Document Title: Serious Breach of Protocol or GCP in CTIMPs and Non-CE Marked Devices

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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
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Summary of Significant Change(s) (for this version only)

Section(s):	Modification:
	Minor administrative changes

Key Points of this Document

- This document sets out the procedures to be followed by all Royal Papworth Staff who are involved in Clinical Trials of Medicinal Products (CTIMPs) and non-CE marked Medical Devices.

- It provides guidance on how serious breaches of the trial protocol must be identified and managed.
- The procedures to be followed to ensure compliance with Regulation 29A of the UK Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004/1031) as amended by Statutory Instrument 2006/1928, are fully detailed.

1 Purpose and Content

a. This document defines the Trust's procedures for determining and managing serious breaches in Clinical Trials of Medicinal Products (CTIMPs) or trials of non-CE marked devices managed by Royal Papworth Trials Unit Collaboration and /or sponsored or hosted by Royal Papworth Hospital.

b. The document states the procedures to be followed to protect patients, maintain the integrity of the trial and comply with legal requirements 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 assessment and reporting procedures that must be followed are specified in section 4.

d. The management of other breaches of protocol or GCP in CTIMPs or other types of studies is outside the scope of this SOP and is described in SOP050: Handling of Protocol Non-Compliance and Regulatory Non-Compliance.

2 Roles & Responsibilities

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

b. Staff involved in Serious Breaches must consult the MHRA web pages (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/404588/GCP_serious_breaches_guide.pdfon Serious Breaches in conjunction with this SOP to ensure that the most up-to-date guidance is followed.

c. Information regarding possible serious breaches should be treated as confidential. Details and ensuing investigations will be made available to staff on a need to know basis. All

individuals interviewed during the investigation will be asked to respect this confidentiality.

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 Procedure

4.1 Definition of a Serious Breach

a. A breach of the protocol or the conditions and principles of GCP is defined as serious if it significantly affects the safety, physical or mental integrity of the trial subjects or the scientific validity of the trial.

b. The flow diagram in Appendix 1 should be used to aid the reporting process of a Serious Breach.

4.2 Examples of Serious Breaches

a. Fraud relating to clinical trial records or data.

b. Persistent or systematic non-compliance with GCP or the protocol that has a significant impact on the integrity of the trial subjects or the scientific value of the trial.

c. Failure to control the investigational medicinal products (IMPs) such that the trial subjects or members of the public are put at significant risk, or that the scientific value of the trial is compromised.

d. Failure to report adverse events, serious adverse events or suspected unexpected serious adverse reactions (SUSARs) in accordance with the legislation, thereby putting the trial subjects or the public at significant risk.

e. A table of examples published by the MHRA is given in Appendix 2.

4.3 Identification of a Serious Breach

a. Breaches may be identified by anyone involved in the conduct, management or monitoring of the trial. Members of the study team may also receive allegations of serious breaches directly or indirectly from whistleblowers or complainants from within or outside Royal Papworth Hospital.

b. Information received in written form must be retained. Where communication is verbal, the person receiving the information should generate a written record. This documentation should be stored in the Trial Master File and Investigator Site File.

c. The flow chart in Appendix 1 shows the process of identifying and reporting serious breaches.

d. The possible breach should be recorded on the protocol deviation log and discussed with the CI/PI within 24 hours of identification of the event. If the CI/PI is unavailable within this time period the possible breach must be discussed with an R&D Senior Manager.

4.4 Assessment, characterisation and follow-up

Once information on a possible breach has been received the following procedure will be followed:

a. The study team should review the guidance from the MHRA website in order to make an assessment of whether the event constitutes a serious breach. Guidance can be sought from an R&D Senior Manager. Information regarding the breach will need to be collated at this stage. This initial review must be undertaken within 24 hours of the incident being identified and reported.

b. If it is thought that there is a possibility that the incident constitutes a serious breach the CI/PI must inform the R&D Department at Royal Papworth Hospital immediately. If Royal Papworth Hospital are not the sponsors, the sponsor must also be informed at the same time.

c. The notification can be by e-mail to an R&D Senior Manager or in person and must be followed up with a phone call to R&D (01223 639708 or 01223 639709) to confirm the report has been received. The initial report must detail the following:

   1. The details of the Trial
   2. Name of the CI, PI and site
   3. How the breach was identified
   4. Details of the breach

d. R&D personnel who receive notification of the breach should immediately notify the Clinical Director of R&D, or their delegated person who will nominate an investigating officer. If Royal Papworth is not the trial sponsor the investigating officer must ensure the sponsor has been informed of the suspected breach.

e. Following on from this initial report a full investigation must be completed by the nominated investigating officer in conjunction with the study team. The reporting deadline for the MHRA must be followed during this review. The investigating officer will:

1. Discuss the episode with relevant research staff to confirm the full nature of the breach.
2. Gather further information and supporting evidence. This should include: assessment of the impact of the breach, review of documentation and systems to assess possible cause or systematic failures.
3. Create a corrective actions plan / including details of any corrective action which has been undertaken.
4. Assess in collaboration with the CI / PI whether any Urgent Safety Measures are required.
5. The review of the associated documentation and the final decision must be signed and dated, and stored within the relevant Trial Master File.
6. For Royal Papworth Sponsored studies: If the breach is not classed as serious following the investigation SOP050: Handling of Protocol Non-Compliance and Regulatory Non-Compliance must be followed.

f. For Royal Papworth Sponsored Studies only:

1. Following initial notification, the sponsors have 7 days to notify the MHRA. If there is clear and unequivocal evidence that a serious breach has occurred the Clinical Director of R&D, or their delegated person will notify the MHRA and investigate and take action simultaneously or after notification. Additional details can be provided to the MHRA after notification.
2. If there is not clear and unequivocal evidence, then further investigation and assessment may be required prior to notification of the MHRA. In this case the MHRA GCP Inspectorate must be contacted to seek advice.

4.5 Notification of a Serious Breach to the MHRA

a. Initial notification can be by telephone, followed by written notification within 7 days of being aware of the breach. Further information on reporting a breach to the MHRA can be found on their website http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con060111.pdf.

b. A Sponsor representative from within the R&D Department will complete the Notification of a Serious Breach Form that can be obtained from the MHRA website (http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/SeriousBreachesReporting/index.htm)

c. The form should be sent by e-mail to the MHRA in accordance with the latest instructions on their website (**GCP.SeriousBreaches@mhra.gsi.gov.uk)**

d. If the MHRA require any further information, this should be provided by R&D or the CI as and when requested.

e. Any corrective and preventative measures that are necessary must be implemented as appropriate. Any Urgent Safety Measures that have been taken should be notified to the MHRA and REC within 3 days of the action that has been taken.

f. All correspondence and documentation that relates to the breach must be retained and copies filed in the Trial Master File and Investigator Site File.

g. Where Royal Papworth is not the sponsor, then study staff will assist the sponsor in all of the above if required. A copy of any documentation sent to, or received from, the sponsor concerning the breach, must be stored in the Investigator file.

5 Risk Management / Liability / Monitoring & Audit

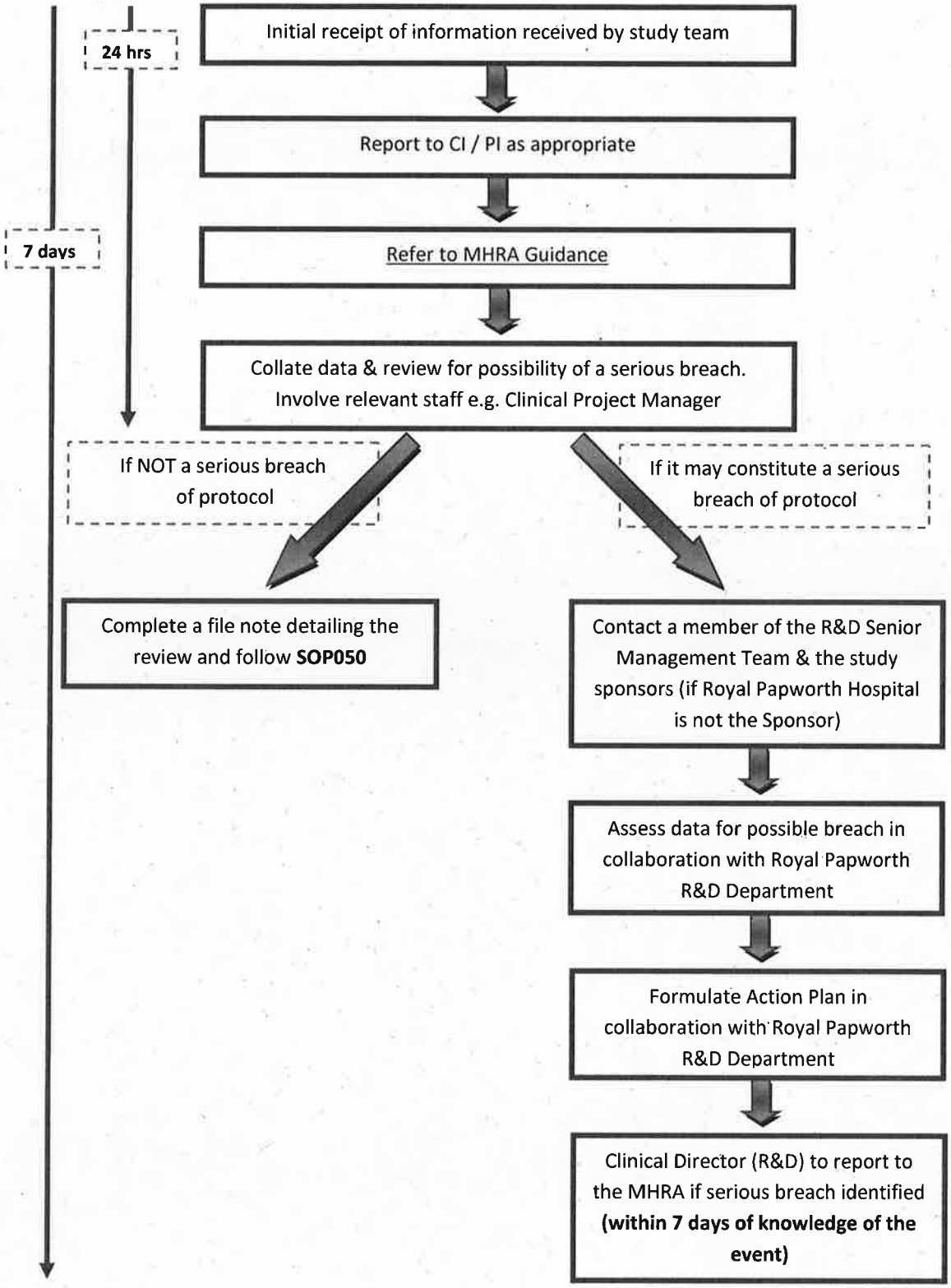
a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

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.

Appendix 1 Serious Breach of Protocol Flow Diagram



Appendix 2 Examples of Serious Breaches Notified to MHRA (this is not an exhaustive list)

The following has been lifted from the MHRA Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol Version 5 (060114).docx (Final 060114) document following permission granted by 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 connect 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 day ago. The	**No,** there was no impact on the safety or physical or mental integrity

	subject did not experience any adverse events and this issue was not likely to affect the data credibility of the trial.	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	**Yes** *Note: not all of the information was provided in the original*

	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.	*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 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.
Indentified 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 be 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**

Further Document Information

Approved by: *Management/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	Current approved version 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 SOP050: Handling of Protocol Non-Compliance and Regulatory Non-Compliance

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	26 September 2014	April 2017	Dr Ian Smith	15 August 2014
3.0				
4.0				

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

..... 9th April 2019

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

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