Notification of Serious Breaches of GCP or the Trial Protocol

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Version 3.0	08 Feb 2010	Formation of Joint Research Office
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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).

The sponsor of a clinical trial shall notify the licensing authority (MHRA in the UK) in writing of any potential 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
And within 7 days of becoming aware of that potential breach.

3. PROCEDURE

The procedure for notification of serious breaches of GCP or the trial protocol is outlined below:

1. Identifying by the study team and notifying the Sponsor of a potential serious breach

2. Assessment of the potential serious breach (against the conditions of GCP or Protocol) by the Sponsor liaising with the study team
3. Initial notification (initial report) to the MHRA within the 7 days of initially becoming aware if meets the conditions of potential serious breach
4. Confirmation of initial notification of a potential serious breach and logging by the GCP inspector who will review the initial notification.
5. Confirmation of classification (is it actual a serious breach or not) by the GCP inspector and request for additional information
6. Informing the REC as well as soon as the MHRA inspector has confirmed it is an actual serious breach
7. Provision of additional information (FU report/s) to the MHRA inspector including the planned corrective and preventative actions (CAPAs)
8. Closure of this serious breach report by the MHRA inspector subject to the agreed CAPAs Implementing the agreed CAPA by the Sponsor and study team.
9. Sponsor's auditing of the CAPA implementation plan and its effectiveness.

For detailed information kindly read
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/905577/Guidance_for_the_Notification_of_Serious_Breaches_of_GCP_or_the_Trial_Protocol_Version_6__08_Jul_2020.pdf

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). The initial report should be made to the RGIT CTIMP generic mailbox at rgit.ctimp.team.imperial.ac.uk copying the Sponsor's RGIT Clinical Trials Manager (CTM)

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 RGIT CTM with the support of other members of the CTIMP teamwill 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 RGIT 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. (*cited on 20 Mar 2023*).

3.3. Initial Notification of Breach to MHRA

The RGIT 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 (*cited on 20 Mar 2023*).

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 (as relevant), 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 (*cited 20 Mar 2023*)

Statutory Instrument 2006/1928: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (*cited 20 Mar 2023*)

Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol, MHRA. Version 6 dated 08/07/2020 (*cited 20 Mar 2023*)

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 v7.6 (*cited 20 Mar 2023*)

5. APPENDICES

Appendix 1 – MHRA expectations for Specific Serious Breach Topics

Should proof of fraud relating to clinical trial records or data be reported as a serious breach?
If the fraud is likely to have a significant impact on the integrity of trial subjects or the scientific value of the data, this will be a serious breach. Although not a legal requirement under Regulation 29A, the MHRA GCP Inspectorate encourages the reporting of all confirmed instances 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 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, for example, a CRO or other contracted organisation and not solely to investigator sites (such as laboratories analysing samples from UK patients/subjects).

Should a breach of GCP or the protocol leading to the death, hospitalisation or permanent disability of a trial subject in the UK be reported as a serious breach?
Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) resulting from a breach of the conditions and principles of GCP or a breach of the protocol, will constitute a serious breach. However, it should be noted that not every SAE or SUSAR would routinely be classified as a serious breach.
Also, 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, for example, via the EudraVigilance database. If the breach also resulted in a *temporary /permanent halt* to the trial, a *substantial amendment* would need to be submitted to the MHRA CTU and a further amendment approved to re-start the trial.

Should a failure to report adverse events, serious adverse events or SUSARs in accordance with the legislation be reported as a serious breach?
If this failure results in trial subjects, or the public, in the UK being put at significant risk, then this will constitute a serious breach, for example, inadequate safety reporting in dose escalation studies may impact on the decision to escalate to the next dose level.

Should persistent or systematic non-compliance with GCP or the protocol be reported as a serious breach?
If this non-compliance has a significant impact on the integrity of trial subjects in the UK or on the scientific value of the trial, this will constitute a serious breach. 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 an investigator repeatedly failing to reduce or stop the dose of an IMP in response to a trigger defined in the protocol (for example, abnormal laboratory results).

Should a failure to control investigational medicinal product(s) be reported as a serious breach?
This will constitute a serious breach if the failure results in trial subjects or the public, in the UK being put at significant risk or the scientific value of the trial being 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.

For trials that are on-going in the UK, should serious breaches that occur at *non-UK sites* be reported?
If a serious breach is identified at an investigator site outside the UK that has a significant impact on the integrity of trial subjects at that non-UK site and is likely to have a significant impact on the integrity of trial subjects in the UK, then this will require notification to the MHRA. For example:

• The cause of the breach may be such that the breach may occur at other trial sites, e.g. death of a subject due to incorrect administration of IMP resulting from erroneous reconstitution instructions in the protocol. It should be noted that as well as having to notify the MHRA of the serious breach, other concerned competent authorities may also need to be informed.
• In relation to the example above, an urgent safety measure (USM) may need to be implemented to address the cause of the breach. If, in order to address the cause of a serious breach, an USM is implemented at UK sites, to amend the conduct of the trial or suspend the trial, the USM notification should be sent by the Sponsor to the MHRA Clinical Trials Unit within 3 days of identifying the measures to be taken (in accordance with Regulation 30), in addition to the serious breach notification to the MHRA Inspectorate.
• If a serious breach is identified at an investigator site outside the UK, which is likely to affect to a significant degree the overall scientific value of the trial and the result will impact on UK patients or the UK public (for example, data will be used in a marketing authorisation application that affects the UK), then this breach should be notified to the MHRA (other concerned competent authorities may also need to be informed).

Appendix 2 – MHRA Notification Examples

Notified by:	Issue:	Would MHRA have expected this case to be notified?
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).	1) Yes, there was significant potential to impact the safety or physical or mental integrity of trial subjects. 2) Yes, • there was impact on the safety or physical or mental integrity of trial subjects or on the scientific value of the trial

	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. 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. 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.	• 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) Yes, there was impact on the safety or physical or mental integrity of trial subjects and on the scientific value of the trial 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.
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	Yes, this subsequently led to enforcement action against the organisation in question.

	not unequivocal evidence of fraud at the time of reporting. One of the studies involved paediatric subjects.	
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.	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.
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

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**
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)
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