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

For Use in:	Research & Development
By:	All staff
For:	All staff involved in the conduct of research
Division responsible for document:	Research & Development
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Name of document author:	Gillian Short
Job title of document author:	Research Governance Coordinator
Name of document author's Line Manager:	Julie Dawson
Job title of author's Line Manager:	Research Services Manager
Supported by:	Julie Dawson NNUH Sarah Ruthven UEA
Assessed and approved by the:	Julie Dawson: Research Services Manager NNUH Sarah Ruthven: Research Manager UEA
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SOP 210 V4.1

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

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2. Definitions of Terms Used / Glossary

AE	Adverse Event
CAPA	Corrective Action Preventive 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	Investigators 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
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File

3. Scope

This SOP describes the process for identifying, recording and reporting cases of non-compliance to the trial protocol, Standard Operating Procedures (SOP's) or Good Clinical Practice (GCP).

- This includes discovery of a course of action or event, which may constitute either a minor non-compliance, a major non-compliance or a serious breach from the approved protocol, SOPs or GCP
- Assessment of severity
- Reporting guidance
- Responsibilities
- Potential MHRA actions
- Follow-up actions

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

4. Introduction

Minor non-compliance

- Retrospective departures or deviations 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

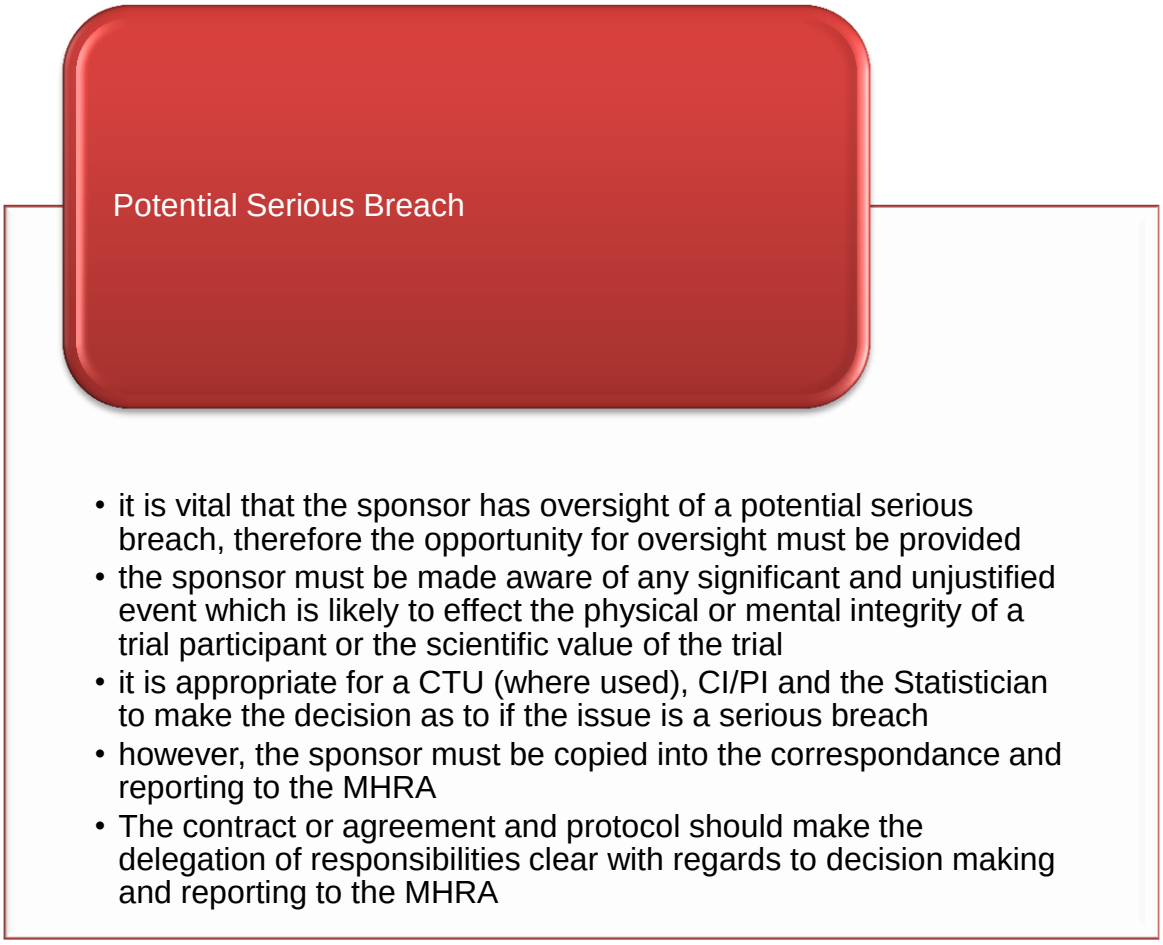
- is a significant and unjustified departure from the protocol, SOP or GCP
- that may not have developed into a **critical** issue but may have the **potential** to do so unless addressed
- Where there are a number of instances of minor non-compliance within a single area of responsibility, this indicates **a systemic quality assurance failure** and so should be collectively treated as major non-compliance
- A corrective action, preventive action investigation (CAPA) should be undertaken and reported by the CI/PI

Serious Breach

- is a significant and unjustified departure from the protocol, SOP or GCP
- 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 assesment and reporting is required as described in section 5 & 6

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.

5. Rules



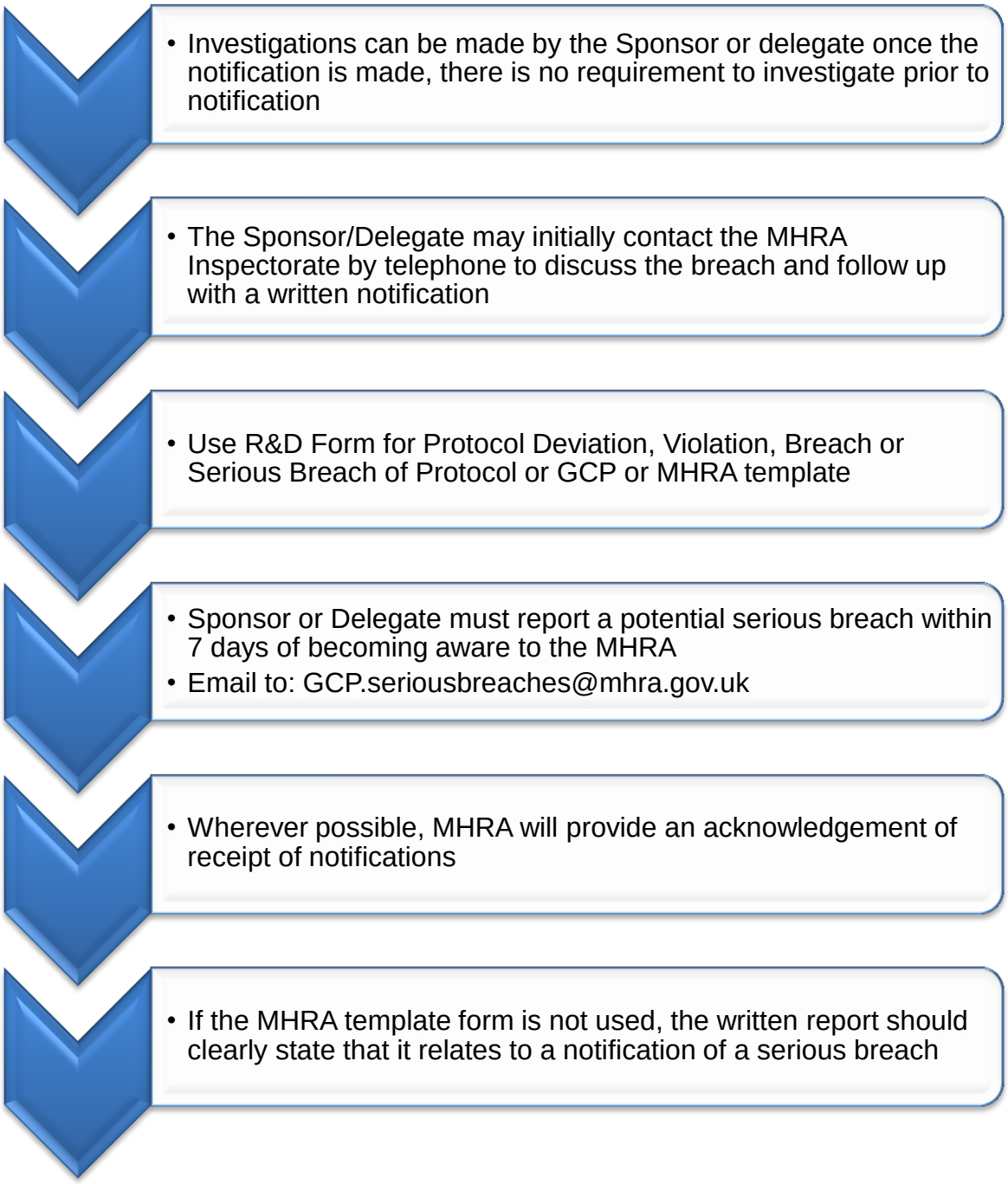
NB: The Delegate is the legal entitiy described within the contract/agreement and protocol. This could be an investigator, statistitian or legal representative.

Serious Breach reporting to Research Ethics Committee (REC) and Health Research Authority (HRA) is required for all research trials. The procedure for the individual ethics organisation should be followed.

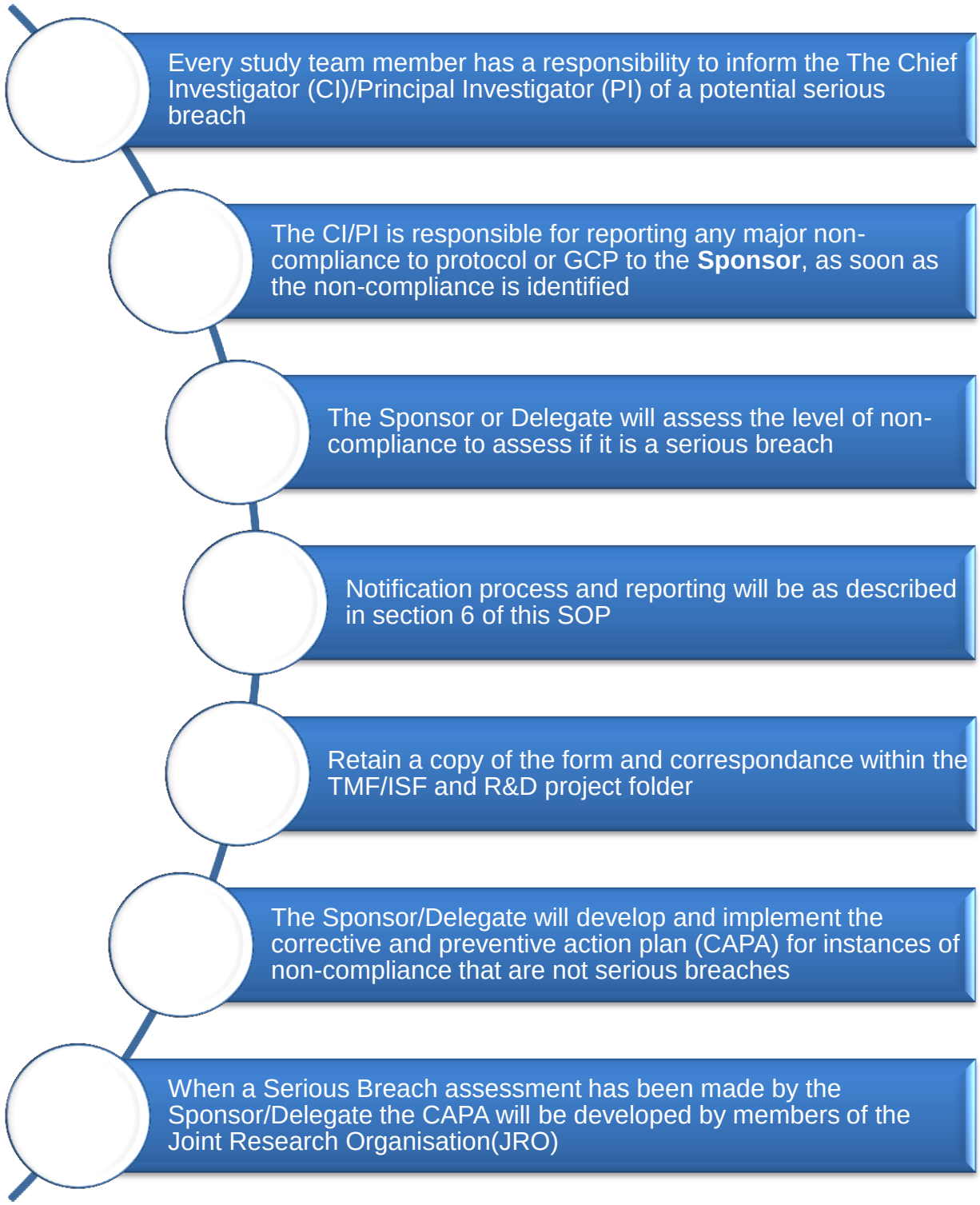
For CTIMP/Medical Device trials the MHRA reporting process must be followed (see sections 5-8 of this SOP).

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

6. Procedure of informing the MHRA



7. Responsibilities



8. Potential Actions by the MHRA

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

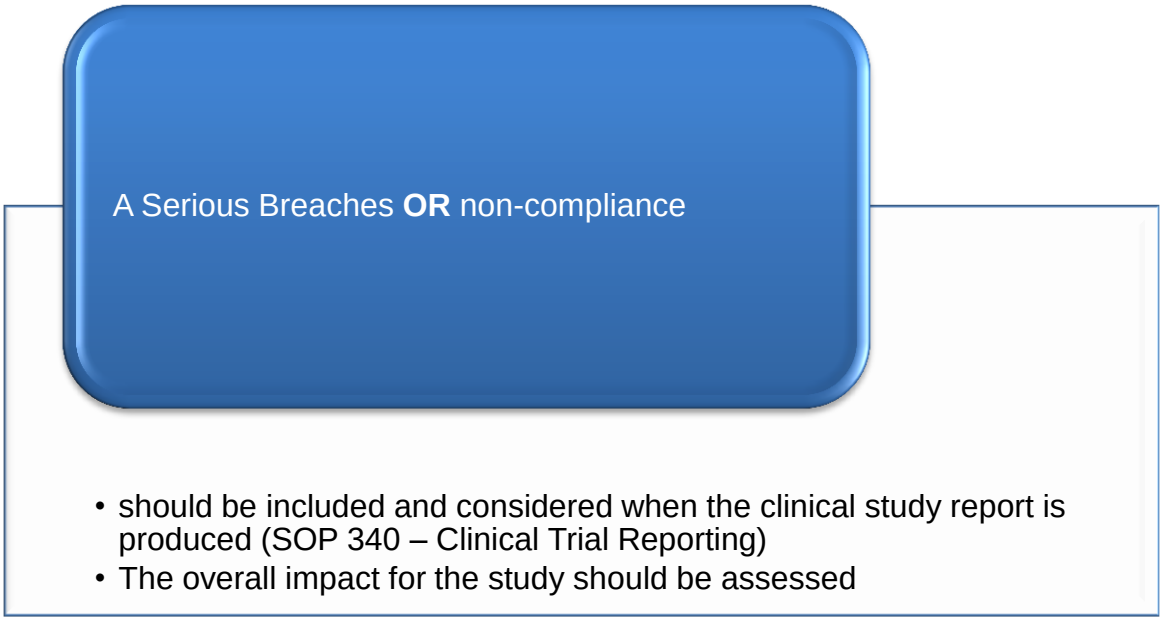
- These will be followed up by the MHRA and if are not completed the MHRA will not close the referral and may perform a triggered inspection

9. Related Documentation

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:

- 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
- **Form for Protocol and Regulatory Non-Compliance Including Serious Breaches** available from the NNUH internet webpage

10. Clinical Trial Reporting



11. Approval

Author:	**Gillian Short**
Role:	**Research Governanace Coordinator**
Signature:	**Gillian Short**
Date:	**09 December 2019**
Approved & Authorised NNUH:	**Julie Dawson**
Role:	**Research Services Manager**
Signature:	**Julie Dawson**
Date:	**09 December 2019**
Approved & Authorised UEA:	**Sarah Ruthven**
Role:	**Research Manager**
Signature:	**Sarah Ruthven**
Date:	**09 December 2019**

12. Reason for Update and Training Implication

This replaces enter SOP 210 v4.0

Update	Reason	Training Implication	Action
Template update Update throughout to reflect current practice	Addition to new template Procedure reviewed for accuracy versus MHRA guidance	Yes	Review SOP and update training matrix