NHS
Royal Papworth Hospital
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Document Title: Handling of Protocol Non-Compliance

Document Number: PTUC SOP050

Staff involved in development: *Job titles only*	Senior R&D Manager, R&D Operational Manager, Clinical Project Managers
Document author/owner:	Senior R&D Manager
Directorate:	Research and Development
Department:	Research and Development
For use by:	NHS Staff Trust-Wide
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Summary of Significant Change(s) (for this version only)

Section(s):	Modification:
	Administrative changes throughout the document.

Key Points of this Document

- This document sets out the procedures to be followed by all Staff who are involved in research in identifying, recording and reporting cases of non-compliance from the trial protocol, Standard Operating Procedures or regulatory requirements.

1 Purpose and Content

a. This document defines the Trust's procedures for determining the nature and extent of non-compliance in Research Studies and Clinical Trials of Investigational Medicinal Products (IMPs) or non-CE marked devices managed by Royal Papworth Trials Unit Collaboration (PTUC) or sponsored by Royal Papworth NHS Foundation Trust.

b. The document states the procedures to be followed to protect patients, maintain the integrity of the trial and comply with legal and Good Clinical Practice guidelines (GCP: 'a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected').

c. The appropriate documentation, assessment and reporting procedures that should be used are specified in section 4.

d. The management of serious breaches of protocol or GCP in CTIMPs is outside the scope of this SOP and is described in SOP051: Serious Breach of Protocol or GCP in CTIMPs and non-CE marked device studies.

2 Roles & Responsibilities

a. This Policy applies to all personnel who are conducting research at the Trust.

b. Staff working on research studies must comply with the requirements set out in section 5.

c. The Chief or Principal Investigator must ensure that they, and their study staff, comply with the requirements set out in section 4.

3 Policy

a. This SOP is mandatory and, as per the Trust's Information Governance and Records Management policies, non-compliance with may result in disciplinary procedures.

4 Definitions

a. Minor protocol non-compliance

A protocol deviation or non-compliance is any deviation from the protocol, study or sponsor procedures that is not approved by the Sponsor/REC/MHRA prior to its implementation. A minor deviation/non-compliance is one that does not impact on the subjects' safety or compromise the integrity of study data. However if left unreported could lead to more major deviations /non-compliance issues further down the line.

b. Major protocol non-compliance

A major deviation/non-compliance is one that may impact on the participant safety or affects the integrity of the study data. Major protocol deviations /non-compliances for studies should be reported by the Principal Investigator (or Chief Investigator for study level non-compliances) using the Protocol Non-Compliance Form (FRM038). The form should be submitted to the Sponsor and copied to the Chief Investigator (if completed by the PI rather than the CI) within 24 hours of becoming aware of the deviation so that the appropriate action and investigation can take place in a timely manner. Reported major deviations require prompt initial assessment by Royal Papworth/Chief Investigator to confirm that the deviation does not constitute:
An Urgent Safety Measure -a measure that has been implemented without prior authorisation by the REC (and MHRA where applicable) in order to protect clinical trial participants from any immediate hazard to their health and safety
OR
a serious breach which would require further investigation and escalated reporting.

c. Serious Breach

A 'serious breach' is defined as a breach **likely** to effect to a significant degree:
the safety or physical or mental integrity of the subjects of the trial; or
the scientific value of the trial

For clinical trials, the requirements for reporting serious breaches should be documented in the protocol and investigator sites should be made aware of their role in reporting (and how to report) at site initiation.

Making a judgment on whether a non-compliance (or persistent non-compliance) is a 'serious breach' and requires reporting as such, is the responsibility of the Sponsor.

If the Sponsor fails to discharge their responsibilities for CTIMPs in reporting serious breaches within the regulatory timeframes it is a criminal offence.

5 Procedure

a. Handling the episode of non-compliance

1. When non-compliance is suspected, further information should be gathered detailing the nature and extent of the episode. Suspected non-compliance can be identified by anyone involved in the conduct, management or monitoring of the trial.

b. The following must then be completed:

1. Complete FRM038: Protocol Non-Compliance Form (http://www.papworthhospital.nhs.uk/research/index/template-documents/)
2. Record full details of the episode and any corrective action that was taken
3. Gather and add any additional comments or explanatory notes as appropriate in collaboration with the CI and Trial Manager
4. The episode of non-compliance should be assessed by the CI or PI and categorised as either a protocol deviation or a serious breach. Sufficient justification must be given for the categorisation.
5. ***If the episode is identified as a Serious Breach the procedures outlined in SOP051: Serious Breach of Protocol or GCP in CTIMPs and non-CE marked device studies should be followed***.
6. The completed NCF(FRM038) must be signed by the CI/PI or delegated to a Sponsor representative. Where there is doubt or dispute as to the category of the episode, the Clinical Director of R&D or their delegated officer will advise
7. The FRM038 should be circulated to the Royal Papworth Hospital R&D QA meeting (mailto:papworth.randdadmin@nhs.net) where it will be reviewed and any necessary corrective actions communicated back to the team.
8. The FRM038 should be circulated to the study project team meeting for Investigator oversight (this will be minuted).

c. Any urgent safety measures that are deemed necessary must be applied according to guidelines and fully documented.

d. The FRM038 must be filed in the TMF, a copy within the relevant patient's CRF and, if applicable, at the Investigator site and at the Sponsor's site.

e. Follow-up of non-compliance

f. The episode should be evaluated to identify any underlying problems; especially if there have been other episodes of a similar nature.

g. Consideration of the need for further training on trial procedures at the site where the episode occurred should be made.

h. Recurring episodes of non-compliance may necessitate an amendment to the protocol.

i. Repeated protocol deviations can accumulate into a serious breach which, once identified, should be reported to the Senior R&D Management team within 24 hours.

j. All FRM038s should be periodically reviewed by the CI and appropriate actions taken to address the causes.

k. Trial Management Groups must be made aware of episodes of non-compliance as they may use this information when considering amendments to the protocol.

l. All episodes of non-compliance should be evaluated, accounted for and considered in the final Study report.

6 Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Investigator and Sponsor Master File.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Further Document Information

Approved by: *Management/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	[Current active version approved date]
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Policy Framework for Health and Social Care Research
Key related documents:	Trust Research Policy SOP051: Serious Breach of Protocol or GCP in CTIMPs and non-CE marked device studies

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	NO	NO	NO	NO	NO	NO	NO
Positive/Negative							

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Version Control

Version	Date effective	Valid to	Approved by	Date of approval
1.0	1 August 2012	June 2014	RDD	13 July 2012
2.0			Dr Ian Smith on behalf of RDD	
3.0				
4.0				

I certify the contents of this SOP has been reviewed and ratified

..... 5th July 2019

Signed by Dr Ian Smith, Clinical Director of R&D — Date

Release Date: 22nd July 2019