nominated lead within the R&D Office within 24 hours of the breach being identified.

The notification can be by email or in person to the Assistant R&D Manager or, in their absence, to the Research Governance & Quality Manager. If appropriate, the notification must be completed using form FRM5.

The nominated lead will escalate potential Serious Breaches to the Sponsorship Oversight Group (SOG) in a CTIMP trial or R&D senior management) in a non-CTIMP study. In both cases, and assurance will be provided to the Governance Oversight Group (GOG) regarding the actions undertaken & completed for the breach.

6.4 Sponsor Assessment of Serious Breach Notification

It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial. Typically, the sponsor will discuss the issue with the CI or delegated individual to identify which section of GCP or the Protocol has been breached and how the breach impacts participant safety and/or scientific integrity of the study. This judgement depends on a variety of factors e.g. 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, the impact of excluding the data from the analysis etc.

Upon receipt of the initial report the identified nominated lead will:

- promptly discuss with the relevant research team to confirm the assessment of seriousness of the breach
- gather any further documentation/supporting evidence for presentation to the SOG & GOG in a CTIMP trial or R&D senior management in a non-CTIMP study
- The final decision of whether the breach meets serious breach of the Protocol and/or GCP will be made by the Sponsor in conjunction with the CI
- Documentation of the review of all associated documents and the final decision must be signed, dated and filed within the relevant R&D file and Trial Master File
- Assess in collaboration with SOG/R&D Senior Management/GOG and the CI, whether any urgent safety measures may need to be implemented
- In the case of studies sponsored by the Trust, to agree with the CI any remedial actions required if the breach does not warrant notification to the MHRA and HRA
- In the case of studies where the Trust is a participating site, to work with the PI to implement any corrective actions as determined by the Sponsor

This assessment must be documented in the R&D file and TMF. If the Sponsor is unclear about the potential for a breach to have significant impact on the scientific value of the trial, the MHRA/HRA should be contacted to discuss the issue.

6.5 Notification of Serious Breach to MHRA and REC - CTIMPS

If the Sponsor obtains clear and unequivocal evidence that a serious breach has occurred, then the Sponsor must notify the MHRA within 7 days of becoming aware of the breach. The Sponsor will investigate and take additional appropriate corrective action simultaneously or after notification to the MHRA.

The completed notification form must be sent to the following email address and an acknowledgement of receipt requested by GCP.SeriousBreaches@mhra.gsi.gov.uk

If thought necessary then the Sponsor representative may initially contact the MHRA Inspectorate by telephone to discuss the breach and follow up with a written notification within 7 days of the Sponsor becoming aware of the breach.

If Urgent Safety Measures have been taken these should be notified to the MHRA and REC within 3 days of the action taken.

In the UK, serious breaches occurring on all studies should also be reported to the relevant ethics committee (at the same time as the report to the MHRA for CTIMPs), within 7 days of being informed.

6.6 Outcome

The outcome of any serious breach along with corrective and preventative measures will be discussed with the PI/CI and research team. Depending on the severity and frequency of the serious breach, the site may require additional training, monitoring and as a last resort the site may be suspended to further recruitment.

7. DISSEMINATION AND TRAINING

7.1 This SOP and associated templates and forms will be uploaded to the RDE Research website shortly after having been released.

7.2 All staff whose activities are subject to this SOP should ensure that they take time to read and understand the content of this SOP.

7.3 If applicable, a training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the contents of this SOP.

8. MONITORING COMPLIANCE AND EFFECTIVENESS OF THIS SOP

8.1 In order to monitor compliance with this SOP, the auditable standards will be monitored as follows:

No	Minimum Requirements	Evidenced by
1.	Breaches identified and logged	ISF
2.	Potential Serious breach is identified and reported to sponsor within 24 hrs on the appropriate form	ISF, R&D safety inbox
3.	Potential serious breach investigated	Email, CAPA
4.	If serious, breach reported in a timely fashion to the appropriate regulatory bodies	Email and Serious Breach Form sent to applicable regulatory body (ies)

8.2 Outcomes from audit will be presented to the R&D Governance Oversight Group (GOG) which will monitor any resulting action plans until all issues have been addressed to satisfaction.

8.3 Issues identified via the audit process which require escalation will be referred to GOG.

9. ARCHIVING ARRANGEMENTS

9.1 The original of this document will remain with the R&D Quality Assurance Coordinator. An electronic copy will be maintained on the R&D section of the Q-Pulse document management system and a pdf copy on the RDE Research website.

9.2 Archive copies must be maintained for any documents which have been superseded. Archive copies in electronic format should be retained indefinitely.

10. REFERENCES

S22 Safety Reporting

S52 Urgent Safety Measures

MHRA guidance on Serious Breaches – https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#report-a-serious-breach

HRA SOP – http://www.hra.nhs.uk/resources/research-legislation-and-governance/standard-operating-procedures/