RD&I	NHS University Hospitals Plymouth NHS Trust **STANDARD OPERATING PROCEDURE**

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The definitive versions of all UHPNT RD&I Dept SOPs appear online, not in printed form, to ensure that up to date versions are used. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the Trust's website: https://www.plymouthhospitals.nhs.uk/research-sops

Non-compliance reporting

SOP No: T6

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Page: **1** of **11**

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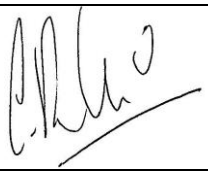
Signature:	
Date:	21st Jan 2019

1 Purpose and Scope

This SOP describes the procedure for identifying, documenting and processing instances of non-compliance at University Hospitals Plymouth NHS Trust (UHPNT).

In accordance with UK clinical trials regulations[1], no person shall conduct a clinical trial otherwise than in accordance with the approved protocol, as may be amended from time to time in accordance with the regulations; and the terms of the request for authorisation to conduct that trial, the application for an ethics committee opinion in relation to that trial, and any particulars or documents, other than the protocol, accompanying that request or that application.

ICH GCP guidance[2]

- Section 4.5.2:
  This article permits changes that involve only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s) to be implemented prior to obtaining ethics approval. It states: "The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s)).
- Section 4.5.3
  The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
- Section 4.5.4
  "The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:
  (a) to the IRB/IEC for review and approval/favourable opinion,
  (b) to the sponsor for agreement and, if required,
  (c) to the regulatory authority (ies)."

SI 1928, item 16 (amended Regulation 29A)[1].

Where there is a failure to adhere to the approved protocol or regulatory application there is a legal requirement to report "**serious breaches**" of GCP or the trial protocol to the competent authority as detailed below:

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of;

(a) the conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time in accordance with the regulations,

within 7 days of becoming aware of that breach.

For the purposes of this regulation, a "serious breach" is a breach which is likely to affect to a **significant** degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial."

The Chief / Principal Investigator (CI /PI) and the Study Sponsor are responsible of for recording, reviewing and reporting of a study non-compliance. The task maybe delegated to another suitably trained individual but the responsibility remains with the CI /PI and Study Sponsor

In scope: research hosted by, and/or sponsored by UHPNT.

Definitions

PI	Principal Investigators
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
HCA	Health Care Assistants
HRA	Health Research Authority
MHRA	Medicines and Healthcare products Regulatory Agency
REC	Research Ethics Committee
RD&I	Research Development & Innovation
RO	Research Office
SOP	Standard Operating Procedure
UHPNT	University Hospitals Plymouth NHS Trust

2 Who should read this document?

All staff involved in conducting research e.g. Chief Investigators (CI), Principal Investigators (PI), Research Nurses & Midwives, Health Care Assistants (HCA), RD&I Managers and Clinical Trial Administrative staff

3 Procedure to Follow

Non-compliances are categorised as follows:

DEVIATIONS are any variance in the approved study protocol, criteria or procedure that does not affect the participant's safety, rights, welfare or the integrity of the study and its resultant data. An example of this would be a participant visit conducted outside of the visit window.

VIOLATIONS to the protocol are deviations that increase the risk or decrease the benefit and/or affect the participant's rights, safety, welfare and/or integrity of the resultant data.

If you believe a protocol violation on a CTIMP does involve a compromise to patient safety, or the integrity of study data you must inform the Chief Investigator or the Clinical Trials Coordinator as soon as possible as this may constitute a:-

SERIOUS BREACH which is a divergence from the protocol: that has a significant impact on: (a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial which must be reported by the sponsor within 7 days of becoming aware of the breach to the MHRA.

The judgment on whether a breach is likely to have a significant impact on the scientific value of the trial 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 key analysis parameters, the impact of excluding the data from the analysis etc.

It is the responsibility of the Sponsor to assess and document the impact of the breach on the scientific value of the trial. If the Sponsor is unclear about the potential for a breach to have significant impact on the scientific value of the trial, the Sponsor should contact the regulatory authority (MHRA) to discuss the issue.

For non CTIMP studies violations should be reported to the sponsor once the researcher is aware of an incident. The sponsor will then consider if this needs reporting the REC, TSC and or DMC.

3.1 Identification of non-compliance

Non-compliance will be identified as follows:

1) In a single site, clinical trial staff may contact the Trial Co-ordinator or the CI, usually by telephone or e-mail, to seek prior approval to deviate from the approved protocol.

2) In a single site, clinical trial staff may contact the Trial Co-ordinator or the CI, usually by telephone or e-mail, to inform coordinating staff that an unapproved deviation has taken place.
3) In a multi-centre clinical trial satellite staff may contact the coordinating centre, usually by telephone or e-mail, to seek prior approval to deviate from the approved protocol.
4) In a multi-centre clinical trial satellite staff may contact the coordinating centre, usually by telephone or e-mail, to inform coordinating staff that an unapproved deviation has taken place.
5) Non-compliance may be detected during on-site monitoring visits or audit.
6) Non-compliance may be detected through central monitoring of study data.

3.2 Documenting non-compliance

All instances of non-compliance should be documented.

A file note or a non-compliance form should be appropriately numbered the following format is an example: Site Number/ 0001 to 9999 (e.g. 01/0001). The coordinating centre itself will usually be designated “00”.

Forms will minimally contain the following information: Site name, relevant department, trial number/visit number (if applicable), description of the incident, classification of the non-compliance, signature of coordinating centre personnel documenting the incident and signatures for responsible person assessing the non-compliance.

3.3 Processing non-compliance reports

1) Site reported non-compliance:
Pass the recorded details to the study sponsor.

3.4 Responsible person

Responsibility for classifying and approving non-compliance lies with the study sponsor.

3.5 Corrective action/preventative action

All instances of non-compliance must be reviewed to determine the root cause. The following points should be considered:

- Was the finding systematic (could other patients/sites be affected) or isolated?
- What was the cause of the finding?
- Was it a genuine error or oversight?
- Was there a lack of training (individual/all)?
- Was there no documented procedure?

- If there was a documented procedure was it not followed or was it inadequate?

The non-compliance report should include details of any planned amendments to referenced documented systems/procedures or details of any requirement for re-training to be undertaken.

3.6 Follow-up

Deviations:
The study team will review file notes or non-compliance reports on a regular basis to see if there are any patterns emerging and if further training or an amendment to the study protocol maybe needed. Multiple minor deviations maybe classed together to be a potential protocol violation or serious breach.

Violations
The file note/non-compliance report should be assessed to see if they may constitute a serious breach. Inform the Chief Investigator, Trials Coordinator and Sponsor immediately if a serious breach is thought to have occurred and pass on copies of the file note/non-compliance report and any other documentation detailing the incident for their review. The serious breach will then be reported by the sponsor to the MHRA in line with current regulations and their local SOP.

For a violation not deemed to be a serious breach a corrective action plan should be put in place and followed up.

3.7 Completed Forms

Completed file notes/non-compliance reports should be placed in the study site file.

3.8 Sponsor reporting of a serious breach to MHRA & REC

The study Sponsor must notify MHRA of serious breaches of GCP or the trial protocol. See 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)

Complete the notification of serious breaches of GCP or the trial protocol form can be found at (https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials) and should be sent to GCP.SeriousBreaches@mhra.gov.uk and to the REC that approved the study. Copies of the report may also be sent to TSC and DMC if appropriate. For non-CTIMP studies protocol violations are reported to the approving REC and TSC and DMC if appropriate.

4 Document Ratification Process

The review period for this document is set as ***default of three*** years from the date it was last ratified, or earlier if developments within or external to the Trust indicate the need for a significant revision to the procedures described.

This document will be approved by the ***RD&I Manager or their Deputy***.

Non-significant amendments to this document may be made, under delegated authority from ***a Senior RD&I manager***, by the nominated author. These must be ratified by ***a Senior RD&I manager***.

Significant reviews and revisions to this document will include a consultation with ***appropriately knowledgeable staff***. For non-significant amendments, informal consultation will be restricted to ***staff*** who are directly affected by the proposed changes.

Dissemination and implementation

4.1. Dissemination of this SOP

4.1.1. New SOPs and new versions of existing SOPs: The Research Governance Manager will be responsible for ensuring authorised SOPs are uploaded on the RD&I intranet site. Internal Trust Staff are expected to use the RD&I intranet site to access latest versions of SOPs and to check the website regularly for updates.

Notice of new or amended procedural documents that have undergone a major amendment will be given *via* the following routes:

• Inclusion in the Trust weekly e-bulletin Vital Signs

• Direct email to Trust Researchers and or teams

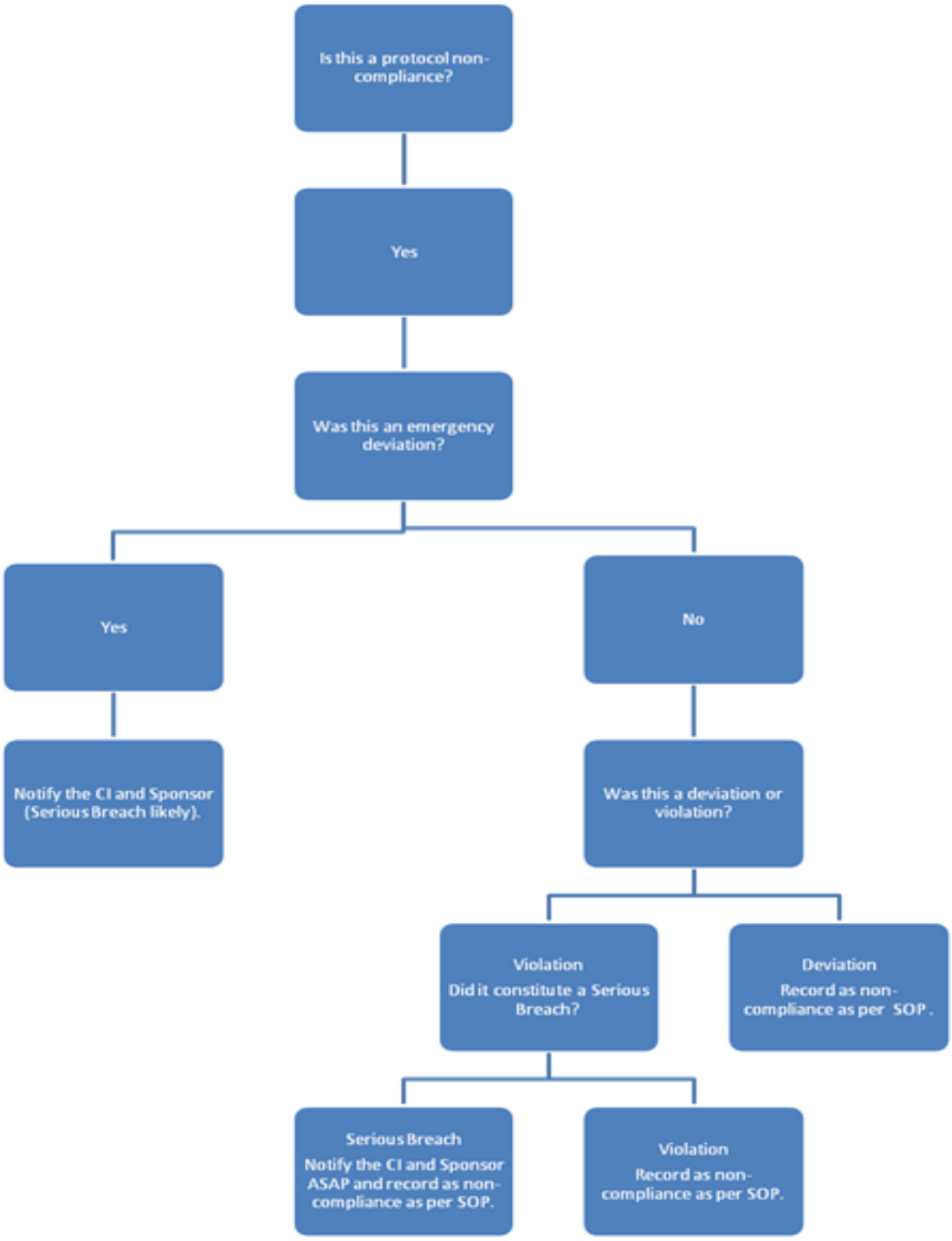
4.2. Training in this SOP

4.2.1. All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.

5 Reference material

1. Statutory Instrument 2004 No. 1031: The Medicines for Human Use (Clinical Trials) Regulations 2004 and Statutory Instrument 2006 No. 1928 - The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.
2. ICH Topic E6; Note for guidance on Good Clinical Practice (CPMP/ICH/135/95).
3. MHRA – Guidance for the notification of serious breaches of GCP or the Trial protocol.

Appendix: Flow diagram of procedure — Appendix 1



Appendix: Examples illustrating breaches classified as serious or non-serious (this is not an exhaustive list) — Appendix 2

1. A breach of GCP or the protocol leading to the death, hospitalisation or permanent disability of a trial subject in the UK. Please note, not every serious adverse event (SAE) or suspected unexpected serious adverse reaction (SUSAR) would routinely be classified as a serious breach, but SAEs/SUSARs resulting from a breach of the conditions and principles of GCP or a breach of the protocol may constitute a serious breach. Submission of a serious breach notification to the MHRA Inspectorate does not obviate the requirement for a SUSAR report, where applicable, to be submitted to the concerned competent authorities e.g. via the EudraVigilance database.
2. Proof of fraud relating to clinical trial records or data, if the fraud is likely to have a significant impact on the integrity of trial subjects or the scientific value of the data.

   Although not a legal requirement under regulation 29A, the MHRA GCP Inspectorate encourages the reporting of <u>all confirmed instances</u> of clinical trial fraud occurring at sites in the UK, which the Sponsor becomes aware of. The reason for this is that, although fraud at one particular trial site may not have a significant impact on scientific value or subject integrity for that particular trial, the MHRA would wish to assess the impact on other trials or subjects/patients at that site.

   If a serious breach or clinical trial fraud is identified at a non-UK trial site, for a trial that is also being conducted in the UK, a serious breach notification should be submitted to MHRA if the fraud is likely to have a significant impact on the integrity of trial subjects in the UK or on the overall scientific value of the trial. A site refers to any site involved in the trial e.g. CRO or other contracted organisation and not solely to investigator sites.
3. Persistent or systematic non-compliance with GCP or the protocol that has a significant impact on the integrity of trial subjects in the UK or on the scientific value of the trial. For example, widespread and uncontrolled use of protocol waivers affecting eligibility criteria, which leads to harm to trial subjects in the UK or which has a significant impact on the scientific value of the trial. Another example would be of an investigator repeatedly failing to reduce or stop the dose of an IMP in response to a trigger (e.g. abnormal laboratory results) defined in the protocol.
4. Failure to control investigational medicinal product(s) such that trial subjects or the public in the UK are put at significant risk or the scientific value of the trial is compromised. If a serious breach occurs due to an IMP defect, a drug defect report may need to be submitted to the MHRA Defective Medicines Reporting Centre (DMRC), in addition to the serious breach notification.
5. Failure to report adverse events, serious adverse events or SUSARs in accordance with the legislation, such that trial subjects, or the public, in the UK are put at significant risk e.g. inadequate safety reporting in dose escalation studies may have an impact on the decision to escalate to the next dose level.

Appendix: Notification examples — Appendix 3

Notified by:	Issue:	Would MHRA have expected this case to be notified?
Sponsor	Dosing error. Ethics Committee & MHRA informed. Subjects withdrawn. The sponsor stated that there were no serious consequences to subjects or data.	No, if there was no significant impact on the integrity of trial subjects or on scientific validity of the trial.
Sponsor	Patient Information Leaflet and Informed Consent updated. 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.*	Possibly not. 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.
Sponsor	Visit date deviation. *A common deviation in clinical trials.*	No. Minor protocol deviation, which does not meet the criteria for notification.
Contractor	Investigator failed to report a single SAE as defined in the protocol (re-training provided).	No, if it did not result in this or 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 should be provided for the impact to be assessed.
Identified during inspection prior to the current requirement to report serious breaches	Investigator site failed to reduce or stop trial medication, in response to certain laboratory parameters, as required by the protocol. This occurred with several patients over a one year period, despite identification by the monitor of the first two occasions. Patients were put at increased risk of thrombosis.	Yes, under the current requirements, this should have been reported as a serious breach.
Sponsor	Becomes aware of fraud at investigator site in the UK, which does not affect the overall scientific value of the Sponsor's trial or the integrity of trial subjects in the UK. However, the Sponsor is aware that the fraudster was involved in trials being sponsored by other organisations.	Although, in this situation, not a legal requirement under 29A, MHRA encourages voluntary reporting of all fraud cases in the UK, because MHRA will wish to establish the impact on the other trials in case subject integrity or the scientific value of those trials was compromised.

6 Amendment History

Version Number:	3.1
Date Of Amendment:	Jan 2019
Details Of Amendment:	Updated Trust and Dept. name; Reduce signature requirement to single senior RD&I Manager.

Version Number:	3.0
Date Of Amendment:	Aug 2017
Details Of Amendment:	Updated SOP template and numbering system. Reviewed and updated SOP.

Version Number:	2.1 (minor amendment)
Date Of Amendment:	Mar 2012
Details Of Amendment:	Cover page - Change of SOP location address.

Version Number:	2.0
Date Of Amendment:	02 December 2009
Details Of Amendment:	Page 3; Definitions updated.