University of Hertfordshire

SERIOUS BREACHES

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for Notification of Serious Breaches of GCP in University of Hertfordshire Sponsored/Co-Sponsored Clinical Trials

SOP Number: gSOP-10-02	**Effective Date:** 10/08/22
Version Number: 2	**Review Date:** 3 years (or as required)

1.0 BACKGROUND

This is a University of Hertfordshire standard operating procedure. This document sets out the procedures to be followed by all University of Hertfordshire (UH) staff who are involved in clinical trials.

It provides guidance on how serious breaches of Good Clinical Practice (GCP)/protocol must be identified and managed. Where there are potential conflicts between different collaborating organisations' SOPs, project level working instructions should be developed, to determine precedence.

For CTIMPs and trials of non-CE marked medical devices 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 of a CTIMP/non-CE marked medical device 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 Clinical Trial Support Network (CTSN) 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 CTSN, the Clinical Trial Support Network Management Group (CTSNMG), the Advisory Group on Research Governance for Clinical Studies (AGRGCS) and Trust R&D where applicable in assessing all reported serious breaches and following the escalation plan.

3.0 APPLICABLE TO

Any UH 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 CTSNMG & Data Managers.

4.0 RESPONSIBILITIES

4.1 For CTIMPS and trials of non-CE marked medical devices the Sponsor or delegate should report serious breaches to the MHRA and the Ethics committee within 7 days of becoming aware. For non-CTIMP studies serious breaches of GCP or the protocol should be reported to the relevant Ethics committee. Any relevant follow up information should be provided as soon as possible.

4.2 All study team members must ensure all potential serious breaches are reported to the Chief Investigator (CI) or delegate, or to the Sponsor immediately. For multicentre trials, any reported events by participating sites to the study coordinator should be notified to the CI.

4.3 The CI or delegated individual (DI) of the study shall be responsible for identifying and/or assessing a potential Serious Breach and reporting to the Sponsor.

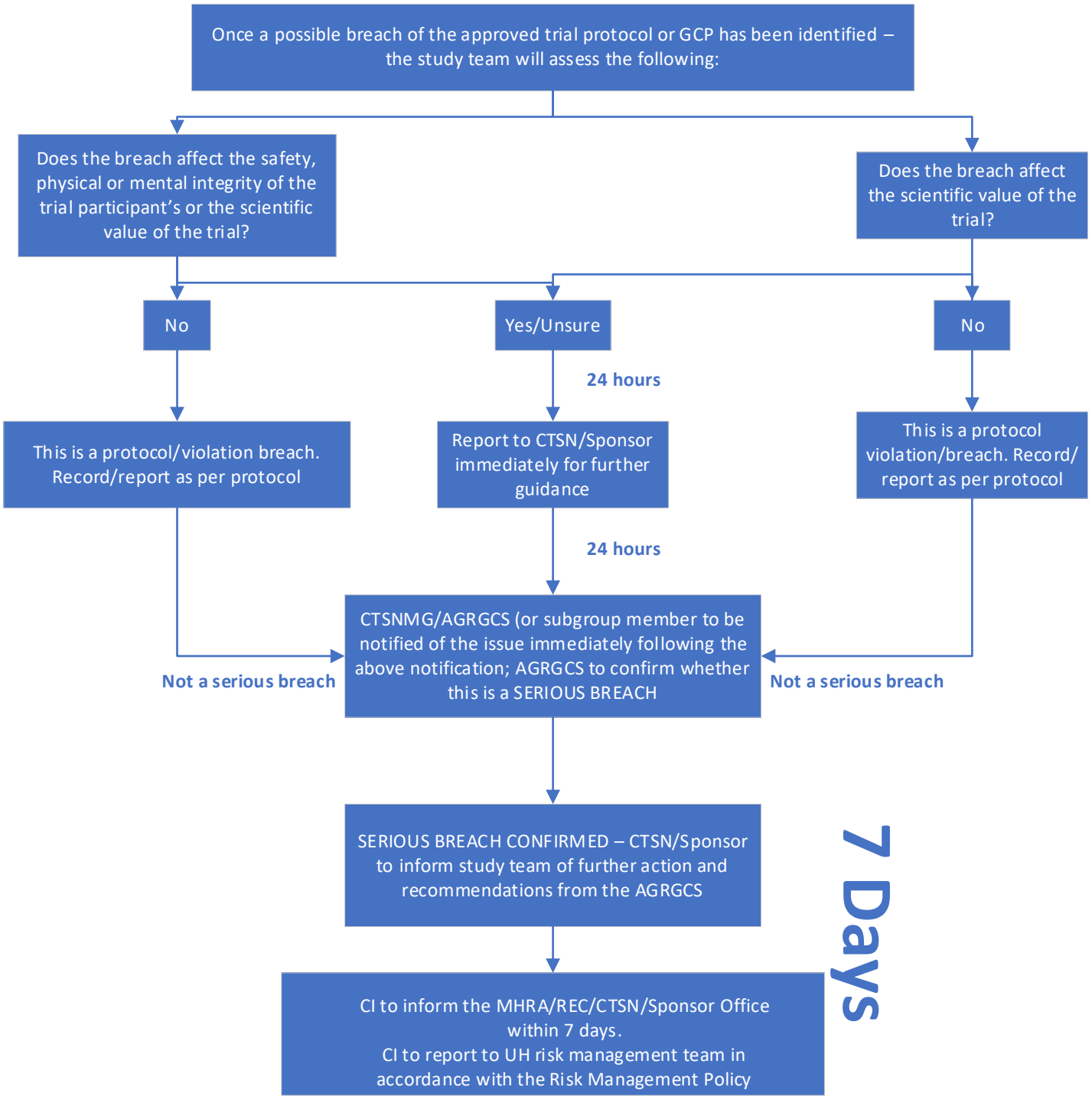
4.4 For sponsored/co-sponsored multicentre trials, the process for identifying breaches should be provided to all participating sites at study set up. The Sponsor should also ensure that adequate procedures are in place as part of the routine monitoring processes to identify potential GCP breaches.

4.5 Any possible serious breaches must be reported to the Sponsor or DI/CTSN immediately (**within 24 hours**). The CTSN will escalate appropriately and ensure appropriate recommendations are made to the CI regarding further management of the breach and notification to participants if required.

The CTSN shall ensure that details of the breach are reported to the UH CTSNMG, AGRGCS and Trust R&D (if co-sponsor).

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 sub-contracted to an appropriately qualified party (e.g. CTSN). In addition, the CTSN 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 Sponsor or delegate/CTSN 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 Sponsor/delegate/CTSN **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 Sponsor/delegate/CTSN should be carried out and should provide the following information:

1) Name of CI and PI at the site where the breach occurred;
2) Full title and IRAS 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/co-sponsored multicentre trials, the process for identifying breaches should be provided to all participating sites at study set up. The Sponsor/co-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/co-sponsor as part of the routine monitoring process, this SOP should be followed to conduct the necessary assessment and reporting required by the Sponsor/co-sponsor.

5.2 Assessment of a Serious Breach

- UH has delegated authority to the Advisory Group on Research Governance for Clinical Studies (AGRGCS) for review of serious breaches reported in UH sponsored/co-sponsored studies. It is the AGRGCS's responsibility to assess the potential impact of the breach on participant safety and data integrity to determine whether it qualifies as a serious breach.

Notifying the Sponsor/delegate/CTSN of a potential Serious Breach

- Upon receipt of an initial breach report, the Sponsor/delegate/CTSN 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 AGRGCS. Should an AGRGCS meeting not be scheduled, an extraordinary governance review panel meeting or a sub group of AGRGCS members will be convened **within 24 hours** to discuss the details of the breach. During these discussions the AGRGCS/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 AGRGCS/sub-group, then the study team will be informed of further actions and recommendations by the AGRGCS/sub-group.

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

- Based on the AGRGCS/sub-group's recommendations, the Sponsor/delegate/CTSN will meet with the study team to discuss the breach and compile evidence to support notification to the REC and MHRA (for CTIMPs and trials of non-CE marked medical devices) and complete the form in Appendix 2. This will then be sent to the CI and related departments e.g. NHS Pharmacy, and the AGRGCS, for approval prior to submission to MHRA.

- The Sponsor/delegate/CTSN 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 Sponsor/delegate/CTSN will collate all available information and complete the Notification of Serious Breaches of GCP or the Trial Protocol form (Appendix 2).

For CTIMPs and trials of non-CE marked medical devices the form will be submitted via e-mail to the MHRA within the 7 day reporting period as defined in the regulations.

For all clinical studies the form will be submitted to the REC within the 7 day reporting period.
The Sponsor/delegate/CTSN Manager 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 Sponsor/delegate/CTSN will review the breach in full to identify the extent of the breach and continue to update the MHRA with new information.

The CI/CTSN/ will compile a project report for submission to the MHRA. The project report will include:

1) Full title of trial, IRAS number, ethics approval number, EudraCT number, version number, date of commencement;
2) Name of CI;

3) List of Sites;
4) Number of participants 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 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 NHS 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 Sponsor/delegate/CTSN will review the project report and submit to the MHRA.

The MHRA may request additional information such as a copy of the protocol, ethics application, SOPs etc. The Sponsor/delegate/CTSN 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 UH's risk management team in accordance with UH UPRs. The Sponsor/delegate/CTSN shall make recommendations to the study team about where further reporting requirements apply.

The Sponsor/delegate/CTSN shall also ensure that details of the breach are reported to the AGRGCS (Ref: Escalation Plan, see UK Policy Framework for Health and Social Care Research).

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

The Sponsor/delegate/CTSN 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 Sponsor/delegate/CTSN may carry out a full audit of the trial and general trial management systems and procedures.

6.0 RELATED DOCUMENTS

- UH Research Framework Policy
- AGRGCS Terms of Reference
- gSOP-02- Adverse Event Reporting
- gSOP-03- Auditing
- gSOP-04- Informed Consent
- gSOP-06- Trial Master File /Site File
- gSOP-07- Research Staff Training
- gSOP-09- Amendments
- 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.
- UK Policy Framework for Health and Social Care Research October 2017

7.0 APPENDICES

- Appendix 1 - Definitions
- Appendix 2 - Potential GCP Breach/ Protocol Violation Form
- Appendix 3 - Examples of Serious Breaches

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
02	10/08/22	Notification of a Serious Breach Form and associated guidance have been updated by the MHRA

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date 25/07/2022**

Pro Vice-Chancellor (Research & Enterprise) Approval
Professor J M Senior

Signature  **Date 08/08/22**

10.0 AGREEMENT

Please detach and retain in your training file

I have read and understood the contents and requirements of this SOP (gSOP-10-02) and accept to follow by UH policies implementing it.

Recipient

Signature: ……Date: ……..……..…..

Name & Position: ……..…

Appendix 1: Definitions

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

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)
A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Trial
A study that looks at the safety or efficacy of a medicine/food stuff/placebo in humans as defined by the Medicines for Human Use Regulations (2004).

Clinical Trial Authorisation (CTA)
Regulatory approval issued by a Competent Authority to conduct a clinical trial within a Member State.

Delegated Individual (DI)
An individual delegated by the PI to carry out their task(s).

Good Clinical Practice (GCP)
As defined in the Regulations.

International Conference on Harmonisation (ICH)
The ICH produced a series of guidelines in 1996, E6 being the guideline on Good Clinical Practice, otherwise known as (ICH-GCP).

Investigational Medicinal Products (IMP)
A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. This 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

Principal Investigator (PI)
A Registered Physician, Dentist, Pharmacist or Registered Nurse who has responsibility for the conduct of the trial at a host site.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any untoward medical occurrence or effect that at any dose results in:
- Death
- Is life-threatening*
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

* "life-threatening" refers to an event in which the patient 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)
UK Competent Authority responsible for regulation of clinical trials.

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 (TMF) will be held at the principal site by the sponsor, Chief Investigator or at the co-ordinating Centre. The TMF should contain all essential documents defined as documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. A Trial Master File should be set up at the beginning of a trial and maintained up-to-date throughout the trial until trial conclusion.

For trials currently running, it is recommended that Section 8 of the ICH-GCP Guideline is followed as guidance in order to meet statutory requirements. However, some of the documents listed may not be available or applicable in many non-commercial trials. The appropriate documentation will vary according to the trial and sponsor requirements.

Appendix 2: Potential GCP Breach/ Protocol Violation Form

Notification of Potential Serious Breaches of Good Clinical Practice or the Trial Protocol

Please complete this notification form and submit to the Sponsor/delegate/CTSN

Name of person reporting potential serious breach:	**Site:**
Contact Details: *Name:* *Site:* *Telephone Number:* *Email:*	**Date Breach Identified by Site:** **Date Breach Notified to Sponsor:**

Details of related study:

Study title:

EudraCT:

Report: Tick appropriately	**Initial Report**	☐	**Follow-up Report** ☐

Please give details of the breach

Potential impact to patient safety and/or data credibility:

☐	Patient safety	☐	Scientific value / data credibility
☐	Patient confidentiality	☐	NA/None
☐	Approval Issues	☐	Other Non-compliances (specify)
☐	IMP		

Please list all known information about the potential breach (You do not need to wait for all information to be collected before submission of this form to the Sponsor. Updates are acceptable)**:**

Nature of Violation/ Deviation:

Response to violation:

Was the subject taken off trial as a result of this violation?

Have any actions been implemented by site in response to the violation?

Potential Serious Breach Notification Form completed by:

Signature: ……Date: ……..

Name & Position: ……

MHRA Form

Notification of Serious Breach of Good Clinical Practice or Trial Protocol

(Ref: UK Statutory Instrument 2004/1031 Regulation 29A, as amended by 2006/1928)

Please forward this notification to **GCP.SeriousBreaches@mhra.gov.uk**

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):*
***Potential* 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

Actual 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:	Issue:	Would MHRA have expected this case to be notified?
IMP	Dosing errors reported: A subject was dosed with the incorrect IMP 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 the rights of trial subjects
	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 persistence leading to a breach of the Regulation and the trial protocol. The issue persisted despite the implementation of a corrective and preventative action plan
	One subject was administered additional doses of IMP. The subject was given instructions to take higher doses of IMP than what was stipulated in the protocol. The subject experienced a severe adverse event as a result	Yes, there was impact on the safety of trial subjects and on the scientific value of the trial
	A subject took IMP that had expired two days ago. The IMP was stable and 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
	Due to an interactive response technologies (IRT) malfunction 50% of subjects assigned to one arm were unblinded in a blinded trial, furthermore this information was submitted to all trial staff at all investigator sites participating in the trial	Yes, this could potentially affect the safety of trial subjects, and this was a systematic issue. It also impacts the robustness and reliability of the data generated

Category:	Issue:	Would MHRA have expected this case to be notified?
Temperature monitoring	IMP temperature excursions reported	Yes, if the situation was not managed and subjects were dosed with IMP assessed as unstable. which resulted in harm/potential harm of 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, and stability data showed it was stable.
IRT issues	Multiple issues with the 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 of trial subjects ad this issue persisted leading to a constant breach of the Regulation or the trial protocol, despite implementation of a corrective and preventative action plan
Potential Fraud	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	Yes, this subsequently led to enforcement action against the organisation in question
Source Data	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 in the subject notes. An audit was carried out by the sponsor and other changes to source data were noted without explanation, potential impacting on data integrity. Follow-up reports confirmed the sponsor concerns over consenting and data changes made to source without an adequate written explanation	Yes, and this needs to be reported when the concerns were raised. Note: not all information was provided in the original notification, the sponsor provided follow up updates

Category:	Issue:	Would MHRA have expected this case to be notified?
Emergency unbinding	A clinical trial subject attended the hospital emergency department, that attempted to contact the hospital (using the phone number listed on the emergency card issued to the subject) in order to break the unblinding code. Pharmacy was 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	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 modification was required to recruit more subjects to meet the endpoint	Yes, subjects were dosed unnecessarily as a result of this error
Protocol compliance	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. 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. Minor visit date deviation. A common deviation in clinical trials.	Yes Yes, subjects were exposed to an increased risk of thrombosis No, a minor protocol deviation, which does not meet the criteria for notification

Category:	Issue:	Would MHRA have expected this case to be notified?
	According to the protocol, a brain CT scan should be performed in the selection visit to exclude brain metastasis (exclusion criteria). The site used a previous version of the protocol where the CT scan wasn't required so 6 patients out of 10 were included without brain CT	Yes, if this had an impact on patient safety
SAE reporting	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
	The investigator was not clear on the reporting requirements for the trial and was incorrectly classifying events as expected, as they were common events seen with that particular disease	Yes, incorrect classification of seriousness criteria, therefore SAEs incorrectly classifies as AEs or under-reporting of large numbers of SUSARs
	The investigator was not documenting all the AEs associated with the trial	Yes, depending on the type of trial, for example inadequate safety reporting on dose escalation studies may impact on the decision to escalate to the next dose level
Consent	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
Access to data	The investigator would not allow any party access to the patient's notes Loss of data due for example to servers' breakdown	Yes, the data therefore could not be verified. The protocol would usually contain a clause to state that Sponsor representative and Regulatory Authorities will have access to the data, and this is also reflected in the informed consent

Category:	Issue:	Would MHRA have expected this case to be notified?
		Yes, clinical trial sponsors and vendor should have agreements in place addressing business continuity and ensuring that clinical trials data are retrievable at any point in time
Randomisat-ion/ stratification errors	Patients incorrectly randomised/stratified according to the protocol	Yes, as this will be likely to have a significant impact on the data
DSMB/DMC	The Data and Safety Monitoring Board (DSMB)/Data Monitoring Committees (DMC), which should be implemented according to the protocol and the clinical trial authorisation in a blinded trial, has in fact not been implemented	Yes, the missing implementation of the DSMB/DMC has significant potential to impact the safety of trial subjects