SERIOUS BREACHES (SPONSORED)

Research & Development

Standard Operating Procedure for Notification of Serious Breaches of GCP in West Hertfordshire Hospitals NHS Trust Sponsored Drug Trials

SOP Number : SOP-10-05	**Effective Date:** October 2021
Version Number: 05	**Review Date:** 2-3 years

1.0 BACKGROUND

This document sets out the procedures to be followed by all West Hertfordshire Hospitals Trust (WHHT) staff who are involved in Clinical Trials of Medicinal Products (CTIMPs) and non-CE marked Medical Devices.

It provides guidance on how serious breaches of Good Clinical Practice (GCP)/protocol must be identified and managed.

The procedures to be followed to ensure compliance with Regulation 29A of the UK Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004/1031) as amended by Statutory Instrument 2006/1928, are fully detailed.

Deviations from clinical trial protocols and GCP occur commonly in clinical trials. The majority of these instances 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. These cases should be documented e.g. in the Case Report Form (CRF) for the trial or the Trial Master File (TMF), in order for appropriate Corrective And Preventative Actions (CAPA) to be taken. In addition, these deviations should be included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data. However, not every deviation from the protocol needs to be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) as a serious breach. The reporting procedures for protocol violation/deviation are usually defined in the clinical trial protocol.

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, the impact of excluding the data from the analysis etc.

It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial. Anyone who is unsure whether a breach has occurred can contact the R&D Office to discuss the situation and clarify whether a breach is classed as serious (examples of possible serious breaches can be found in Appendix 3).

2.0 PURPOSE

- To outline procedures for identifying a potential serious breach of GCP or protocol violation
- To describe the process for notification of serious breaches of GCP or the approved trial protocol
- To ensure appropriate assessments are carried out by relevant parties and fully documented
- To outline the role of the Research & Development Steering Group (RDSG) in assessing all reported serious breaches and following the escalation plan

3.0 APPLICABLE TO

Any Trust employee involved with clinical research including, but not limited to, Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Consultants, Co-Investigators, Clinical Trial Pharmacists, Research Managers, Statisticians, Research Nurses, Allied Health Professionals, Trial Coordinators, the RDSG & Data Managers.

4.0 RESPONSIBILITIES

4.0.1 All researchers must ensure all possible serious breaches are reported to the Chief Investigator (CI) immediately or as stated in protocol. For multicentre trials, any reported events by participating sites to the study coordinator should be notified to the CI.

4.0.2 The CI or delegated individual (DI) of the study shall ensure that any reported possible serious breaches are reported as stated in protocol and Trust SOPs.

4.0.3 For sponsored multicentre trials, the process for identifying breaches should be provided to all participating sites at study set up. The Sponsor should also ensure that adequate procedures are in place as part of the routine monitoring processes to identify potential GCP breaches.

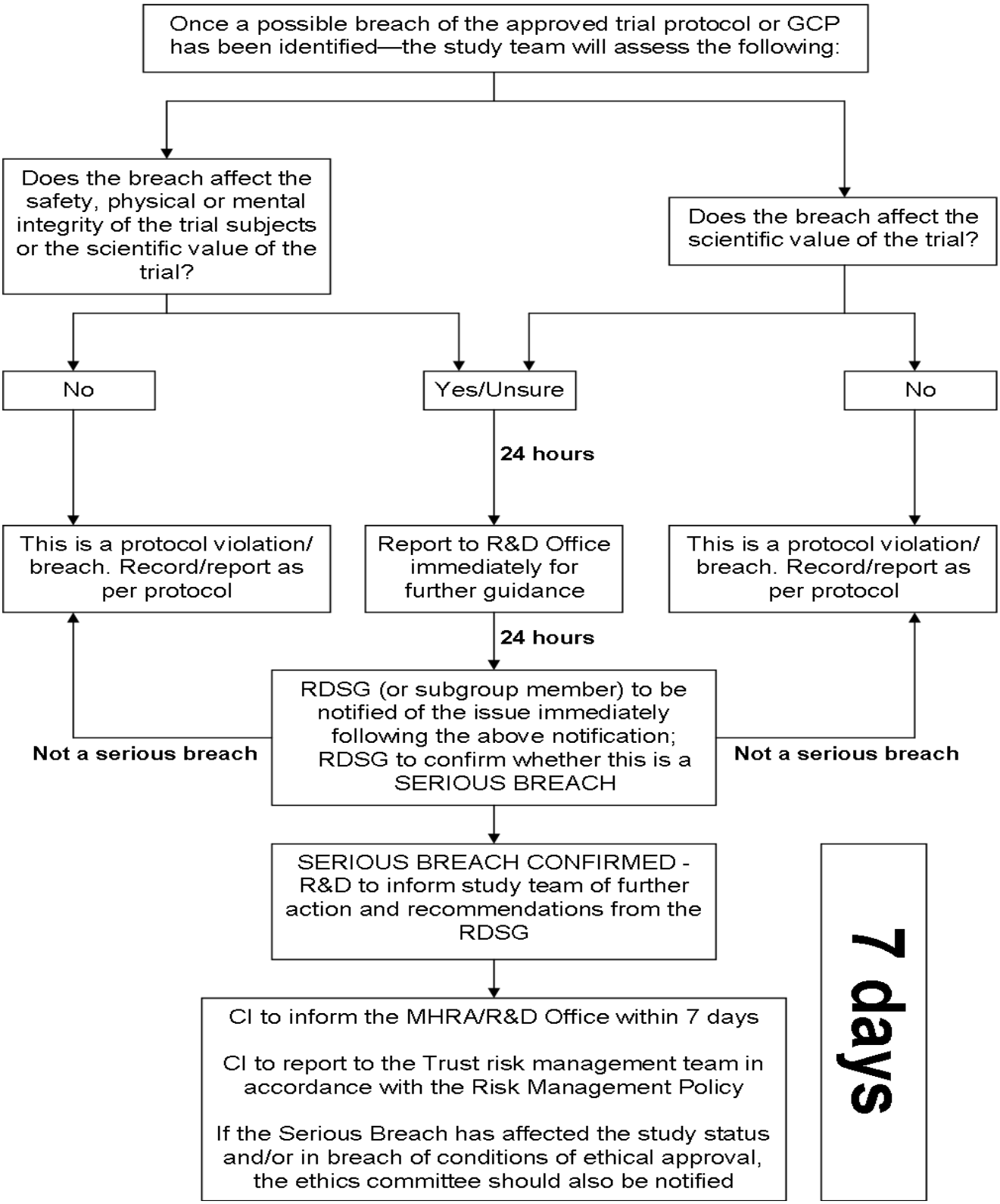
4.0.4 For any possible serious breaches reported to the R&D Office, the RDSG/RDSG Sub-group (Director of R&D, Associate Director of R&D, clinical representation as required) shall be informed immediately (**within 24 hours**) and ensure appropriate recommendations are made to the CI regarding further management of the breach and notification to patients if required.

4.0.5 The R&D Office shall also ensure that details of the breach are reported to the Trust RDSG.

4.0.6 The R&D Office and the CI shall ensure that all reported serious breaches are reported to MHRA within 7 days and any relevant follow up information is provided ASAP.

5.0 PROCEDURE

Timeframes for reporting serious breaches of GCP or the trial protocol



5.1 Identifying and Notifying Sponsor of a Serious Breach

- It is the responsibility of the CI and PI to continually monitor the conduct of the clinical trial; this

may be delegated to a suitably qualified or experienced member of the research team or subcontracted to an appropriately qualified party (e.g. coordinating centre). In addition the R&D Office may audit the trial as part of their Quality Assurance procedures.

- If a possible protocol violation and/or GCP breach has been identified, the CI should carry out an assessment as illustrated in the flow diagram above to confirm if the event affects the safety, physical or mental integrity of the trial subject or the scientific value of the trial. If yes, this should be treated as a possible serious breach and should be investigated further. Immediate reporting to the R&D Office is also required. However, if the event only relates to a protocol violation, then record the event as per protocol requirements.

- Any potential serious breaches of GCP identified either through monitoring, audit or by other means must be reported to the R&D Office **within 24 hours** of the breach being identified by the study team using the form in Appendix 2. For multicentre trials, the 'clock starts' when the event has been either identified by the Sponsor or when the event has been reported to CI by the participating site.

- If the event is considered to be a possible serious breach of GCP, then the initial reporting to the R&D Office should be carried and should provide the following information:

1) Name of CI and PI at the site where the breach occurred
2) Full title and RD number of the clinical trial
3) An explanation of how the breach was identified
4) Details of the breach
5) Details of any immediate corrective actions
6) Assessment of the impact the breach will have on the trial subjects and/or scientific integrity

- For sponsored multicentre trials, the process for identifying breaches should be provided to all participating sites at study set up. The Sponsor should also ensure that adequate procedures are in place as part of the routine monitoring processes to identify potential GCP breaches.

- If a possible breach has been reported by a PI at a participating site or identified by the Sponsor as part of the routine monitoring process, this SOP should be followed to conduct the necessary assessment and reporting required by the Sponsor.

5.2 Assessment of a Serious Breach

- The Trust has delegated authority to the RDSG for review of serious breaches. It is the RDSG's responsibility to assess the potential impact of the breach on patient safety and data integrity to determine whether it qualifies as a serious breach.

Notifying the RDSG of a potential Serious Breach

- Upon receipt of an initial breach report, the R&D Office will discuss the issue with the CI/DI to identify which section of GCP or the protocol has been breached and how the breach impacts the subject/participant safety and/or the scientific integrity of the trial.

- All of the information gained during these discussions will be provided to the RDSG. Should an RDSG meeting not be scheduled, the R&D Office will organise an extraordinary RDSG meeting or convene a sub group of RDSG members **within 24 hours** to discuss the details of the breach.

During these discussions the RDSG/sub-group will make an assessment of the event and consider if it qualifies as a serious breach of GCP. If the event is considered to be a serious breach by the RDSG/sub-group, then the study team will be informed of further actions and recommendations by the RDSG/sub-group.

- Once the event is considered to be serious by the RDSG/sub-group, the 7 day reporting period will commence.

- Based on the RDSG/sub-group's recommendations, the R&D Office will meet with the study team to discuss the breach and compile evidence to support notification to the MHRA and complete the form in Appendix 2. This will then be sent to the CI and related departments e.g. Pharmacy, Director of R&D and the RDSG, for approval prior to submission to MHRA.

- The R&D Office will work with the study team to identify the extent of the breach and to initiate any Urgent Safety Measures (USMs) that may be required.

5.3 Initial Notification of Breach to MHRA

The R&D Office will collate all available information and complete the Notification of Serious Breaches of GCP or the Trial Protocol form (Appendix 2).

The form will be submitted via e-mail to the MHRA within the 7 day reporting period as defined in the regulations.

The Associate Manager of R&D will be the contact person for all correspondence with the MHRA.

5.4 Provision of Additional Information to the MHRA

Once the initial notification has been submitted to the MHRA, the R&D Office will review the breach in full to identify the extent of the breach and continue to update the MHRA with new information.

The CI/R&D Office will compile a project report for submission to the MHRA. The project report will include:

1) Full title of trial, ethics approval number, EudraCT number, version number, date of commencement
2) Name of CI
3) List of Sites
4) Number of subjects recruited
5) Brief description of the trial
6) Summary of the breach including rationale
7) Summary of actions taken
8) Assessment of impact of breach to subject/participant safety
9) Assessment of the scientific integrity of trial
10) Statement from CI (if not the person completing the report)

If the incident involves other departments such as Pharmacy, then departmental specific assessments for point 8 and 9 should be performed. For the assessment of scientific integrity of the trial, the CI of the study should liaise with the named statistician on the trial to complete the data integrity assessment and provide supporting documentation.

The R&D Office will review the project report and submit it to the MHRA.

The MHRA may request additional information such as a copy of the protocol, ethics application, SOPs etc. The R&D Office will liaise with the study team to obtain additional documents and submit them to the MHRA.

5.5 Other Reporting Requirements and Implementing Corrective and Preventative Action (CAPA)

Any possible serious breach may also require reporting to the Trust's risk management team in accordance with Trust policy. R&D Office shall make recommendations to the study team about where further reporting requirements apply.

The R&D Office shall also ensure that details of the breach are reported to the Trust R&D Steering Group (Ref: Escalation Plan, Appendix 4).

The breach may also require reporting to the ethics committee if it is in breach of the ethical conditions of study approval.

The R&D Office will work with the study team to devise a formal plan of Corrective And Preventative Action (CAPA) to address the breach. The CAPA should be submitted to the MHRA in the final report.

Depending on the initial assessment of seriousness and impact, the R&D Office may carry out a full audit of the trial and general trial management systems and procedures.

6.0 RELATED DOCUMENTS

- Standard Operating Procedures Working Group Terms of Reference
- Membership of Standard Operating Procedures Working Group
- SOP-02- SAEs (Sponsored)
- SOP-04- Informed Consent
- SOP-05- SAEs (Hosted)
- SOP-06- Trial Master File
- SOP-07- Research Staff Training
- SOP-08- Role of CI, pharmacy, nuclear medicine and R&D
- SOP-09- Amendments
- SOP-11- Sponsor Oversight
- Statutory instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004.
- Statutory Instrument 2006/1928: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.
- Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol, MHRA.
- Notification of Serious Breach of Good Clinical Practice or Trial Protocol (form)- Please visit the MHRA website to download the latest MHRA Serious Breach Notification Form.

7.0 APPENDICES

Appendix 1 - Definitions
Appendix 2 - Potential GCP Breach/ Protocol Violation Form

Appendix 3 - Examples of Serious Breaches
Appendix 4 - Escalation Plan

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
SOP-10-05	**October 2021**	1. Change from general Standard Operating Procedures (gSOP) to SOP 2. Removal of the '10.0 Agreement' from the template - all agreement signatures will be collated on a new 'SOP Signature Sheet Document' 3. Updates to the appendices in accordance with current MHRA documentation 4. Addition of Appendix 4: Escalation plan 5. Other minor changes and clarifications of terms following review
gSOP-10-04	**10/2017**	Minor amendments following review
gSOP-10-03	**07/05/2014**	Minor amendments following review
gSOP-10-02		SOP modified for implementation at ENHT/WHHT
gSOP-10-01 (MVCC)		SOP modified for implementation at MVCC

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date** 28/10/2021

R & D Steering Group Approval

Signature  **Date** 28/10/2021

Appendix 1: Definitions

Adverse Event (AE)
An unfavourable outcome that occurs during or after the use of a drug or other intervention, but is not necessarily caused by it.

Case Record Form (CRF)
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject

Chief Investigator (CI)
The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI. For Trust sponsored trials, the CI had been delegated the pharmacovigilance responsibility for identification, recording and reporting of safety events, including submission of Development Safety Update Reports (DSURs) to the MHRA and REC.

Clinical Trial
A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. A Study Type.

Delegated Individual (DI)
An individual delegated by a person of responsibility to carry out their task(s).

Good Clinical Practice (GCP)
Good Clinical Practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.

International Conference on Harmonisation (ICH)
International Conference for Harmonisation, a collaboration between regulators and the pharmaceutical industry in Europe, the United States and Japan to establish common standards for clinical trials. ICH GCP is a widely recognised standard for Good Clinical Practice in clinical trials.

Investigational Medicinal Products (IMP)
A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a Clinical Trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial - a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation, b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or c) used to gain further information about the form of that product as authorised under the authorisation.

MHRA Clinical Trial Authorisation (CTA)
This is the authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) to conduct a Clinical trial of an investigational medicinal product (CTIMP). No CTIMP can commence in the UK without both a CTA and a favourable ethical opinion. Applications to the MHRA and the Research Ethics Committee (REC) may be made in parallel.

Principal Investigator (PI)
The investigator responsible for the research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any adverse event or adverse reaction that results in:

- death
- is life-threatening*
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- or is a congenital anomaly or birth defect

Comment: Medical judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

* Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

Statutory Instrument (SI)
Legal means of implementation of EU Clinical Trials Directive into UK law. SI 1031 (2004), subsequently amended by SI 1928 (2006), SI 2984 (2006), SI 941 (2008) and SI 1184 (2009).

The Medicines & Healthcare products Regulatory Agency (MHRA)
The MHRA is the competent authority for the UK in relation to the Directive 2001/20/EC and the Clinical Trials Regulations, and for Medical Devices, the competent authority in relation to the Medical Devices Regulations 2002.

The Regulations
Medicines for Human Use (Clinical Trial) Regulations 2004 transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031. This became effective on the 1st May 2004. An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928.

Trial Master File
The Trial Master File contains all essential documents held by the sponsor/Chief Investigator which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced.

Appendix 2: Potential GCP Breach/ Protocol Violation Form

Notification of Serious Breach of Good Clinical Practice or Trial Protocol

Please complete this notification form and submit to R&D Office

Initial Report	☐
Follow-up Report	☐
Follow-up Report number (number follow-up reports sequentially from 01).	
MHRA GCP ID (if known)	
Name and Contact Details of Reporter	
Organisation of Reporter	
Details of Individual or Organisation committing breach	
Confirm if the Individual or Organisation committing breach have been made aware	Yes ☐ No ☐

Contact details for Individual/Organisation committing breach (if different from the above):	
Clinical trial details (for each trial include as a minimum; EudraCT number, CTA number, IRAS number, study title, Sponsor, UK Chief Investigator name and REC name)	
Trial/s type	Commercial ☐ Non-Commercial ☐
Confirm which other parties have been notified and when e.g. other competent authorities, EMA, CQC, HRA, REC, other GxPs etc	
Date Breach Identified by Sponsor	
Date Breach Notified to MHRA	

Please give details of the breach

Breach summary *(provide a brief top-level summary of the breach):*

<u>Potential</u> impact to (select all that apply):

Patient Safety or physical or mental integrity ☐

Data Integrity (scientific value of the trial) ☐

Incident information:

Explain the breach and what has happened. Include any background information, context required to understand the incident.

Other relevant information:

(i.e. study status, site(s), ethics, trust, CRO /sponsor details etc.)

Please give details of the action taken:

***Impact Assessment**:*

What is the extent of the issue and the impact? This should be investigated and reported. The issue may need to be reviewed across sites, trials, sponsors, electronic systems etc to determine the extent of the issue and impact. Provide full details of the impact assessment, include what has been looked at and how this has been done i.e. methodology should also be included here. If this is not known at the time of report provide details of when this will be available and submitted as a follow-up report.

Root Cause Investigation:

The root cause investigation by your organisation should be explained including details of investigations by other organisations (e.g. CRO/ethics/trust), the results and outcomes of the investigations. If this is not known at the time of report provide details of when this will be available and submitted as a follow-up report

Corrective & Preventative Action (CAPA) Plan:

Provide a clear measurable CAPA plan including any actions already taken/implemented. Include details of which organisation is responsible for each action (e.g. Sponsor, CRO, CRA, site etc) and a timeline. Also include how the incident will be transparently reported in the final report/publication and how this incident will be documented in the TMF for future inspection. If this is not known at the time of report provide details of when this will be available and submitted as a follow-up report

<u>Actual</u> impact to (select all that apply):

Patient Safety or physical or mental integrity	☐	Data Integrity (scientific value of the trial)	☐
No significant impact	☐		

Appendix 3: Examples of Serious Breaches

Category	Notifier	Details of Breach Reported	Is this a Serious Breach?
IMP	Sponsor	Dosing errors reported: 1) A subject was dosed with the incorrect IMP, which was administered via the incorrect route (the IMP used was from a completely different clinical trial to the one the subject was recruited to).	**Yes,** there was significant potential to impact the safety or physical or mental integrity of trial subjects.
		2) A subject was dosed with IMP from the incorrect treatment arm. In addition, some months later, the subjects in an entire cohort were incorrectly dosed with IMP three times daily when they should have been dosed once daily.	**Yes,** ● there was impact on the safety or physical or mental integrity of trial subjects or on the scientific value of the trial. ● this issue was systematic and persistent leading to a constant breach of the conditions and principles of GCP in connection with that trial or the trial protocol. ● this issue persisted despite the implementation of a corrective and preventative action plan.
		3) One subject was administered 6 additional doses of IMP. The subject was to receive IMP on day 1 and 8 but instead received IMP on days 1 to 8. The subject experienced a severe adverse event as a result.	**Yes,** there was impact on the safety or physical or mental integrity of trial subjects and on the scientific value of the trial.
		4) A subject took IMP that had expired two days ago. The subject did not experience any adverse events and this issue was not likely to affect the data credibility of the trial.	**No,** there was no impact on the safety or physical or mental integrity of the trial subject or on the scientific value of the trial. In addition, the assessment of the breach identified this as a single episode and a detailed corrective and preventative action plan was implemented.

Temperature monitoring		IMP temperature excursions reported	**Yes**, if the situation was not managed and subjects were dosed Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol Version 6, 08 Jul 2020 10(12) with IMP assessed as unstable, which resulted in harm/potential to harm subjects. **No,** if the excursions had been managed appropriately (e.g. IMP was moved to alternative location/quarantined as necessary and an assessment (by qualified personnel) illustrated that there was no impact on subject safety and data integrity.
IRT issues	Sponsor	Multiple issues with the Interactive Response Technology (IRT) system across several clinical trials leading to the dispensing of expired IMP and a shortage of IMP at investigator sites in time of subject visits.	**Yes,** there was impact on the safety or physical or mental integrity of trial subjects and this issue persisted leading to a constant breach of the conditions and principles of GCP in connection with that trial or the trial protocol, despite the implementation of a corrective and preventative action plan.
Potential Fraud	Sponsor Identified during inspection	On two separate occasions the sponsor identified issues with the same organisation. First with consenting and then with potential irregularities in recruitment and consenting. However, there was not unequivocal evidence of fraud at the time of reporting. One of the studies involved paediatric subjects. A potential serious breach was identified, but not reported (documentation in the Sponsor's TMF identified that there may have been fraud at an investigator site, re-use of previous time point data in later time points). The Sponsor had investigated and the issue was subsequently found to be a genuine error and not fraud.	**Yes,** this subsequently led to enforcement action against the organisation in question. **No**, on this occasion. *However, had this been identified as fraud impacting on the integrity of the data, then this serious breach would not have been notified within the regulatory timeframe (i.e. 7 day window).*

Source Data	Sponsor	Concerns were raised during monitoring visits about changes to source data for a number of subjects in a trial, which subsequently made subjects eligible with no explanation. An audit was carried out by the Sponsor and other changes to source data were noted without explanation, potentially impacting on data integrity. Follow-up reports sent to MHRA confirmed the Sponsor concerns over consenting and data changes made to source without an adequate written explanation.	**Yes** *Note: not all information was provided in the original notification, the sponsor provided follow up updates*
Emergency unblinding	Sponsor	A clinical trial subject attended A&E who attempted to contact the pharmacy department (using the phone number listed on the emergency card issued to the subject) in order to break the unblinding code. Pharmacy were unable to code break in a timely manner, as a result, the subject withdrew from the clinical trial feeling unhappy that the pharmacy was not available in an emergency situation.	**Yes,** as this had significant potential to harm the subject if unblinding would have affected the course of the treatment.
Sample processing	CRO	A cohort had invalid blood samples as they were processed incorrectly. As a result one of the secondary endpoints could not be met. Therefore, a substantial amendment was required to recruit more subjects to meet the endpoint. Subjects were dosed unnecessarily as a result of this error.	**Yes**
Protocol compliance	CRO	Subject safety was compromised because repeat electrocardiograms (ECGs) were not performed, as required by the protocol. The ECGs were required as part of the safety monitoring due to the pharmacology of the IMP. Also, there was inadequate quality control (QC) of the interim safety reports used for dose escalation which has potential for stopping criteria to be missed if adverse events (AEs) were not transcribed from the source to the safety report.	**Yes**

	Identified during inspection	Investigator site failed to reduce or stop trial medication, in response to certain laboratory parameters, as required by the protocol. This occurred with several subjects over a one year period, despite identification by the monitor of the first two occasions.Subjects were exposed to an increased risk of thrombosis.	**Yes**
	Sponsor	Minor visit date deviation. *A common deviation in clinical trials.*	**No**, a minor protocol deviation, which does not meet the criteria for notification
SAE reporting	Contractor	The investigator failed to report a single serious adverse event (SAE) as defined in the protocol (re-training provided).	**No,** if this did not result in other trial subjects being put at risk, and if it was not a systematic or persistent problem. In some circumstances, failure to report a SUSAR could have significant impact on trial subjects. Sufficient information and context should be provided for the impact to be assessed adequately.
Consent	Sponsor	Patient information leaflet and informed consent updated, but at one trial site this was not relayed to the patients until approximately 2-3 months after approval. More information on the potential consequences of the delay should have been provided.	**No**, if this was not a systematic or persistent problem and if no harm to trial subjects resulted from the delay. **Yes**, if there was a significant impact on the integrity of trial subjects (e.g. there was key safety information not relayed to subjects in a timely manner.
Reporting	MHRA (CTU)	The GCP Inspectorate was notified that a substantial amendment had been submitted regarding changes to dosing on a first in human study, as a result of an SAE after dosing the initial subject. The sponsor had temporarily halted the trial and only after further investigation had assigned the SAE as unrelated. The sponsor had not notified the CTU of the “urgent safety measure” implemented or reported the SAE as a potential SUSAR.	**Yes**
Site Files	NRES	The early destruction of investigator site files (i.e. one study had only been completed a year earlier and one study was still ongoing).	**Yes**

Invitation of patients	Member of public	A member of public received a named invite to be a volunteer in a clinical trial (no specific trial mentioned). However, this person was not on the organisation's volunteer database and had not participated previously in a study. On further investigation by MHRA, it was revealed that the organisation had contracted the use of a mail shot organisation to send a generic mail shot to a list of people in a specific location, over a certain age. This had been approved by the REC.	**No**

Appendix 4: Escalation plan

Serious Breaches of GCP and Critical Audit Findings in Clinical Research

Summary
This paper summarises the process for escalating findings of non-compliance relating to the governance of clinical research activity.

CONTENTS

1. Identification of non-compliance in clinical research

Non-compliance in clinical research may be identified through one of 3 routes:

1. By the clinical research study team conducting the trial
2. Through monitoring or auditing conducted by the R&D Department
3. Through monitoring or auditing conducted by partners

2. Categories of non-compliance in clinical research

Serious breach: A breach in compliance with clinical trial protocol or GCP regulations which is likely to affect to a significant degree the safety of the trial participant or the scientific validity of the trial.

Critical Finding: Where evidence exists through audit that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that

- the safety or well-being of trial subjects either has been or has significant potential to be jeopardised, and/or,
- the clinical trial data is unreliable and/or,
- there are a number of Major non-compliances across areas of responsibility, indicating a systematic quality assurance failure, and/or,
- where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances.

3 Reporting of non-compliance in clinical research

Reports of serious breaches and critical findings will be provided to:

- The R & D Steering Group
- The Risk and Quality Committee

All potential serious breaches of GCP in Trust sponsored studies are reported to the R&D Dept in accordance with the SOP on Notification of Serious Breaches of GCP

All confirmed serious breaches of GCP in hosted studies must be reported as required by the sponsor and in accordance with the SOP. It is the sponsor's responsibility to inform the PI.

In all cases, potentially serious breaches and critical audit findings are escalated to a governance review panel comprising of the following:

- Associate Medical Director [R & D]

- Director of R & D
- Senior Research Nurse

This panel may choose to consult further with the Medical Director

If any panel member is involved in the trial being reviewed, the next most senior clinician within the management structure will be called upon for their professional opinion.

The panel is responsible for reviewing non compliance reports, agreeing and taking the appropriate managerial action and if necessary notifying the relevant regulatory authority within the appropriate period. Where notification to a regulatory authority is required, a copy of this notification will also be sent to the Medical Director.

If a risk to organisational reputation is identified, the Medical Director is responsible for alerting the communications teams as appropriate.

Additionally the RDSG will review all clinical trial audit reports generated by the R&D Department.

Incidents relating to all clinical trials are also reported to the Trust via Datix and to the R&QC. Quarterly oversight of these incidents will be undertaken by the RDSG.