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MANAGING BREACHES OF GOOD CLINICAL PRACTICE OR THE STUDY PROTOCOL - STANDARD OPERATING PROCEDURE

Introduction and Aim

"Serious Breach" is a particularly significant concept for clinical trials of investigational medicinal products (CTIMPs). This is because there are specific legal requirements to identify and report them contained in the UK Clinical Trial Regulations (see Regulation 29A).

All clinical research studies (CTIMPs and non-CTIMPs) taking place in Cardiff and Vale University Health Board (CAVUHB) and Cardiff University (CU) must be run in accordance with the principles of Good Clinical Practice (GCP) and the relevant regulations, to maintain the safety of participants and to ensure consistent practice and scientific quality.

Serious breaches should, therefore, be recorded for all studies and reported to the Sponsor. For CTIMPs they should be reported to the Research Ethics Committee (REC) and to the Medicines and Healthcare Products Regulatory Agency (MHRA). For non-CTIMP research they should be reported to the Sponsor and ethics committee in accordance with the NRES Standard Operating Procedures.

Objectives

- to outline the procedure to be followed when a breach of GCP or the approved protocol is identified in studies sponsored or hosted by the CAVUHB or CU.
- to outline the actions that should be taken when a breach is classified as 'serious'

Scope

This procedure applies to all individuals involved in research studies taking place within the UHB or CU, including those with honorary contracts or in any other organisation that has a current contract with the CAVUHB or CU for use of its SOPs

Equality and Health Impact Assessment	An equality impact assessment has been carried out on the Research Governance Policy under which this Procedure falls. No adverse impact has been identified.
Documents to read alongside this Procedure	Investigating and Handling Allegations of Research Misconduct Procedure (UHB145) Training requirements for research staff, including Good Clinical Practice SOP (UHB 317)
Approved by	Joint Research Governance Group

Accountable Executive or Clinical Board Director	Medical Director
Author(s)	R&D Manager

Disclaimer

If the review date of this document has passed please ensure that the version you are using is the most up to date either by contacting the document autho or the Governance Directorate.

Summary of reviews/amendments			
Version Number	**Date of Review Approved**	**Date Published**	**Summary of Amendments**
1.0	08/04/2014	23/06/2014	New document
2.0	17/10/2017	30/11/2017	• Title change to reflect this SOP covers the recording and reporting of non-serious and serious breaches • Transferred to new UHB Template, addition of objectives and scope sections. • Minor updates to terminology • Clarification that breaches can be identified via central monitoring by the data manager as well as by the research team or study monitor. • Updated contact details for R&D office • Clarification for studies where the trial management has been delegated to a CTU the notification requirements and the roles and responsibilities will be detailed in the protocol and in the agreement between the CTU and the UHB. • Updated links to MHRA guidance for the notification of serious breaches of GCP or the trial protocol and Notification of

			Serious Breach of Good Clinical Practice or Trial Protocol Form • Updated reference document.
3.0	21/10/2020	15/12/2020	The procedure has been reviewed at 3 year review date. Minor changes and typos corrected throughout and slight change to reporting detail in sections 2.4 and 2.8.
4.0	18/07/2024	12/11/2024	The procedure has been reviewed to make it a joint procedure between Cardiff and Vale and Cardiff University under the Joint Research Office. Procedure has been adapted to increase oversight as a sponsor and host organisation

1 WHEN SHOULD THIS SOP BE USED

- A research study sponsored by either Cardiff and Vale University Health

Board (CAVUHB) or Cardiff University (CU) who sit within the Cardiff JRO

- A co-sponsored study where the sponsorship agreement states that the Cardiff JRO SOPs will be followed

- An externally sponsored research study hosted by a Cardiff JRO organisation

Definitions

Non-Compliance

Non-compliances of GCP and/or Protocol will be categorised as either a Deviation, Violation or Serious breach:

i. **Deviation:** A planned or unplanned departure from the protocol or GCP that does not increase risk or decrease benefit or; does not have a significant impact on the participant's rights, safety or welfare; and/or on the integrity of the data. N.B Ad-hoc planned deviations may be permitted under GCP if they are required to protect participant safety (though if they become regular, an amendment to the protocol should be considered). Approval of such events will need to be approved by the Sponsor on a case by case basis, documented in a study file note and the protocol deviation log.

ii. **Violation:** A planned or unplanned departure from the protocol or GCP that increases the risk or decreases the benefit or; may have an impact on the participant's rights, safety or welfare; and/or on the integrity of data.

Protocol waivers are planned deviations or waivers to the protocol. These types of non-compliances are not acceptable in CTIMPs Sponsored by CU or CAV UHB, they constitute a deliberate breach of Regulation 29 of SI 2004/1031.

iii. **Serious Breach**: A breach of the protocol or GCP which is likely to effect to a significant degree

(a)the safety or physical or mental integrity of the trial participants or (b) the scientific value of the Trial.

Examples of serious breaches can be found in Appendix 1

A sponsor of a clinical trial should list all significant protocol non-compliances in the clinical study report (CSR) or publication and must assess whether any

of these non-compliances should be reported to the MHRA under Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [SI 2004/1031], as amended, as a serious breach of GCP and the protocol.

2 PROCEDURE(S)

The following procedure outlines process for when;

- 2.1 A JRO organisation is sponsor and is using a CTU/CRO for full project management
- 2.2 A JRO organisation is sponsor but is not using a CTU/CRO for full project management
- 2.3 Externally sponsored study hosted at CAVUHB

2.1 JRO Sponsored Studies using a CTU/CRO for full project management

For studies using a CTU/CRO for full project management, detection, reporting and tracking of non-compliance and assessment and reporting of Serious Breaches will be carried out in accordance with the CTRU/CRO's own SOPs and any study specific SOPs.

The division of responsibility for assessing and reporting Serious Breaches will be defined in the study specific agreement between the CTU/CRO and JRO organisation as sponsor.

Where CTU/CRO or study specific SOPs do not cover any aspect of management of non-compliance or Serious Breaches then this SOP will be followed.

Where management of non-compliance or Serious Breaches is not delegated to the CTU/CRO then this SOP will be followed.

2.2 JRO Sponsored Studies not using a CTU/CRO for full project management

2.2.1 Reporting of non-compliance directly from the Study Team

In accordance with the terms of CAVUHB and CU Sponsorship in Principle, the Chief Investigator (CI) (or their delegate) is required to report incidences of non-compliance and potential serious breaches to the relevant Sponsor Lead in the JRO Research Governance Team.

The CI, Principal Investigator (PI) or other member of the research team can identify that a non-compliance with either GCP or the protocol has occurred. Where the non-compliance has been identified by a member of the research team, they are to inform the PI of the non-compliance.

The PI or delegated member of the team records the non-compliance on the Non-Compliance Form (FRM/003/12) including details of any initial corrective/preventative actions and makes an initial assessment of whether the non-compliance may constitute a serious breach

Where the PI or delegate suspects that the non-compliance may constitute a serious breach, the PI or delegate reports the non-compliance via email to the research governance team within the JRO within **24 hours** of becoming aware.

Where the non-compliance is not considered to be a serious breach the PI or delegated member of the team forwards the non-compliance form (FRM/003/12) to the research governance team within the JRO via email within **15 working days** and it is logged.

If the JRO governance team, suspects that a Serious Breach may have occurred, they will report their concerns immediately to the Quality Assurance (QA) Lead or member the Senior Management Team (SMT) for review.

Non-compliances may also be detected by the JRO during routine or triggered Monitoring Visits or Audits. In this case non-compliances will be recorded as findings on the Monitoring Report. If, as a result of the monitoring visit the JRO team member conducting the visit suspects that a serious breach may have occurred, they will report their concerns immediately to the QA Lead or SMT member.

2.2.2 Non-compliances and serious breaches identified retrospectively

A serious breach may also be detected retrospectively during review of the Monitoring Visit Report by the QA Lead or member of SMT. If the QA Lead or member of SMT suspects that a serious breach may have occurred, they will report their concerns immediately to the JRO governance team, who will liaise

with the PI or delegate as necessary to collect further information on the non-compliance and to determine whether the non-compliance constitutes a serious breach

2.2.3. Where the sponsor categorises the non-compliance as non-serious

Where a non-compliance meets the criteria for a Deviation or Violation and is not categorised as a Serious Breach, the JRO governance team determines whether any further corrective and preventative actions are required, taking advice from the SMT where necessary; action may include training in designated areas and/or amendment to the study protocol.

Where further corrective and preventative actions are required, the JRO governance team informs the PI in writing by email copying in the JRO Director outlining the corrective and preventative actions required and a time frame for completing them by.

Cessation of further recruitment may be required until corrective and preventative actions are complete.

For a CTIMP, if a temporary halt in recruitment or study suspension is deemed necessary, this will be reported (following the Safety Reporting in CTIMPs SOP) to the Research Ethics Committee and Regulatory Authority by way of substantial amendment within 15 days.

The JRO governance team will ensure that all remedial action is completed satisfactorily within the specified time frame. Where it is not, the JRO governance team reports the matter to the SMT:

- The senior management team re-reviews the non-compliance to determine whether the unresolved issue now constitutes a Serious Breach and should follow 2.2.4
- The SMT takes further actions to pursue resolution of the non-compliance as appropriate on a case by case basis. This may include liaising with the relevant R&D Lead and the Clinical Board Lead (in cases where the CI holds substantive employment with CAVUHB) or Academic School (for CIs substantively employed by CU).
- If necessary, a For-Cause audit may be undertaken. In addition, for cause audits of other studies conducted by the study team may be undertaken, and/or authorisation of new studies may be delayed until conditions are met

When conditions are met, a decision will be taken by the JRO governance team and SMT as to whether more frequent monitoring than originally planned is required.

2.2.4. Where the study is a CTIMP and the JRO sponsor categorises the non-compliance as a Serious Breach

The JRO governance team immediately informs the SMT and JRO Director. In addition, appropriate senior management within the relevant organisation will be informed of the serious breach. For CAVUHB, this will include the Director of R&D, Medical Director, Chief Investigator and Clinical Director of relevant directorate(s), For CU, this will include the College Dean of R&I and Head of School/College. Where the PI holds a substantive contract with the other JRO partner organisation the escalation outlined above will be followed in each organisation. Where the serious breach has taken place at a non-Cardiff NHS site the JRO governance team also informs the Director of R&D from that site (or R&D contact listed in the study agreement) of the Serious Breach.

The JRO governance team or delegate reports the breach to the Research Ethics Committee and the Regulatory Authority within **7 days** of the Serious Breach being confirmed.

The JRO governance team liaises with the JRO Director, the Director of R&D and the QA Lead or member of SMT as appropriate to decide:

- whether a For-Cause Audit or investigation of Research Misconduct should be undertaken.
- whether temporary cessation of further recruitment or suspension of the study at the trial site is required:
    - what remedial action is required as a result of the breach.
    - whether audit of other studies conducted by the study team should be undertaken, and/or authorisation of new studies should be delayed until actions/conditions are met.
    - whether the Serious Breach affects other CTIMPs/Medical Device Trials Sponsored by a JRO organisation.

If a temporary halt in recruitment or study suspension is deemed necessary this will be reported to the Research Ethics Committee and Regulatory Authority within **15 days** by way of substantial amendment.

The relevant Regulatory Authority and Research Ethics Committee each reviews the breach and informs the Sponsor and Investigator of any action required including suspension or termination of the study.

The JRO governance team or delegate ensures that all remedial action/conditions required of the PI by the JRO, Research Ethics Committee and applicable Regulatory Authority is completed satisfactorily.

The JRO governance team or delegate tracks the serious breach until conclusion, ensuring related correspondence is filed in the Trial Master Files.

When actions/conditions are met, the JRO governance team will confirm that any study suspension may be lifted. This must be done by way of substantial amendment to the Research Ethics Committee and Regulatory Authority. The substantial amendment must be approved by the Research Ethics Committee, Regulatory Authority and JRO before the study recommences.

The JRO governance team with the QA Lead or member of SMT will also determine whether more frequent monitoring than originally planned is required.

2.2.5. Where the study is a non-CTIMP and the JRO sponsor categorises the non-compliance as a Serious Breach

The JRO governance team immediately informs the SMT and JRO Director. In addition, appropriate senior management within the relevant organisation will be informed of the serious breach. For CAVUHB, this will include the Director of R&D, Medical Director, Chief Investigator and Clinical Director of relevant directorate(s), For CU, this will include the College Dean of R&I and Head of School/College. Where the PI holds a substantive contract with the other JRO partner organisation the escalation outlined above will be followed in each organisation. Where the serious breach has taken place at a non-Cardiff NHS site the JRO governance team also informs the Director of R&D from that site (or R&D contact listed in the study agreement) of the Serious Breach.

Per NRES SOPs the CI reports the serious breach to the relevant Research Ethics Committee within **7 days** of becoming aware of the breach. The JRO governance team or delegate ensures that the CI is aware of the obligation and that the obligation is fulfilled.

The relevant Research Ethics Committee reviews the breach and informs the Sponsor and Investigator of any action required including suspension or termination of the study.

The JRO governance team liaises with the JRO Director and the QA Lead or member of SMT as appropriate to decide appropriate corrective and preventative actions (CAPAs).

In the context of a Serious Breach, examples of CAPAs might include:
Corrective Actions (actions taken in the immediate and short-term to correct the effects of the Serious Breach):

- whether a For-Cause Audit or investigation of Research Misconduct should be undertaken.
- whether temporary cessation of further recruitment or suspension of the study at the trial site is required.

- what remedial action is required as a result of the breach, in relation to any affected study participants e.g. whether participants need to be notified of the breach, whether certain study assessments need to be repeated, whether a re-consent process needs to take place (N.B. any attempts to repeat study assessments or re-consent participants must be approved by a Research Ethics Committee and potentially the trial IDMC/TSC).
- whether audit of other studies conducted by the study team will be undertaken, and/or authorisation of new studies should be delayed until actions/conditions are met.
- whether an audit of a wider service or trial system is required (e.g. sample management, information governance);
- whether trial staff need to be re-trained in trial-specific or general procedures/SOPs or GCP;

Preventative Actions (actions taken in the medium-term/ or to be taken in the future to prevent the Serious Breach occurring again):

- increase JRO and/or CTU audit and monitoring of the trial (or specific aspects of a trial) for a set period of time;
- amending the trial protocol or patient-facing documents (N.B. this will require an amendment to the Research Ethics Committee and/or Competent Authority, e.g. the MHRA)
- ensure trial staff are trained/re-trained;
- consider the training and experience of current study staff and increase options for support of less-experienced staff;
- re-writing trial procedures and SOPs
- implement practical updates such as adding notifications to participant medical records, the trial database, CRF etc.;
- arrange for re-validation of software and/or equipment used in the trial;
- implement more far-reaching changes, such as a change in IMP supplier/manufacturer, labs or vendors/suppliers/sub-contractors;

The JRO SMT should consider whether there is any impact on the delivery of clinical (and not only research) services and notify the appropriate Clinical Directorate in CAVUHB. They should consider whether the Serious Breach is isolated (specific to that trial) or systematic (potentially affecting a number of studies Sponsored by a JRO Sponsor organisation).

The JRO governance team or delegate ensures that all remedial actions/conditions required of the PI by the JRO and the Research Ethics Committee is completed satisfactorily.

The JRO governance team or delegate tracks the serious breach until conclusion, ensuring related correspondence is stored in the study specific Trial Master File.

When actions/conditions are met, the JRO governance team will confirm that any study suspension may be lifted. The JRO governance team with the QA Lead or member of STM will also determine whether more frequent monitoring than originally planned is required.

2.3. Studies with an external sponsor and are hosted in CAVUHB

2.3.1. Reporting of non-compliance for externally Sponsored studies

The PI or other member of the research team can identify that a non-compliance with either GCP or the protocol has occurred. Where the non-compliance has been identified by a member of the research team, they are to inform the PI of the non-compliance.

The PI or delegate records the non-compliance on the non-compliance form provided by the Sponsor or on the JRO Non Compliance Form (FRM/003/12) if no Sponsor form has been provided. The PI or delegate makes an initial assessment of whether the non-compliance may constitute a serious breach.

Where the PI or delegate suspects that the non-compliance may constitute a serious breach the PI or delegate reports the non-compliance to the Sponsor and to their JRO governance team within **24 hours** of becoming aware.

Where the PI or delegate does not suspect that a serious breach has occurred the PI or delegate reports the non-compliance to the Sponsor using the procedure required by the study Sponsor

The Sponsor requests further information and makes an evaluation of whether the non-compliance constitutes a serious breach

2.3.2. Where the sponsor categorises the non-compliance as non-serious

The PI or delegate undertakes the action required (e.g. patient withdrawn or continues) by the sponsor in accordance with the sponsor's SOPs.

If the PI or delegate had previously reported the non-compliance to the JRO as a possible serious breach, then the PI or delegate informs the JRO governance team of the sponsor decision.

2.3.3. Where the sponsor categorises the non-compliance as a Serious Breach

As per the NRES SOPS and, where relevant, the Medicines for Human Use (Clinical Trials) Regulations, the Sponsor/CI is responsible for informing the relevant Research Ethics Committee and any relevant Regulatory Authority within **7 days** of becoming aware of the serious breach.

The PI or member of the research team notifies the JRO governance team immediately and logs the Serious Breach.

The JRO governance team or delegate immediately informs the JRO Director, Director of R&D, Medical Director, CI and Clinical Director of relevant directorate(s) of the serious breach. Where the PI holds a substantive contract with another institution, relevant persons at the employing institution are also informed.

The JRO governance team liaises with the JRO Director, the Director of R&D and the QA Lead or member of SMTas appropriate to decide:

- whether a For-Cause audit or investigation of Research Misconduct should be undertaken.
- whether audit of other studies conducted by the study team will be undertaken, and/or authorisation of new studies should be delayed until actions/conditions are met

If the sponsor deems it necessary, temporary halt to further recruitment or suspension of the study at a Cardiff JRO site may be required. The sponsor is responsible for informing the Research Ethics Committee and any relevant Regulatory Authority within any relevant timelines if such a suspension is required.

The PI keeps the JRO governance team informed of all communication with and outcomes of the reviews conducted by the sponsor, Research Ethics Committee and any relevant Regulatory Authorities.

The sponsor is responsible for ensuring that all remedial actions/conditions required of the PI by the sponsor, Research Ethics Committee and any relevant Regulatory Authority is completed satisfactorily.

The JRO governance team or delegate tracks the serious breach until conclusion, storing related correspondence in the study specific folder.

3.0 TRAINING

Education and support should be available from the JRO for researchers who are involved in conducting CAVUHB or CU Sponsored CTIMPs. JRO staff should receive relevant training (internal and external as necessary) in order for them to become competent auditors and monitors.

4.0 IMPLEMENTATION

The Clinical Board R&D Leads should facilitate implementation by ensuring that all relevant research active personnel within their Boards are aware of the Procedure and the implications for their practice.

5.0 EQUALITY

An equality impact assessment has been carried out on the Research Governance Policy, under which this Procedure falls. No adverse impact has been identified.

6.0 AUDIT

The JRO is responsible for overseeing the operational management of Research Governance and for providing assurance of robust Research Governance arrangements in CAVUHB and CU.

It will be necessary to ensure that CTIMPs Sponsored by CAVUHB or CU are being carried out in accordance with this Procedure.

Where resources allow, random Research Governance audits will be carried out by the JRO to ensure that all processes comply with this Procedure.

7.0 REVIEW

The procedure should be reviewed every 3 years, or more regularly if important new legislation so requires.

8.0 ASSOCIATED DOCUMENTS

Investigating and Handling Allegations of Research Misconduct Procedure (UHB145)
Training requirements for research staff, including Good Clinical Practice SOP (UHB 317)
Sponsor Assessment of a serious breach (FRM/003/03)
Non-compliance form (FRM/003/12)
Non-compliance Log (FRM/003/09)

Corrective and Preventative Actions Template (TPL/001/02)

9.0 REFERENCES

International Conference on Harmonisation: Harmonised Tripartite Guideline for Good Clinical Practice E6 (CPMP/ICH/135/95), European Commission (1996).

Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. European Commission. Official Journal of the European Communities (2005), Luxembourg, L91/13-19.

The Medicines for Human Use (Clinical Trials) Regulations (SI2004/1031).

The Medicines for Human Use (Clinical Trials) Amendment Regulations (SI2006/1928).

The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations (SI2006/2984).

The UK Policy Framework for Health and Social Care 2017.

Appendix 1 – Examples of Serious Breaches Notified to MHRA (this is not an exhaustive list)

As taken from MHRA guidance for the notification of serious breaches of GCP or the trial protocol
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/404588/GCP_serious_breaches_guide.pdf

Notifier	Details of Breach Reported Breach Reported	Is this a Serious Breach? Is this a Serious Breach?
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). **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. **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. **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.	 **Yes,** there was significant potential to impact the safety or physical or mental integrity of trial subjects. **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. **Yes**, there was impact on the safety or physical or mental integrity of trial subjects and on the scientific value 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.
Notifier	**Details of Breach Reported es** **Details of Breach Reported**	**Is this a Serious Breach?** **Is this a Serious Breach?**
Sponsor	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 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.
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.
Sponsor	On two separate occasions the Sponsors identified issues with the same organisation. First with consenting and then with potential fraud 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.
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 of the information was provided in the original notification, the Sponsor provided follow-up updates.*

Notifier	**Details of Breach Reported e Reported**	**Is this a Serious Breach? Breach?**
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 treatment.
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**
CRO	Subject safety was compromised because repeat ECGs were not performed, as required by the protocol. Also, there was inadequate QC of the interim safety reports used for dose escalation which has potential for stopping criteria to be missed.	**Yes**
Contractor	The Investigator failed to report a single 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 a significant impact on trial subjects. Sufficient information and context should be provided for the impact to be assessed adequately.
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	**Yes**

	an increased risk of thrombosis.	
Notifier	**Details of Breach Reported e Reported**	**Is this a Serious Breach? Breach?**
Identified during inspection	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.	**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).*
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).
Sponsor	Visit date deviation. *A common deviation in clinical trials.*	**No**, a minor protocol deviation, which does not meet the criteria for notification.
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**
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**
Notifier	**Details of Breach Reported e Reported**	**Is this a Serious Breach? Breach?**
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	**No**

	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.	

Notification of Serious Breach of Good Clinical Practice or Trial Protocol Form

The current version of the form can be found at:-

https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#report-a-serious-breach

JRO REFERENCED DOCUMENTS

Cardiff and Vale UHB Research Governance Policy (UHB 099)

Oversight and Monitoring in Research SOP (UHB 247)

Non compliance form (FRM/003/12)

ACKNOWLEDGEMENT

This procedure was based on information in Sheffield Teaching Hospital NHS Foundation Trust R&D SOP C125 Version 1, 05 November 2013.