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<h1>Notification of Serious Breaches of GCP or the Trial Protocol</h1>	
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1. PURPOSE

This SOP describes the process for notification of serious breaches of GCP or the approved trial protocol. This SOP also outlines the processes taken at the RGIT to assess and report a serious breach of a clinical trial which is sponsored by Imperial College or Imperial College Healthcare Trust to the MHRA.

2. INTRODUCTION

The EU GCP Directive 2005/28/EC was transposed into UK law as the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 and regulates in tandem with the Medicines for Human Use (Clinical Trials) Regulations 2004.

Under the amendment it is a requirement that serious breaches of GCP or the trial protocol are reported to the Medicines and Healthcare products Regulatory Agency (MHRA). The amended regulations state:

- “29A.** 1. 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 regulations 22 to 25, within 7 days of becoming aware of that breach.
2. For the purposes of this regulation, a “serious breach” is a breach which is likely to effect 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.”

These stipulations were incorporated into regulation to:

1. Enhance the safety of trial subjects/patients by seeking to ensure that the licensing authority is promptly informed of such serious breaches, in order to take appropriate action in response to the breach and/or,
2. To take the information regarding serious breaches into account when assessing future applications for clinical trial authorisation, and applications for marketing authorisation, which include data from trials affected by serious breaches.

It is the responsibility of the trial sponsor or a person legally authorised by the sponsor to carry out the notification procedure within 7 days of becoming aware of the breach. This responsibility can be delegated by the sponsor.

Deviations from clinical trial protocols and GCP occur commonly in clinical trials. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. These cases should be documented as per RGIT_SOP_037 Management of protocol deviations,

violations and urgent safety measures. In addition, these deviations should be included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data. However, not every deviation from the protocol needs to be reported to the MHRA as a serious breach.

The MHRA define a serious breach as:

- Any serious breach of:
 - (a) the conditions and principles of good clinical practice in connection with that trial (as defined in UK legislation); or
 - (b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25.
- For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:
 - (a) the safety or physical or mental integrity of the subjects of the trial (*this should be relevant to trial subjects in the UK*); or
 - (b) the scientific value of the trial.

The judgement 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 the impact of the breach on the scientific value of the trial. Anyone who is unsure whether a breach has occurred can contact a Clinical Trial Manager and/or Research Governance Manager to discuss the situation and clarify whether a breach is classed as serious (examples of possible serious breaches can be found in appendix 2).

3. PROCEDURE

The procedure for notification of serious breaches of GCP or the trial protocol can be divided in to 5 key areas:

1. Identifying and notifying the Sponsor of a serious breach
2. Assessment of a serious breach
3. Initial notification to the MHRA
4. Provision of additional information to the MHRA
5. Planning and Implementing corrective action and preventative action (CAPA)

3.1. Identifying and Notifying Sponsor of a Serious Breach

It is the responsibility of the Chief Investigator and Principal Investigator(s) to continually monitor the conduct of the clinical trial; this may be delegated to a suitably qualified or experienced member of the research team or sub-contracted to an appropriately qualified party. In addition, RGIT may audit the trial as part of their Quality Assurance procedures. Any breaches identified either through monitoring, audit or by other means must be reported

to the RGIT Clinical Trial Manager (CTM) within 24 hours of the breach being identified and confirmed.

Initial reporting to the CTM should be carried out via telephone, email or in person, and should inform of (but not limited to):

1. Name of Chief Investigator and Principal Investigator at the site where the breach occurred.
2. Full title of the clinical trial and Sponsor reference number (Documas)
3. An explanation of how the breach was identified
4. Details of the breach
5. Details of any initial corrective actions
6. Assessment of the impact the breach will have on the trial subjects/patients and/or scientific integrity.

If the initial notification is performed via telephone, the reporting applicant should follow up with written notification of the potential serious breach. The 7 day reporting period begins on day 0 (i.e the day the sponsor is informed of the potential serious breach). If the CTM is unavailable, the initial report should be made to the RGIT generic mailbox at RGIT@imperial.ac.uk

If the incident relates to research misconduct and/or fraud, refer to RGIT_SOP_36 Research Fraud and Misconduct.

3.2. Assessment of a Serious Breach

Upon receipt of an initial breach report the CTM will discuss the issue with the Chief/Principal Investigator to identify which section of GCP or the protocol has been breached and how the breach impacts of subject/participant safety and/or the scientific integrity of the trial.

The CTM and/or RGIT Research Facilitator will meet with the Chief/Principal Investigator and the study team to discuss the breach and compile evidence to support notification to the MHRA. Any concerns should be escalated to the QA Manager and/or Head of Research Governance and Integrity.

The CTM will work with the Chief/Principal Investigator to identify the extent of the breach and to initiate any Urgent Safety Measures that may be required. For steps on urgent safety measures refer to RGIT_SOP_037 Management of protocol deviations, violations and urgent safety measures this SOP which can be found on the [SOP, Associated Documents & Templates page](#).

3.3. Initial Notification of Breach to MHRA

The CTM will collate all available information and complete the Notification of Serious Breaches of GCP or the Trial Protocol form. This form can be obtained from the [MHRA website](#)

The form will be submitted via e-mail to the MHRA within the 7-day reporting period defined in regulation. The form will be sent to:

GCP.SeriousBreaches@mhra.gov.uk

The CTM will be the contact person for all correspondence with the MHRA.

3.4. Provision of additional information to the MHRA

Once the initial notification has been submitted to the MHRA, the RGIT will review breach in full to identify the extent of the breach and the CTM will forward all new information to the MHRA.

The Chief/Principal Investigator will compile a project report for submission to the MHRA. The project report will include:

1. Full title of trial, ethics approval number, EudraCT number, version number, date of commencement
2. Name of Chief Investigator
3. List of Sites
4. Number of subjects recruited
5. Brief description of the trial
6. Summary of the breach including rationale
7. Summary of actions taken
8. Assessment of impact of breach to subject/participant safety and/or scientific integrity of trial
9. Statement from Chief Investigator (if not the person completing the report)

The CTM will review the project report and submit to the MHRA

The MHRA may request additional information such as a copy of the protocol, ethics application, SOP's etc. The CTM will liaise with the study team to obtain additional documents and submit them to the MHRA.

3.5. Planning and Implementing CAPA

The RGIT will work with the study team to devise a formal plan of CAPA to address the breach. The CAPA plan will be submitted to the MHRA on their request. In the event where MHRA has confirmed the reported breach is not classified as a serious breach, a CAPA plan should remain.

Depending on the initial assessment of seriousness and impact, the RGIT may carry out a full audit of the trial and general trial management systems and procedures.

The RGIT will keep a log of potential serious breaches within the office.

The RGIT will publish general information on the breach, in an anonymised form to educate and inform researchers about errors that can occur in the trial process and to facilitate an open environment for reporting such occurrences.

3.6. Serious breach reporting for non-CTIMPs studies

When notified of a potential serious breach, the event should be reviewed in a timely manner by the Research Governance manager (RGM). The RGM should request further information in order to assess the severity of the breach and whether it meets the serious breach definition.

If the breach is considered a serious breach, the RGM/CI should report to the research ethics committee (REC) within 7 days of becoming aware of that breach. The CI/RGM

should provide details to REC of when the breach occurred, the location, who was involved, the outcome and any information given to participants. An explanation should be given, and the REC informed what further actions will be taken to correct the issue. In the event consideration by the REC is no longer appropriate, for example where the study has closed, any reports provided may be referred to the Health Research Authority at breaches.nres@nhs.net for consideration.

If the breach is not considered a serious breach, the CI should create a CAPA plan (with the support of the RGM if required) and ensure this is implemented.

4. REFERENCES

Statutory instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004.

Statutory Instrument 2006/1928: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.

Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol, MHRA. Version 5 dated 04/05/2018

RGIT_SOP_037 Management of protocol deviations, violations and urgent safety measures

RGIT_SOP_036 Research Fraud and Misconduct.

Standard Operating Procedure for Research Ethics Committee v7.4

5. APPENDICES

Appendix 1 – MHRA Notification Examples

Notified by:	Issue:	Would MHRA have expected this case to be notified?
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>1) Yes, there was significant potential to impact the safety or physical or mental integrity of trial subjects.</p> <p>2) 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>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>3) 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>4) 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.</p>
Sponsor	<p>IMP temperature excursions reported.</p>	<p>. Yes, if the situation was not managed and subjects were dosed with IMP assessed as unstable, which resulted in harm/potential to harm subjects.</p> <p>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.</p>
Sponsor	<p>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.</p>	<p>Yes, this subsequently led to enforcement action against the organisation in question.</p>
Sponsor	<p>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.</p>	<p>Yes</p> <p>Note: not all of the information was provided in the original notification, the Sponsor provided follow-up updates.</p>

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.
Researcher	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
Researcher	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
Researcher	Early destruction of investigator site files	Yes
Researcher	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)