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SOP 210 Managing Protocol and Regulatory Non-Compliance including Serious Breaches

For Use in:	Research
By:	All staff
For:	All staff involved in the conduct of research
Division responsible for document:	Research & Development
Key words:	Managing Protocol and Regulatory Non-Compliance, Serious Breaches
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Date of approval:	24.10.2023
To be reviewed before: This document remains current after this date but will be under review	24.10.2026 (3 years, unless legislation or process changes)
Reference and / or Trust Docs ID No:	14825
Version No:	5

Version and Document Control:

Version No:	Date of update	QPulse Change Request reference (CR no.)	Change Description	Author
4	September 2023	12, 96, 109, 142	Template update Update throughout to reflect current practice, form added as appendix, MHRA form link included	Basia Brown

This Standard Operating Procedure (SOP) is available on the Research & Development pages on the NNUH website

Copies downloaded from the website are only valid on the day of downloaded.

SOP 210 Managing Protocol and Regulatory Non-Compliance including Serious Breaches

1. Contents

2. Definitions of Terms Used / Glossary

AE	Adverse Event
CAPA	Corrective Action Preventative Action
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
HRA	Health Research Authority
ISF	Investigator Site File
JRGC	Joint Research Governance Committee
JRO	Joint Research Organisation
MHRA	Medicines and Healthcare Products Regulatory Agency
PI	Principal Investigator
R&D	Research and Development
REC	Research Ethics Committee
RIN	Research and Innovation Services
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File

3. Objectives

This SOP describes the process for identifying, recording and reporting cases of non-compliance to the trial protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and / or ISO14155, for studies sponsored by NNUH and UEA.

This SOP also provides guidance on informing NNUH R&D Department of any non-compliance for hosted studies.

4. Scope

- To clarify which events may constitute either a minor non-compliance, a major non-compliance or a serious breach from the approved protocol, SOPs, GCP or ISO14155
- To provide reporting guidance to regulatory bodies and Sponsor / R&D department
- To define responsibilities
- To highlight potential MHRA actions
- To describe follow-up actions

5. Purpose

To ensure actions are carried out in accordance with the regulatory guidance:

- ICH E6 GCP Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004
- Statutory Instrument 2004/1031, as amended by Statutory Instrument 2006/1928
- ISO14155 - for studies involving medical devices

6. Events

The main events covered are:

Minor non-compliance:

- A retrospective departure or deviation from the protocol which will not have an effect on the safety of the trial subjects or the outcome of the study which is neither critical or major and so **not** likely to effect to a significant degree the safety or physical or mental integrity of the trial participant or the scientific value of the trial

A file note is adequate to document the non-compliance and assess any impact to the trial

Major non-compliance:

- A significant and unjustified departure from the protocol, SOP, GCP or ISO14155 that may not have developed into a **critical** issue but may have the **potential** to do so unless addressed.
- Where there are a number of instances of minor non-compliance within a single area of responsibility, this indicates **a systemic quality assurance failure** and so should be collectively treated as a major non-compliance

A corrective action, preventive action investigation (CAPA) should be undertaken and reported by the CI/PI

Serious Breach:

- A significant and unjustified departure from the protocol, SOP, GCP or ISO14155 which **is** likely to effect to a **significant** degree the safety or physical or mental integrity of the trial participant or the scientific value of the trial

Serious Breach assessment and reporting is required as described in section 8.

Additionally, a serious breach may include inappropriate, insufficient or untimely corrective action/s regarding previously reported major non-compliances and/or where the Trial Master File (TMF) does not comply with the regulations, is not readily available or accessible or is incomplete to an extent that it impedes or obstructs inspection.

7. Rules

Non compliance / Potential serious breach
• it is vital that the sponsor has oversight of a potential serious breach, therefore the opportunity for oversight must be provided • the sponsor must be made aware of any significant and unjustified event which is likely to affect the physical or mental integrity of a trial participant or the scientific value of the trial • it is appropriate for a CTU (where used), CI/PI and the Statistician to make the decision as to whether the issue is a serious breach however, the sponsor must be copied into the correspondence and reporting to the MHRA • The contract or agreement and protocol should make the delegation of responsibilities clear with regard to decision making and reporting to the MHRA

NB: The Delegate is the legal entity described within the contract/agreement and protocol. This could be an investigator, statistician or legal representative.

Serious Breach reporting to Research Ethics Committee (REC) is required for all research trials. See section 8 of this SOP

For CTIMP/Medical Device trials the MHRA reporting process must be followed (see sections 8.1 of this SOP).

For NNUH Sponsored CTIMP/Medical Device trials a Serious Breach will be reported to the Joint Research Governance Committee (JRGC).

8. Procedure NNUH - Regulatory reporting of serious breaches

8.1 Reporting for CTIMPS and Medical Devices studies

	• For CTIMPS / Medical device studies where NNUH act as a Sponsor, the R&D Department must be notified as soon possible - ideally within 24 hrs of breach being identified. • This can be done by email (office.rd@nnuh.nhs.uk), phone or in person.
	• Investigations can be made by the Sponsor or delegate once the notification is made, there is no requirement to investigate prior to notification.
	• The Sponsor/Delegate may initially contact the MHRA by telephone to discuss the breach and follow up with a written notification
	• Use R&D Form for "**Protocol and Regulatory Non-Compliance Including Serious Breaches** " (Appendix 1) or MHRA template *https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/905578/Notification_of_Serious_Breach_Form_v7.docx*
	• Sponsor or Delegate must report a potential serious breach to the MHRA within 7 days of becoming aware • Notify the relevant ethics committee at the same time as the report to the MHRA • Email to: GCP.seriousbreaches@mhra.gov.uk cc to the ethics committee which gate the original approval
	• Wherever possible, MHRA will provide an acknowledgement of receipt of notifications
	• If the MHRA template form is not used, the written report should clearly state that it relates to a notification of a serious breach

8.2 Reporting for non CTIMP / non-Medical Device studies

	• For non CTIMPS / non-Medical device studies where NNUH or UEA acts as a Sponsor, R&D Department /RIN must be notified as soon possible, ideally with 24 hrs of breach being identified. • This can be done by email, phone or in person: • NNUH R&D office office.rd@nnuh.nhs.uk • UEA RIN: researchsponsor@uea.ac.uk
	• Any initial discussions with R&D / RIN need to be followed up by a written report
	• Use form for "**Protocol and Regulatory Non-Compliance Including Serious Breaches** " (Appendix 1)
	• For non-CTIMP / non-Medical device studies research, serious breaches of GCP or the protocol should be reported to the relevant ethics committee.

- Sponsor or Delegate must report a potential serious breach within 7 days of becoming aware to relevant ethics committee
- Email ethics committee which gave original approval for the study

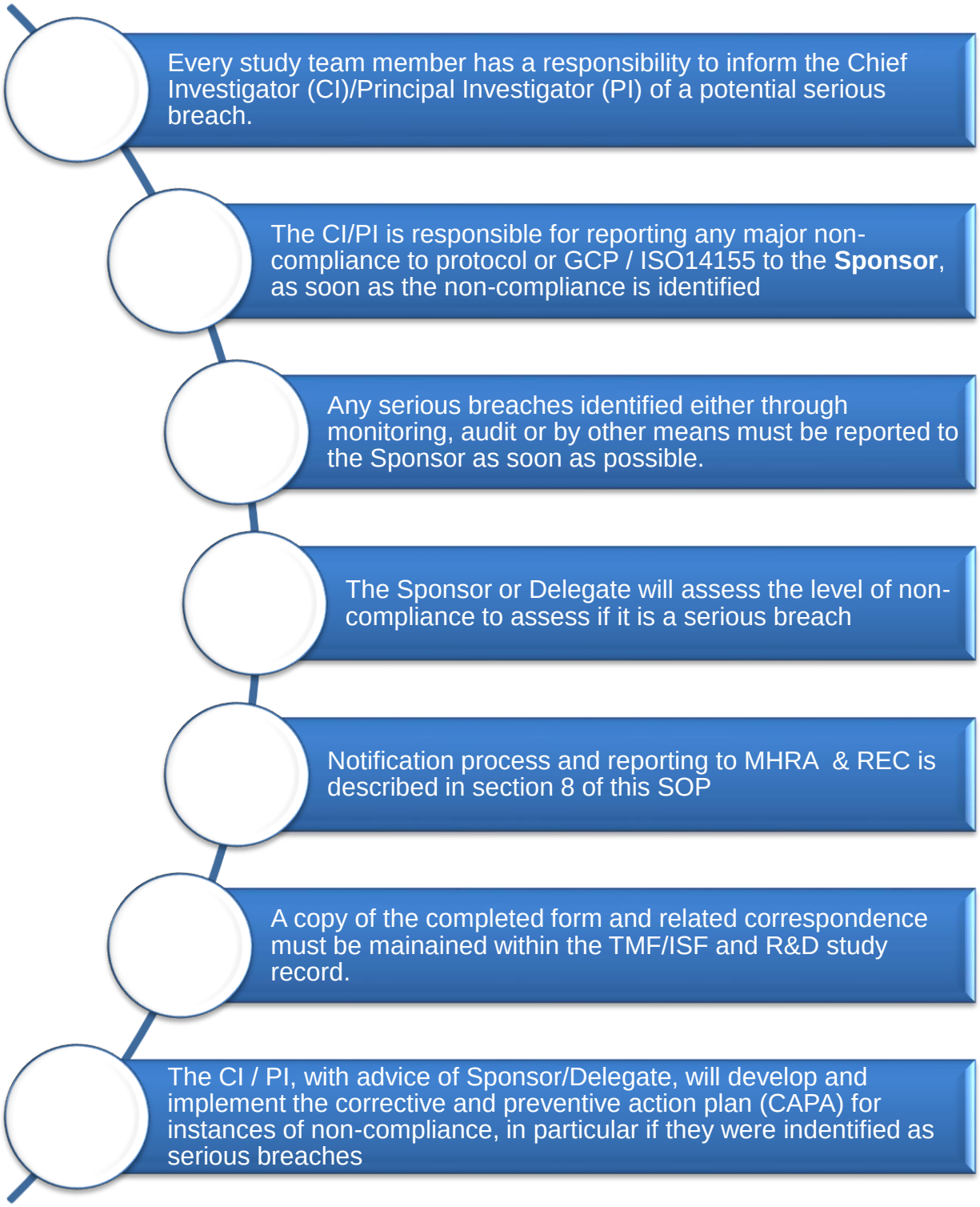
- Wherever possible, REC will provide an acknowledgement of receipt of notifications

9. Reporting of Major and Minor non compliances

Although the regulatory reporting of major and minor non compliances is voluntary, the expectation is that, for any NNUH sponsored studies, any non-compliance and near misses will be raised for the attention of the R&D department. These can be reported via a copy of a file note or email to office.rd@nnuh.nhs.uk with a summary of the non-compliance.

If a CTU is involved in managing a study sponsored by NNUH, study specific agreements can be made on the process of informing the R&D Department of non serious breaches, e.g: CTU can provide a summary of non-compliance within agreed time intervals.

10. Responsibilities



Upon receipt of a serious breach notification, the MHRA will log and review the notification, and a variety of actions may be taken, depending on the nature of the breach and its potential impact e.g.

- Acknowledgement of receipt, but no immediate action e.g. if appropriate action has already been taken by the sponsor. The case may be examined during future MHRA inspections
- Request for additional information from and investigation by, the Sponsor. If insufficient information is provided in the initial notification to assess the impact of the breach, follow-up information will be requested
- Sharing of information with other concerned parties, in accordance with the regulations and applicable agreements e.g. to concerned Ethics Committees, other competent authorities, MHRA Clinical Trials Unit
- Investigation by the MHRA, for example, triggered inspection(s)
- Implementation of urgent safety measures, where appropriate
- Suspension or termination of a clinical trial authorisation, where appropriate
- Referral for enforcement action e.g. infringement notices, criminal investigation
- Referral to professional bodies e.g. the General Medical Council

Actions requested by the MHRA must be taken seriously and completed in a timely manner

- These will be followed up by the MHRA and if not completed the MHRA will not close the referral and may perform a triggered inspection

11. Other considerations

11.1 Safety reporting

If the safety or physical or mental integrity of the trial participant has been affected by the non-compliance or serious breach, then the procedure for reporting an Adverse Event (AE) or Serious Adverse Event (SAE) must be followed. See the following SOPs:

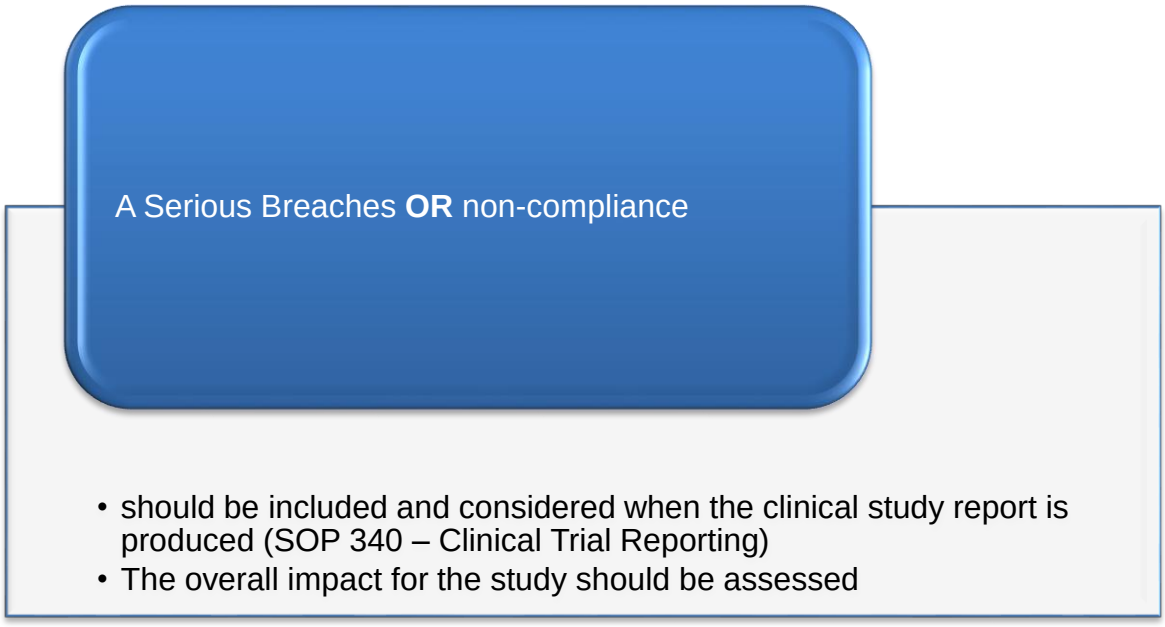
SOP No.	SOP Title
SOP 205	Adverse Events: Identifying, Recording and Reporting for CTIMPs Sponsored by the Norfolk and Norwich University Hospitals NHS Foundation Trust
SOP 206	Adverse Events: Identifying, Recording and Reporting adverse events for Non-CTIMP Healthcare Research Studies
SOP 207	Adverse Events: Identifying, Recording and Reporting Adverse Events for Device Trials
SOP 230	Urgent Safety Measures

11.2 Internal incident reporting

Organisational incident reporting procedures need to be considered and followed on identification of non-compliance.

For any non-compliances which took place on NNUH premises please refer to DATIX reporting procedure on Trust Intranet.

11.3 Clinical Trial Reporting



12 Informing NNUH R&D department of non-compliances for hosted studies.

The R&D department should be informed of non-compliances for hosted studies. For serious non compliances this, ideally, should be done by copying the R&D department (office.rd@nnuh.nhs.uk) into correspondence to the Sponsor.

For any non-serious breaches R&D can be informed by providing regular summaries of non-compliances.

13 References and Related Documents

References	
ICH GCP E6 / SI 2004/1041	
Form for Protocol and Regulatory Non-Compliance Including Serious Breaches available from the NNUH internet webpage	
Research Ethics Committee – Standard Operating Procedures v 7.5.1 August 2021	
SOP No.	**SOP Title**
SOP 205	Adverse Events: Identifying, Recording and Reporting for CTIMPs Sponsored by the Norfolk and Norwich University Hospitals NHS Foundation Trust
SOP 206	Adverse Events: Identifying, Recording and Reporting adverse events for Non-CTIMP Healthcare Research Studies
SOP 207	Adverse Events: Identifying, Recording and Reporting Adverse Events for Device Trials
SOP 230	Urgent Safety Measures

14 Approval

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Approved & Authorised UEA	Sarah Ruthven
Role	Research Manager
Signature	DocuSigned by: Sarah Ruthven 50D5F3BEE2F04C1...
Date	13 November 2023 | 4:41 GMT

15 Training Implication

Training Implication	**Yes**
Actions required	• Additional training may be required

Appendix 1

Joint Arrangements for Research

Form for Protocol and Regulatory Non-Compliance Including Serious Breaches

To be used in conjunction with SOP 210 Managing Protocol and Regulatory Non-Compliance including Serious Breaches

Title of Trial/Acronym:	
Sponsor:	NNUH ☐ University of East Anglia ☐
IRAS number:	
Sponsor Reference (R&D/RIN number):	
Chief Investigator:	
Research Ethics Committee Reference:	
Eudract Reference (if applicable):	
NCTU NCR Report Reference (if applicable):	
Name of Institution / Site:	
Report type:	Initial ☐ Follow-up ☐ Final ☐
Report dates: (DD/MM/YY)	Initial: Follow-up: Final:

Section 1: Description of Non-compliance
(include dates, participant identifiers, location of event(s) / organisations involved and names of staff involved in non-conformance, if known and appropriate)

Identified by:		
Is this a serious breach of GCP or Protocol?	Yes ☐	No ☐

Section 2: Reasons
(What are the root cause (s) / investigation results)

Corrective actions: (Please list as many as required)	Lead Person & Target Date (DD/MM/YY)	Date Completed (DD/MM/YY)

Preventative actions: (Please list as many as required)	Lead Person & Target Date (DD/MM/YY)	Date Completed (DD/MM/YY)

Please supply contact details where further information may be obtained:

Person to contact:

Phone number:

Email address:

If the study is sponsored by NNUH please send the completed form to office.rd@nnuh.nhs.uk .

If the study is sponsored by the University of East Anglia and Hosted by NNUH, please scan and email the form to researchsponsor@uea.ac.uk and office.rd@nnuh.nhs.uk .