

Reference Number: UHB 235 Version Number: 3		Date of Next Review: 21/10/2023 Previous Trust/LHB Reference Number: n/a
MANAGING BREACHES OF GOOD CLINICAL PRACTICE OR THE STUDY PROTOCOL - STANDARD OPERATING PROCEDURE		
Introduction and Aim <p>“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).</p> <p>In addition, in Cardiff and Vale University Health Board (UHB) all studies, CTIMP and non-CTIMP should be run to Good Clinical Practice (GCP)-equivalent standards to ensure consistent practice and scientific quality.</p> <p>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 ethics committee in accordance with the NRES Standard Operating Procedures.</p>		
Objectives <ul style="list-style-type: none"> • 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 UHB. • to outline the actions that should be taken when a breach is classified as ‘serious’. 		
Scope <p>This procedure applies to all individuals involved in research studies taking place within the UHB, including those with honorary contracts or in any other organisation that has a current contract with the UHB for use of its SOPs.</p>		
Equality 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	Research Governance Group	

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Accountable Executive or Clinical Board Director	Medical Director
Author(s)	Research Governance Team
<u>Disclaimer</u> 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 author 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	17/10/17	30/11/17	<ul style="list-style-type: none"> • 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

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			<p>Breach of Good Clinical Practice or Trial Protocol Form</p> <ul style="list-style-type: none"> 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.

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GLOSSARY

ABBREVIATIONS AND DEFINITIONS

CI - Chief Investigator
 CTIMP - Clinical Trial of Investigational Medicinal Product
 EU - European Union
 GCP - Good Clinical Practice
 ICH - International Conference for Harmonisation
 IMP - Investigational Medicinal Product
 ISF – Investigator Site File
 JRO – Joint Research Office
 MHRA - Medicines and Healthcare products Regulatory Agency
 NRES – National Research Ethics Service
 PI - Principal Investigator
 R&D - Research & Development
 REC - Research Ethics Committee
 RGF - Research Governance Framework
 RGG - Research Governance Group
 RGT - Research Governance Team
 SOP - Standard Operating Procedure
 UHB – Cardiff and Vale University Health Board

Chief Investigator - The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for the research at all sites. The main application for ethical review should be submitted by the CI.

Principal Investigator - The investigator responsible for the research site where the study involves specified procedures requiring site specific assessment by the local R&D Office. For multi site studies, there should be one PI for each research site. In the case of a single-site study, the CI and the PI will normally be the same person.

External Sponsor – This means any Sponsor of a CTIMP other than Cardiff and Vale UHB. An External Sponsor may be a Commercial organisation (e.g. a Pharmaceutical company) or a Non-Commercial organisation (e.g. another Local Health Board, NHS Trust or University, including Cardiff University).

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1 WHEN SHOULD THIS SOP BE USED

The procedure described in this SOP should be followed when a breach of GCP or the study protocol is identified in:

- A research study sponsored by the UHB;
- A co-sponsored study where the sponsorship agreement states that the UHB SOPs will be followed;
- An externally sponsored research study hosted by the UHB (see section 2.7).

2 PROCEDURE(S)

2.1 IDENTIFICATION OF GCP OR PROTOCOL BREACHES

WHAT IS A BREACH?

Protocol and GCP breaches occur in research studies. These can be serious or non-serious in nature. **Not every deviation from the Protocol represents a serious breach that must be reported to the regulatory authorities – the majority are technical deviations that do not result in harm to the study subjects or significantly affect the scientific value of the reported results of the study.** Breaches of this type, while they must be documented, are not serious breaches or reportable.

WHAT IS DEFINED AS A SERIOUS BREACH

This is a breach which is likely to effect to a significant degree:

The safety or physical or mental integrity of the subjects; or

The scientific value of the study.

The breach may be of the conditions and principles of GCP; or of the Protocol relating to that trial. The judgement on whether a breach is likely to have a significant impact on the scientific value of the study depends on a variety of factors e.g. the design of the trial, the type and extent of the data affected by the breach, the overall contribution of the data to the key analysis parameters and/ or the impact of excluding the data from the analysis. Examples of serious breaches can be found in Appendix 1.

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2.2 DOCUMENTATION OF ALL BREACHES (UHB SPONSORED STUDIES)

When identified, all breaches of GCP or protocol must be clearly and systematically documented and retained in the Investigator Site File (ISF) e.g. in file notes (and highlighted in a file note log), in order for appropriate corrective and preventative actions to be taken. Documentation of the breach will include as a minimum:

- full details of the breach
- the date and time of its occurrence
- any remedial action undertaken
- assessment by the CI or PI (or delegated individual) as to whether the breach is serious (include signature, date and time)

Where it has been agreed that the R&D Office staff or their delegate will monitor the study, the study monitor will review all breaches and associated documentation during monitoring visits. The monitor will assess whether each breach has been adequately identified and documented and will make an independent assessment of the severity of the breach. If the monitor notes a pattern of repetition of non-serious breaches this may amount to a quality control failure and become serious and reportable for that reason. The monitor will therefore scrutinise not only individual breaches but also the overall quality of management within the trial. All breaches and quality control failures will be reported fully in the monitoring reports.

All breaches that occur during the course of a research study must be considered when the study report is written as they may have an impact on the analysis or interpretation of the data and they may need including in the study report.

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2.3 NOTIFYING THE UHB OF A SUSPECTED SERIOUS BREACH (UHB SPONSORED STUDIES)

A suspected serious breach in a UHB sponsored or co-sponsored study that is detected by a member of the research team, the Study Monitor or Data Manager must be reported by the individual identifying the breach to the R&D Office within 24 hours of the breach being identified.

Initial reporting to the R&D Office must be undertaken by email

Research.Governance@wales.nhs.uk or by telephoning the R&D Office on 029 2074 5871. A member of the R&D Office will acknowledge receipt of the notification. It is the responsibility of the reporting individual to contact the R&D Office if no acknowledgement is received within 72 hours of notification. The following information is required when notifying potential serious breaches:

- The name of the CI and PI at the site where the serious breach occurred
- Full title of the clinical trial and R&D number
- An explanation on how the breach was identified
- Full written description of the breach
- Details of any initial corrective actions

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.

2.4 UHB SPONSOR ASSESSMENT OF A SUSPECTED SERIOUS BREACH

Upon receipt of a suspected serious breach notification the R&D Office personnel receiving the notification will immediately inform the JRO Director. If the JRO Director is not available the notification will go to one of the R&D Lead of the UHB sponsored study in which the serious breach has occurred.

The JRO Director (or alternate as above) will, identify a review group to assess the potential serious breach. The review group should:

- Normally include at least three people. Where possible the review

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group should include the JRO Director (or alternate as above), the CI and normally one or more of the following: Trial Manager, Monitor, Co-investigator)

- Consult experts if required e.g. Data Manager, Statistician
- Identify which section of GCP or the protocol has been breached and how this may impact on the safety or physical or mental integrity of the study participants, or the scientific value of the study
- Reach a consensus as to whether the breach fulfils the criteria for a serious breach. The assessment will include review of the deviations/violations to ascertain whether isolated /systematic incident, patient(s) harmed or put at risk and impact on scientific value of the study. The assessment must be documented in the Study File and a copy retained in the R&D Office central 'Suspected Breaches Folder' for ease of reference. **Note:** For CTIMP studies, if the potential for a breach to have significant impact on the scientific value of the trial is unclear, advice should be sought from the MHRA
- Compile evidence to support notification to the MHRA
- Identify the extent of the breach and to determine whether the breach constitutes an Urgent Safety Measure or requires a substantial amendment.

2.5 NOTIFICATION TO THE MHRA AND THE REC OF A SERIOUS BREACH (UHB SPONSORED STUDIES)

Serious breaches occurring for CTIMP studies must be notified within specific timescales to both the MHRA and REC by the Trial Sponsor (see 2.5.1). For UHB sponsored studies the R&D Director will nominate a 'Sponsor Representative' (who will normally be a member of the R&D Office) to take on this role.

Serious breaches occurring in non-CTIMP studies only require reporting to the REC and responsibility for this notification is delegated by the UHB to the CI (see 2.5.2).

2.5.1 NOTIFICATION FOR CTIMP STUDIES ONLY

If the R&D Office (on behalf of the UHB) obtains clear and unequivocal evidence that a serious breach has occurred in a CTIMP study (as defined in Regulation 29A), then the nominated Sponsor Representative must notify the MHRA and REC within 7 days of receiving notification. The Sponsor Representative will investigate the serious breach and take additional appropriate corrective action simultaneously or after notification. A template form for notifications of serious breaches to the MHRA is available (see Appendix 2).

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The completed notification form should be sent to both:

- the MHRA by email (GCP.SeriousBreaches@mhra.gsi.gov.uk)
- the REC by email or post

An acknowledgement of receipt should be requested and filed in the study folder and 'Suspected Breaches Folder'.

Note: If thought necessary then the MHRA Inspectorate may initially be contacted by telephone to discuss the breach but a written notification follow up must also be submitted within 7 days of the R&D Office becoming aware of the breach.

The Sponsor Representative should inform the relevant Chief Investigator and/or Principal Investigators (as applicable) of the breach notification. Communication in this regard will facilitate the implementation of corrective and preventative actions.

The Sponsor Representative must also consider if there are any other relevant MHRA Departments that require to be notified to comply with other legislation (e.g. notification to the Clinical Trials Unit (CTU) if the breach constitutes an urgent safety measure or if a substantial amendment is required due to a temporary halt in the study or to the Defective Medicines Report Centre if the breach involves defective medicines or IMP recall).

For further advice refer to 'Guidance for the Notification of Serious Breaches of GCP or the trial protocol' available on the MHRA website. (Appendix 1)

2.5.2 NOTIFICATION FOR NON- CTIMP STUDIES

For non-CTIMP studies, the Notification of Serious Breach Form (Appendix 2) should be completed by the Chief Investigator (or delegated other) and submitted to the REC and copied to the R&D Office. All subsequent correspondence on this matter, between the CI and the REC, should also be copied to the R&D Office.

2.6 FOLLOWING REGULATORY AUTHORITY NOTIFICATION (UHB SPONSORED STUDIES)

Following the initial notification of serious breach to the MHRA and/or the REC, the R&D Office, on behalf of the Sponsor, will perform a further review of the breach and prepare a report for consideration by the Research Governance Group (RGG). Appropriate corrective actions will be implemented and any further information on the breach notified to the MHRA and/or REC. Any follow up reports should be

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- Clearly identified as a follow up
- Identify the unique reference number given by the MHRA and/or REC on acknowledgement of initial report:
- Be sent directly to the person dealing with the initial query (unless otherwise instructed).

Copies of all correspondence relating to the breach will be securely retained by the R&D Office in the central 'Suspected Breaches Folder'. Cross referencing file notes will be placed into the relevant study sponsor files. Where it is deemed appropriate, documentation may be copied across to the sponsor file for archiving.

The Research Governance Team will undertake a review every 3 months of all suspected serious breaches which have been reported to the R&D office (including both sponsored and hosted studies). This review and report will be presented to the Research Governance Group. This review will aim to identify any pattern of related breaches that need to be addressed by the Sponsor or reported to the Regulatory Authorities. This review will be documented in the Research Governance Group minutes.

2.7 BREACHES IN EXTERNALLY SPONSORED STUDIES HOSTED BY THE UHB

If a suspected serious breach is identified by the research team or via audit, it should be notified directly to the study sponsor contact person within 24 hours by the PI, delegate or other. The following information is required when notifying potential serious breaches:

- The name of the CI and PI at the site where the serious breach occurred
- Full title of the clinical trial and R&D number
- An explanation on how the breach was identified
- Details of the breach
- Details of any initial corrective actions

The R&D Office must also be notified that a suspected serious breach has occurred within the UHB. The notification must be emailed or by telephoning the R&D Office on 029 2074 5871. A member of the R&D Office will

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acknowledge receipt of the notification. It is the responsibility of the reporting individual to contact the R&D Office if no acknowledgement is received.

The CI/PI will be responsible for ensuring that the R&D Office is notified of the Sponsor assessment of the reported suspected serious breach as soon as this is confirmed.

In situations where there may be disagreement between the investigator and external Sponsor over the assessment of a serious breach, the UHB will exercise due diligence and give consideration as to whether it has a responsibility to direct report to the Regulatory Authorities. This decision will be made by the R&D Director (or delegate) and documented in the R&D Office central 'Suspected Breaches Folder' for ease of reference. A cross referencing file note should be placed in the Investigator Site File.

All serious breaches occurring on studies hosted by the UHB and notified to the R&D Director will be reported to the RGG for consideration.

All non-serious breaches should be documented as described in section 2.2 unless Sponsor specific instructions exist.

3.0 TRAINING

Education and support should be available from the UHB R&D Office for researchers who are involved in conducting UHB Sponsored CTIMPs. UHB R&D Office 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 UHB R&D Office is responsible for overseeing the operational management of Research Governance and for providing assurance of robust Research Governance arrangements in the UHB.

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

Where resources allow, random Research Governance audits will be carried out by the UHB R&D Office 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 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.

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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	Is this a Serious Breach?
Sponsor	<p>Dosing errors reported:</p> <p>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).</p> <p>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.</p> <p>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.</p> <p>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.</p>	<p>Yes, there was significant potential to impact the safety or physical or mental integrity of trial subjects.</p> <p>Yes,</p> <ul style="list-style-type: none"> • 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. <p>Yes, there was impact on the safety or physical or mental integrity of trial subjects and on the scientific value of the trial</p> <p>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</p>

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		and a detailed corrective and preventative action plan was implemented.
Notifier	Details of Breach Reported	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	Yes Note: not all of the information was provided in the original notification, the Sponsor provided follow-up updates.

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	over consenting and data changes made to source without an adequate written explanation.	
Notifier	Details of Breach Reported	Is this a Serious 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.

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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
Notifier	Details of Breach Reported	Is this a Serious 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. <i>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).</i>
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. <i>More information on the potential consequences of the delay should have been provided.</i>	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. <i>A common deviation in clinical trials.</i>	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	Yes

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	reported the SAE as a potential SUSAR.	
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	Is this a Serious 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 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 2 - 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>

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UHB REFERENCED DOCUMENTS

Cardiff and Vale UHB Research Governance Policy (UHB 099)

Oversight and Monitoring in Research SOP (UHB 247)

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This procedure was based on information in York Foundation Trust R&D Unit SOP R&D /S04 version 5, 22 April 2013.