Portsmouth Hospitals University NHS Trust

Standard Operating Procedure (SOP) for Reporting and Managing Non-Compliance and Serious Breaches in Clinical Research

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CONTENTS

1. INTRODUCTION

It is the Sponsor's responsibility to ensure that research is undertaken in compliance with the approved protocol and SOPs and in accordance with GCP and regulatory requirements.

It is a legal requirement, described in Regulation 29A of the Medicines for Human Use Act 2004 (as amended 2006) that all serious breaches of Good Clinical Practice (GCP) or the trial protocol on Clinical Trials of an Investigational Medicinal Product (CTIMPs) are reported to the licensing authority. In the UK this is the Medicines and Healthcare products Regulatory Agency (MHRA). In addition all serious breaches, on CTIMP or Non-CTIMP studies, must be notified to the appropriate Research Ethics Committee (REC).

The MHRA and the REC should be notified of a serious breach within seven days of its identification.

2. PURPOSE

The purpose of this document is to describe the process of reporting and managing non compliances and serious breaches upon identification. This includes guidance on the procedure for reporting to the appropriate regulatory bodies, Research Ethics Committee and other stakeholders.

3. SCOPE

This SOP applies to research studies both Sponsored and Hosted by Portsmouth Hospitals University NHS Trust. This includes at other sites for which PHU is responsible.

3.1. Who should use this SOP

- All individuals involved in research studies taking place within PHU (hosted or sponsored); or
- All individuals involved in research studies taking place at another site, where PHU is the Sponsor.

3.2. When this SOP should be used

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

- A research study sponsored by PHU; or
- Co-sponsored studies where the sponsorship agreement states that PHU SOPs will be followed; or
- A research study hosted but not sponsored by PHU (see Section 6.7 only).

The Trust recognises that some external sponsors, networks, funders and employers may require the use of their own SOPs for the good governance of research. In such cases it is the responsibility of the PHU user (including those individuals contracted to work on behalf of the Trust), to ensure that the external SOP is compatible with the procedure outlined below in this SOP. If the external SOP contradicts the Trust's procedure then approval must be sought in writing from a member of the Research Senior Management Team.

In the event of an infection outbreak, flu pandemic or major incident, the Trust recognises that it may not be possible to adhere to all aspects of this document. In such circumstances, staff should take advice from their manager and all possible action must be taken to maintain ongoing patient and staff safety.

4. ABBREVIATIONS & DEFINITIONS

Abbreviation	Meaning
CAPA	Corrective and Preventative Action (Plan)
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
Hosted	Refers to an externally sponsored study for which Portsmouth Hospitals NHS Trust are acting as a site
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
PHU	Portsmouth Hospitals University NHS Trust
PI	Principal Investigator
R&I	Research and Innovation
REC	Research Ethics Committee
RGRG	Research Governance & Risk Group
SOP	Standard Operating Procedure
Sponsored	Unless otherwise specified, this refers to a study for which Portsmouth Hospitals University NHS Trust are the Sponsor
TMF	Trial Master File

Term	Definition
Deviation	A deviation is a departure from one or more of the protocol, SOP, GCP or regulatory requirements that have been identified retrospectively, which is neither critical or major and so not likely to effect to a significant degree: • The safety or physical or mental integrity of the trial participant • The scientific value of the trial For example: • Lab time points missed or late

	• Missed data points in CRF's as a result of error (rather than an intention to mis-record information) • Missed/out of window follow up visits due to unforeseen circumstances.
Breach	A breach is a significant and unjustified departure from the protocol, SOP, GCP or regulatory requirements that may not have developed into a critical issue but may have the potential to do so unless addressed. Where there are a number of instances of deviations within a single area of responsibility, this indicates a systematic quality assurance failure and so should be collectively treated as a breach. For example: • Significant and unjustified non-compliance with relevant legislation or Good Clinical Practice (ICH GCP) • A number of breaches or legislation or GCP within one area, indicating systematic quality assurance failure • A failure to comply with legislative requirements including annual reporting requirements
Serious Breach	A 'serious breach' is defined by the Medicines for Human Use (Clinical Trials) Regulations 2004 as a breach which is likely to affect to a serious degree: • The safety or physical or mental integrity of the subjects of the trial; and/or • The scientific value of the trial. For example: • The safety, well being or confidentiality of participants has been jeopardised or has the potential to be jeopardised • Reported data are unreliable or absent • Inappropriate, insufficient or untimely corrective action has taken place regarding major non compliance • Where there are a number of breaches across areas of responsibility, indicating a systematic quality assurance failure • Lack of adequate documentation available to reconstruct the study or failure to maintain an appropriate Trial Master File (TMF) Examples of serious breaches notified to the MHRA are provided in Appendix 1.
PHU Sponsored Studies	Studies which Portsmouth Hospitals University NHS Trust have ultimate responsibility for the initiation, management of and financing. They take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting.

Research Study Team	The people involved in the conduct of a research project. There may be different research teams for the project at different sites.

5. DUTIES AND RESPONSIBILITIES

Role	Responsibilities
Chief/Principal Investigator	▪ Ensure that they and the study team are GCP compliant. ▪ Ensure all other study team members are trained in this procedure, as applicable. ▪ Report any breaches and suspected serious breaches to the Sponsor within 24 hours. ▪ Assist with all reports to the regulatory authorities, including prompt responses to the Sponsor's requests for further information. ▪ Document and have oversight over all breaches on their study and to report all systematic breaches to the Sponsor. ▪ Ensure that any Corrective and Preventative Actions (CAPA) are implemented across all sites where applicable in a timely fashion.
Research Study Team	▪ Ensure that they are personally GCP compliant. ▪ In the absence of the Investigator report any breaches to the Sponsor within 24 hours. ▪ Assist with all reports to the regulatory authorities, including prompt responses to the Sponsor's requests for further information. ▪ Notify the CI of all identified breaches (including non-serious).
PHU Research Office	▪ Ensure that this procedure is reviewed and updated as necessary. ▪ Provide training in this procedure as required.
Research & Development (R&D) Manager	▪ Lead and provide oversight of investigations into all suspected serious breaches. ▪ Ensure appropriate reporting of ongoing investigations to appropriate management groups. ▪ Communicate clearly assigned actions and timelines pertinent to those involved in investigations. ▪ Ensure timely completion of investigations, and CAPA plans thereafter. ▪ Ensure organisational learning is recorded and disseminated of suspected/confirmed serious breaches.
PHU Research Office (as Sponsor)	▪ Assess all breaches reported to them within the specified time periods. ▪ Investigate suspected breaches, collating information on the event, classification and action taken. ▪ Submit all reports to the regulatory bodies, unless delegated to another appropriate individual. ▪ Work in conjunction with the Research Governance & Risk Group (RGRG)/Research Delivery Meeting (RDM) to monitor the

	Investigator's progress in following their CAPA.
RGRG (Sponsored Only)	▪ Review all breaches reported by the PHUResearch Office including the corresponding CAPA. ▪ Work in conjunction with the R&D Manager to review the implementation of CAPA plans by investigators.

6. PROCESS

6.1. Identification of GCP or Protocol Deviation

GCP or protocol deviations are normally identified by:

- The Investigator or members of the research team during the day-to-day running of the study; or
- Internal auditing of the study documents to ensure GCP compliance; or
- Periodic monitoring undertaken by or on behalf of the Sponsor.

Upon identification, the manner in which the non-compliance should be reported will depend on whether it is a deviation, breach or serious breach.

Process for Managing Breaches in PHU Sponsored Studies

6.2. Reporting and Management of Deviations

6.2.1. Reporting a Deviation

Deviations tend to be identified during routine monitoring activities, but can be identified at any time by anyone. Often the deviation comes down to human error and is usually discussed between the study monitor and the research team to ensure full understanding of the Protocol and that there is no systemic issue. Multiple instances of the same protocol deviation may be lead to a breach or serious breach.

Instances of deviations will be captured in the monitoring or audit report. If deviations cannot be resolved at the time of identification, a Corrective and Preventative Action plan (CAPA)

will be put in place in accordance with the CAPA SOP (PHU/RDSOP/020). Alternatively, the deviation can be recorded on a deviation record form.

6.2.2. Management of Deviations

Often a deviation can be resolved at the time of identification, however if this isn't possible then a CAPA will be put in place.

Upon notification the CI will have 60 calendar days in which to respond and complete the CAPA plan. This requires the CI to explain what action they will take, not necessarily take the action at this point.

Failure to respond to notification of deviation can constitute a breach as per the definition above.

6.3. Reporting and Management of Major Non Compliance (Breach)

6.3.1. Reporting a **Major** Non-Compliance (Breach)

All identified breaches must be fully documented by the Investigator using the 'Study Breach Record and Reporting Form' (see section 8). This includes at a minimum:

- A full description of the breach including the date and time it occurred;
- The Chief Investigator's assessment of whether the breach is serious;
- Any corrective actions immediately undertaken.

The Chief Investigator's assessment should take place as soon as possible but **within 48 hours of the breach being identified**. Where the Chief Investigator cannot be contacted this assessment may be delegated to the PI or other investigator.

The PHU Research Office as Sponsor should be notified **within 24 hours** (see 6.4.2) of the CI's assessment. The Research Office will log the Breach on the Safety Database.

6.3.2. Management of a **Major** Non-Compliance (Breach)

In accordance with the CAPA SOP, a CAPA will be written to resolve the breach. The CI will have **30 calendar days** in which to respond and complete the CAPA plan. This requires the CI to explain what action they will take, not necessarily take the action at this point.

Failure to respond to the CAPA within 30 calendar days will result in escalation to the research senior management teamand may constitute a serious breach as per the definition above. Further action to be taken will be at the discretion of the research senior team.

6.4. Reporting and Management of a Serious Breach

6.4.1. Reporting a **Serious Breach**

All identified breaches must be fully documented by the Investigator using the 'Study Breach Record and Reporting Form'. This includes at a minimum:

- A full description of the breach including the date and time it occurred;
- The Chief Investigator's assessment of whether the breach is serious;
- Any corrective actions immediately undertaken.

The Chief Investigator's assessment should take place **within 24 working hours of the breach being identified**. Where the Chief Investigator cannot be contacted this assessment may be delegated to the PI or other investigator.

1. The **Sponsor** should be notified **within 24 working hours** if the breach is considered to be serious or there is any doubt regarding the classification (see section 6.4.2).

2. Where applicable, the **MHRA** will be notified of the serious breach **within 7 days** of the Sponsor (PHU Research Office) becoming aware of the breach (see section 6.4.4).

3. The **REC** will be notified of the serious breach **within 7 days** (see section 6.4.4).

6.4.2. Notification to PHU as Sponsor

All breaches should be reported to the Research Office **within 24 working hours** by:

- Email: research.office@porthosp.nhs.uk *(include 'SERIOUS BREACH' in the subject if the breach is assessed as serious)*

The Research Office will acknowledge receipt of the Study Breach Record and Reporting Form by email. However the individual submitting the form **should contact the PHU Research Office by telephone on: 023 9228 6236** if no acknowledgement is received.

6.4.3. Sponsor Assessment of the Suspected Serious Breach: **Research Office Procedure**

Upon receipt of a breach notification the recipient in the ResearchOffice, will immediately notify the R&D Manager. Should they be unavailable an appropriate senior member of staff should be notified (for example the Head of Research, Director/Deputy Director of Research or Trust Lead Research Nurse).

The recipient in the Research Office will record the breach on the Safety Database and follow the Research Office Study Breach Tracker (see section 8) in order to track the reporting process and associated deadlines.

The R&D/Senior Manager will review the record form and request clarification or evidence where required.

If additional information is required, a meeting should be held as soon as possible (and within the 7day MHRA/REC notification period) with the Investigator, their research team and any relevant medical experts. The purpose of this meeting is to gather evidence and the facts related to the breach so that the R&D/Senior Manager or equivalent individual, on behalf of PHU as Sponsor, is able to make an informed decision on whether the breach is considered serious.

If required the R&D/Senior Manager will contact the MHRA by telephone on: 020 3080 6000 for further advice.

If the breach is considered to be:

- serious; and
- represents a hazard to patients; and
- requires urgent remedial action

then the process described in PHU/RDSOP/006 Reporting Urgent Safety Measures in Clinical Research is to be followed in addition to the steps outlined below.

The assessment of the breach will be based upon all evidence received by the Sponsor (Research Office) and will be documented in writing by the Sponsor's representative using the MHRA's '**Notification of Serious Breach of GCP or Trial Protocol' form** if applicable. This form is available from the MHRA webpage. The representative will write all reports to the regulatory authorities in relation to the serious breach; however the Sponsor retains the right to delegate all or sections of this to the Investigator.

6.4.4. Initial Report to the Regulatory Authorities

It is a legal requirement that all serious breaches on CTIMP/MHRA notifiable studies are reported to the MHRA **within 7 days** of the Sponsor becoming aware of the breach.

The REC that originally granted approval must also be notified **within 7 days** both for CTIMP and Non-CTIMP studies.

The R&D/Senior Manager or equivalent individual will send the initial report to:

- the MHRA via email: GCP.SeriousBreaches@mhra.gov.uk *(CTIMPs only)*
- the REC by email: https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/search-research-ethics-committees/ *(visit this website to find the latest contact details for the REC)*

Please Note: an acknowledgement that the report has been received should be requested.

The MHRA may contact the PHU Research Office to discuss the report and request further information if required. The MHRA may also give advice on any urgent measures that will need to be implemented immediately.

Further advice on the MHRA review process is available in the following document: 'Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol'

6.4.5. Follow-up report and CAPA Plan

Following notification to the appropriate regulatory authorities, the R&D/Senior Manager or equivalent individual will conduct a further review of the serious breach. The aim of this review is to:

- Collate evidence and accounts from those involved in order to produce a full report of the serious breach including timelines, events and the impact of the breach on participant safety or the scientific integrity of the trial;
- Develop a list of CAPAs to be implemented to address the immediate issues and to prevent the breach from happening again. (See SOP for CAPAs, PHU/RDSOP/020 for CAPA template use)

This follow-up report will be written by the R&D/Senior Manager as representative of the Sponsor, but PHU may delegate sections to the Investigator. The report shall be completed using the MHRA's 'Notification of Serious Breach of GCP or Trial Protocol' form if applicable.

The R&D Manager will submit the final report to the Senior Management Team along with the CAPA. It is the responsibility of the Investigator to carry out the CAPAs and the responsibility of the Sponsor and RGRG to monitor their progress. The report and CAPA will also be reviewed by the RGRG at their next meeting for oversight and to ensure all learning opportunities are utilised.

Following review by the Senior Team, the R&D Manager will send the report to the MHRA (CTIMP studies) and the REC for their information. Acknowledgement should be requested and both authorities may take further action depending on the severity of the breach. As sponsor, PHU may implement a temporary halt to study activities whilst the investigation take place. Following full investigation and CAPA resolution, the study may restart or be terminated depending on the outcome of the investigation. More information on potential actions by the MHRA can be found within their Serious Breach guidance.

6.5. Documenting Non-Compliance

A record of all non-compliance and a copy of all documents (including correspondence) should be filed within the Investigator Site File (ISF)/Trial Master File (TMF) and the electronic R&I file by the Research Team and Research Office staff respectively.

Additionally, any deviation/breach/serious breach that presents as an immediate learning opportunity for the PHU Research Department, should also be reported on the Trust incident record system- DATIX. All PHU staff have access to this system and have the opportunity for training as part of their day job. If there is any doubt whether to complete a DATIX report, research staff members should check with their line manager.

6.6. Breaches in PHU Sponsored Multi-site Studies Hosted by an Non-PHU Site

All suspected breaches should be reported by a member of the site's research team to the CI using the 'Study Breach Record and Reporting Form'. Upon receipt the CI will follow the process outlined in Section 6.3/4. The CI should keep a record of all reported breaches (including non-serious) within the study TMF.

CIs of multi-site studies must ensure all research teams are aware of their responsibilities in relation to reporting serious breaches and other safety measures.

Information regarding the breach will be recorded on the Safety Database by a member of the Research Office Team.

Process for Managing Breaches in PHU Hosted Studies

6.7. Breaches in Externally Sponsored Studies Hosted by PHU

All serious breaches identified on studies that are externally sponsored but hosted by PHU should be notified immediately to the PHU Research Office and the Sponsor's representative as detailed in the study Protocol.

Where available, the PI should follow the Protocol or the Sponsor's own instructions to report the serious breach. Otherwise, all breaches should be documented using the 'Study Breach Record and Reporting Form' (see Section 8). A copy of the completed report should be filed within the ISF.

If the PHU Research Office receives notification from an external Sponsor of a serious breach that has taken place at PHU; the R&D Manager (or appropriate Senior Manager) will request further information and details of the initial corrective actions. A template email for this request has been provided in Appendix 2.

All correspondence and documents associated with the breach must be filed within the ISF or TMF and the electronic R&I file.

Information regarding the breach will be recorded on the Safety database by a member of the Research Office Team.

Summary for Sponsored and Hosted Studies

6.8. Summary of breach management in PHT Sponsored and Hosted studies

	How to record	Notify Research Office	Research Office to notify MHRA & REC	Record on Safety Database
Deviations *(PHU Sponsored study)*	Can be recorded in a monitoring/audit report or on a Trial Deviation Form	Yes, if not identified during PHU monitoring activity. Inform the Research Office as soon as possible	No	No
Breach *(PHU Sponsored study)*	Use Study Breach Record and Reporting Form *(see section 8)*	Within 24 hours	No	Yes
Serious Breach *(PHU Sponsored study)*	Use Study Breach Record and Reporting Form *(see section 8)*	Within 24 hours	Yes	Yes
Breach on a PHU Hosted study	Consult study protocol/SOP.	Immediately notify of Serious Breach	Sponsor responsibility	Yes

7. TRAINING REQUIREMENTS

- **All** research staff should be trained in this procedure.
- Evidence of training shall be required for PHU sponsored studies and Research Office staff.

"The Research Dept., will endeavour to notify staff of SOP developments that may be relevant to them. SOPs are available on the Research department website. Updates on SOPs will feature in Research newsletters and communications and disseminate at local research meetings. It is the responsibility of all research active staff to ensure that they read the issued updates that may be relevant to them.

When a new SOP is authorised, or when an existing SOP is revised, self directed training must be carried out by all staff to which the SOP is relevant and this training documented in their training record. A template is provided to support this process. A study specific SOP training plan will be developed for investigators on high risk PHU Sponsored studies.

Staff should take time to read and fully understand the SOP and relevant documents, ensuring that they are able to implement the SOP when required. If clarification is needed then the trainee should approach their line manager and the SOP Controller who will arrange additional training. All staff should complete their training prior to the published implementation date which will normally be between 2-6 weeks after publication.

All staff are responsible for maintaining their own SOP Training Records and copies must be made available to line managers, the SOP Controller or study monitors on request."

8. REFERENCES AND ASSOCIATED DOCUMENTATION

Associated Documents

- Safety Database, G:\Research and Development - Research Office\SAFETY
- Study Breach Record and Reporting Form - available from SOPs and Templates (porthosp.nhs.uk)Research Office Study Breach Tracker
- Notification of Serious Breach of Good Clinical Practice or Trial Protocol - available from http://www.mhra.gov.uk
- PHU/RDSOP/006 Urgent Safety Measures SOP
- PHU/RDSOP/020 CAPA SOP
- Trial Deviation Form

References

- UK policy framework for health and social care research
- The MHRA Good Clinical Practice Guide 2012 (Grey Guide)
- Medicines for Human Use Act (2004, SI 1031) - available from http://www.legislation.gov.uk/uksi/2004/1031/made
- Medicines for Human Use Act Amendment No.2 (2006, SI 2984) - available from http://www.legislation.gov.uk/uksi/2006/2984/contents/made
- Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol - available from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/705179/Guidance_for_the_Notification_of_Serious_Breaches_of_GCP_or_the_Trial_Protocol_Version_5.1__04-05-2018_.pdf
- REC SOP - Research Ethics Committee – Standard Operating Procedures - Health Research Authority (hra.nhs.uk)
- University Hospitals of Leicester NHS Trust Support Office SOP S-1016, Procedure in the Event of Non-Compliance in research sponsored by UHL

9. VERSION HISTORY LOG

Version	Date Implemented	Details of Significant Changes
1.0	01/07/2012	N/A
2.0	07/04/2016	Addition of Protocol deviation definition, addition of reference to Incident and Breach tracker, additional information regarding SOP training

		added and minor typographic changes
3.0	09/09/2019	1. Routine review 2. Incorporation of minor and major non-compliance reporting and management 3. Update of REC contact details 4. Research Office name changed to R&I Office 5. Removal of R&I fax number 6. Method of breach acknowledgement by R&I Office changed from telephone to email 7. Removed use of whiteboard to track breaches in the R&I office 8. Update of MHRA guidance in appendix 1 9. Update to flowchart (appendix 3), minor typographic changes
4.0		Updated trust logo Updated trust naming convention throughout Updated reference to R&I Office to Research Office Updated terminology- non-compliances to deviations, major non-compliances to breaches etc. Update to duties/responsibilities Updated timeframe for breaches Update to escalation communication routes Update to internal investigation report process Addition of recording pertinent reports to DATIX Update to deviation notifications to Research Office Update to some reference links

10. APPENDICES

10.1. Appendix 1 - Examples of Notifications to the MHRA

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

	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.	
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 an increased risk of thrombosis.	**Yes**
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**
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**

Extract from: Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol, V6.0, MHRA, www.mhra.gov.uk

10.2. Appendix 2 - Email Template: Externally Sponsored Serious Breach at PHU Site

Dear [PI],

We have received notification of a Serious Breach in the [STUDY SHORT NAME] trial for which you are PI at our site. I understand that this Breach has been reported for Portsmouth Hospitals University NHS Trust. [BRIEF SUMMARY OF NOTIFICATION].

We must now follow up this notification and request that you please provide a written summary of events from a PHU perspective, including a Corrective and Preventative Action Plan.

We need to understand:

- The reasons why the breach occurred
- How we can immediately correct any errors made at a local level
- What we might put in place organisationally, to ensure that this can't happen again.
- How the breach impacted the patient or patients (please provide an overview)

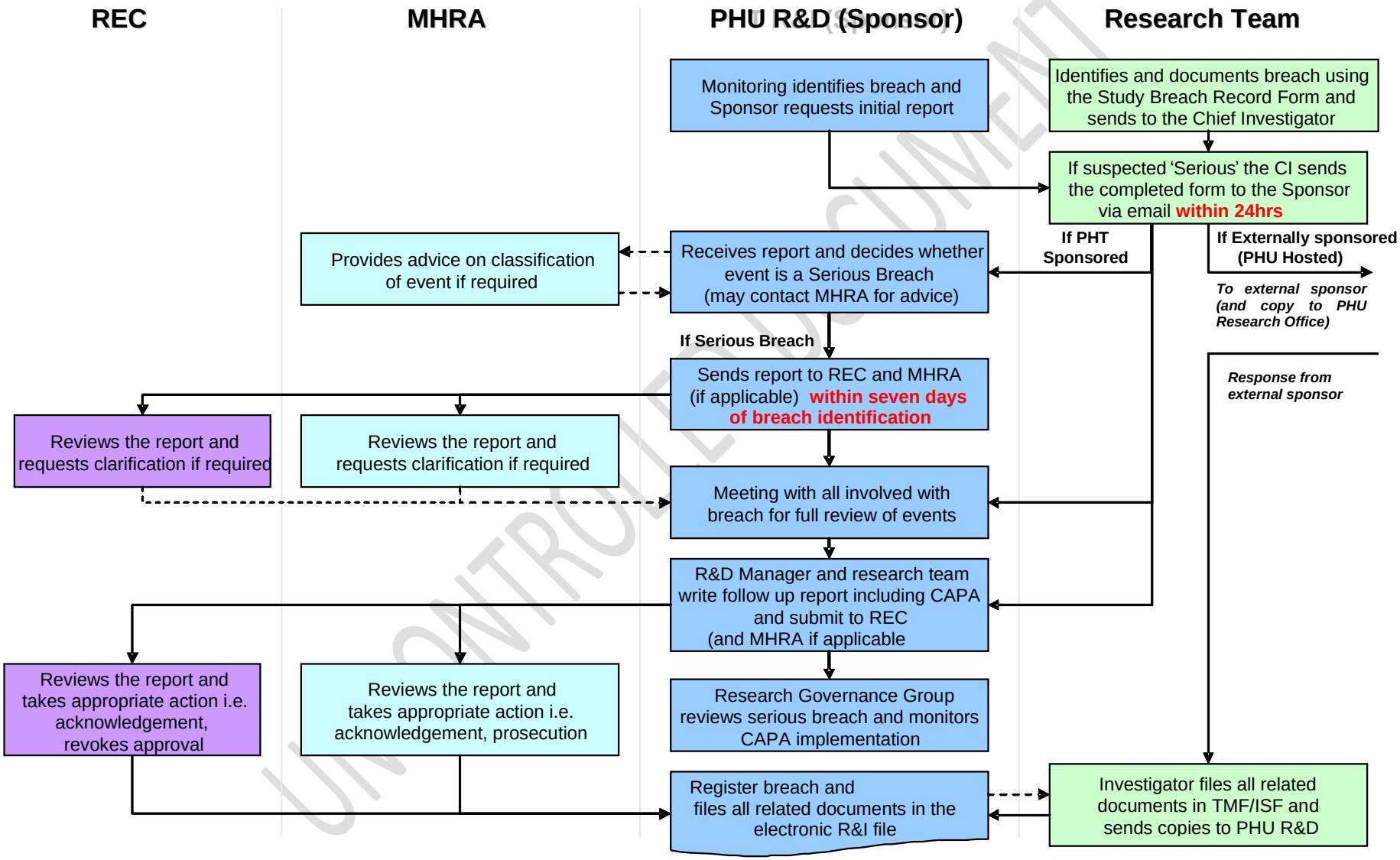
Please do not hesitate to contact me should you wish to discuss this further.

Please provide your written summary to us within the next 7 days.

Kind regards

[Research Manager/R&D Manager]

10.3. Appendix 3 - Flowchart: Reporting a Serious Breach



10.4. Training Record

Portsmouth Hospitals University NHS Trust

CONFIRMATION OF SOP TRAINING RECORD

A copy of this record may be kept in your personal training file to confirm your training in a specific SOP. The research department or your line manager may request copies to verify your training. If required by a study Sponsor a record may also need to be kept in the Trial Master Files (TMF) or Investigator Site Files (ISF).

SOP Details: To be completed by the SOP Controller	
Title of SOP	Standard Operating Procedure (SOP) for Reporting Serious Breaches in Clinical Research
Reference Number	PHU/RDSOP/002
Version	4.0, 10 January 2024
Issue Date	16 January 2024
Implementation Date	30 January 2024

Personnel Details	
Name	
Job Title & Research Role	
Date of Training	
Nature of Training	Self Directed
Records of any meetings to clarify details in SOP	

Signatures
I confirm that I have read and consider myself to be sufficiently trained in the above Standard Operating Procedure with regards to my individual roles and responsibilities Signature of Trainee …… Date ……
I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities

Signature of Trainer …… Date …….
Additional Notes & Signatures
Signature of Trainer (where appropriate) I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date …….