RD SOP 09 Notification of a Serious Breach of GCP or the Clinical Trial Protocol

Greater Manchester Mental Health NHS Foundation Trust
Title of Standard Operating Procedure: RD SOP 09 Notification of a Serious Breach of GCP or the Clinical Trial Protocol

Document Summary: This standard operating procedure (SOP) describes the procedure for reporting and management of serious breaches to study protocol and/or Good Clinical Practice (GCP) in clinical trials of investigational medicinal product (CTIMP) and other research studies.

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Head of R & I

Target Audience: Trust-wide, Research Community, Internal and External Researchers

Consultation: R & I Office, research community and R & I Committee members

Approval Committee: R & I Committee

Cross Reference Document(s): Research Approval Policy All Trust R & I SOPs

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1. Introduction

The Medicines for Human Use (Clinical Trials) Regulations (2004 [Statutory Instrument 2004/1031]) and subsequent amendment (2006 [Statutory Instrument 2006/1928]), require that serious breaches of Good Clinical Practice (GCP) or the clinical trial protocol are notified to the licensing authority. In the UK, this is the Medicines and Healthcare Products Regulatory Agency (MHRA). Regulation 29A of the Regulations states: “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.

For the purpose 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.”

The Department of Health UK Policy Framework for Health and Social Care Research (updated March 2018) requires that the principles of Good Clinical Practice (GCP) are applied to all NHS research involving patients and that the safety of research participants is given priority at all times.

2. Purpose

This document describes the process for identifying and reporting a serious breach of GCP or the approved clinical trial protocol to the R & I Office, Sponsor, HRA/REC and the MHRA.

3. Roles and Responsibilities

3.1 Duties within the organisation

It is the responsibility of the Research Governance co-ordinator (or proxy) to make Trust R & I SOPs available to all research active staff working on Trust-approved research studies.

It is the responsibility of the study Chief Investigator (CI) or local Principal Investigator (PI) to ensure that up-to-date copies of Trust R & I SOPs are available to research staff.
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It is the responsibility of the study Chief Investigator or local Principal Investigator to inform the Research Governance Co-ordinator of the names of all research staff involved on a study so that copies of SOPs can be distributed appropriately.

It is the responsibility of the study Chief Investigator or Principal Investigator to designate if the SOPs of another organisation are to be followed for a study. For example those of a Clinical Research Network or commercial sponsor. If there is significant conflict between the external SOP and the Trust R & I SOP it is the responsibility of the CI or PI to resolve these with the Research Office prior to starting the study.

It is the personal responsibility of all staff to follow Trust (or the designated alternative organisations) procedural documents.

3.2 Specific to this SOP

It is the responsibility of the Sponsor, or a person legally authorised by the Sponsor, if this function has been delegated by the Sponsor to another party, to notify the MHRA within 7 days of becoming aware of the breach.

In accordance with Statutory Instrument 2004/1031 as amended by Statutory Instrument 2006/1928, the Sponsor retains legal responsibility even if the function is delegated.

For Trust hosted trials and other studies, it is the responsibility of the PI and the research team to report any issues and incidents to R & I office as soon as possible.

4. Procedure

4.1 Identifying Serious Breaches

Deviations from clinical trial protocols and GCP can occur in clinical trials. The majority of these instances are technical deviations or errors 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 discussed with the PI and documented in the Case Report Form (CRF) for the trial and in the Trial Master File, to facilitate appropriate corrective and preventative actions to be taken.

These deviations should be included and considered when the clinical study report is produced, as cumulatively they may have an impact on the analysis of the data. However, not every deviation from the protocol needs to be reported to the HRA and MHRA and as a serious breach. R & I Office should always be made aware of deviations to help monitor and oversee the delivery of research at the Trust.

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, 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 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, for example 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, or the impact of excluding the data from the analysis. It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial.

The above definition of a serious breach is applicable to all types of clinical research studies run at the Trust.

4.2 Who needs to be notified of a serious Breach?

All research run at the Trust (either sponsored or hosted by GMMH) is subject to the Trust Confirmation of Capacity and Capability Approval. Any breaches/ incidents/ near misses have to be reported to the R & I Office to ensure R & I oversight.

Studies which do not involve an investigational medicinal product are subject to HRA/REC Approvals. Therefore any breaches should be notified by the Sponsor to REC which issued favourable opinion for the study.

Clinical trials involving investigational medicinal product are subject to MHRA approval in addition to HRA/REC Approvals. Therefore any breaches on those types of trials have to be reported by the Sponsor to MHRA licencing authority.

4.3 Notifying the CI/PI, R & I and the Sponsor of a serious breach

It is expected that all events are notified by a member of the study team with no delay and in parallel: a/ to R & I and b/ to the study CI (for sponsored studies) or to PI (for hosted studies). This is to ensure prompt clinical follow up on any potential safety issues. Person reporting the event will also have to submit a DATIX report.

All breaches must be reported to the study Sponsor within 24 hours of the breach being identified. If a potential serious breach is identified during a monitoring visit by the Trust R & I Office, or the R & I Office is alerted of a potential serious breach, the Sponsor organisation will be notified as soon as possible by a member of the R & I Office team.

A potential serious breach occurring in a trial sponsored or hosted by the Trust should be reported to the R & I office (by telephone – 0161 358 1659 and by email – email
address: researchoffice@gmmh.nhs.uk) who will assess the incident. The initial report should contain the name of the Principal Investigator, the full title of the study and the R & I Office Project Identification Number, details of the potential serious breach and any details of any corrective actions implemented.

Any breach in a sponsored or hosted study should also be reported on Datix by clinical teams. In case of any technical difficulties R & I office will take details of the incident and report on DATIX on the clinical team behalf. When creating DATIX report, event should be classed as ‘research related’ to ensure accurate escalation and review. For reporting pathways and form refer to intranet guidance: https://newintranet/IMandT/SystemsTeam/Documents/D/Datix/DIF1%20Incident%20Reporting%20Pathway.pdf

Researchers should retain details of the serious breach and notification to the sponsor within the trial site file so that an audit trail is available.

4.4 Notifying the MHRA

Notification to the MHRA GCP Inspectorate should be made within 7 days of the Sponsor becoming aware of the breach. If the Sponsor has clear and unequivocal evidence that a serious breach has occurred (as defined in Regulations), the default position is for the Sponsor to notify the MHRA first, within 7 days, and investigate and take action simultaneously, or after notification. A template form for notifications of serious breaches to the MHRA is available from the R & I Office or from the MHRA website: https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

The Sponsor may initially contact the MHRA Inspectorate by telephone to discuss the breach and follow up with written notification within 7 days of the Sponsor becoming aware of the breach.

In other cases, some degree of investigation and assessment may be required by the Sponsor prior to notifying the MHRA in order to confirm that a serious breach has actually occurred.

4.5 Notifying the Health Research Authority (HRA)

In the case of a CTIMP, the sponsor is required to notify the HRA of a serious breach within 7 days in parallel with MHRA reporting. The report form prescribed on the MHRA website should be used and a copy should be provided to the trial REC.

In case of other research reports of serious breaches should give details 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 action the sponsor plans to take.
In circumstances where 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 (breaches.nres@nhs.net) for consideration.

### 4.6 Corrective and Preventative Action Plan (CAPA)

The Sponsor organisation and the Investigator team will produce a formal plan of action to address the breach. This will be submitted to the MHRA on request. For hosted trials, where identified issue stems from Trust local practices, relates to Trust/vendor facilities or is a direct result of a failure in study management locally, R & I Office will lead on CAPA management and communications with the Sponsor. R & I will oversee event management to support the PI and the research team.

### 4.7 Potential actions by the MHRA

Upon receipt of a serious breach notification, the MHRA will log and review the notification, and a variety of actions may be taken, depending on the nature of the breach and its potential impact:

- Acknowledgement of receipt, but no immediate action, for instance if appropriate action has been already taken by the Sponsor. (The case may be examined during future MHRA inspections).
- Request for additional information and investigation by the Sponsor. If insufficient information is provided in the initial notification to assess the impact of the breach, follow-up information will be requested.
- Sharing of information with other concerned parties, in accordance with the regulations and applicable agreements, for example to the relevant ethics committees, other competent authorities, MHRA Clinical Trials Unit.
- Investigation by the MHRA, for example, triggered inspection(s).
- Implementation of urgent safety measures, where appropriate.
- Suspension or termination of a clinical trial authorisation, where appropriate.
- Referral for enforcement action, for instance infringement notices, criminal investigation.
- Referral to professional bodies, for example the General Medical Council.
5. References and Bibliography


UK Policy Framework for Health and Social Care Research v3.3 07/11/17  

MHRA guidance on reporting serious breaches:  
https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

HRA/REC guidance on reporting serious breaches (section 10.72 GAfREC):  

6 Associated Trust Documents

- RDSOP 15 - Writing a GCP Compliant Protocol for CTIMP’s
- RDSOP 16 - Preparing a GCP-compliant protocol – non-CTIMP’s

DATIX reporting pathways  