SOP number	**51.009**	Version	**5.0**
Title	**Notification of serious breaches of Good Clinical Practice or the trial protocol for clinical trials of investigational medicinal products**		

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Approved by Signature	Chloë Cowan Date
Released by Signature	Chloë Cowan Date

SOP category	NHS GG&C Sponsor R&I
Staff category	

Staff Category	**R**	**A**	**C**	**I**
Research Governance Manager		X		
Lead Pharmacist Clinical Trials R&I	X			
Sponsor Pharmacy	X			
Research Governance Team	X			
Glasgow University Research Governance Team	X			
All R&I Staff				X
Chief Investigators (NHSGGC Sponsored and co-sponsored trials)			X	
Principal Investigators			X	

1. Scope

This procedure applies to all Clinical Trials of Investigational Medicinal Products (CTIMPs) Sponsored/Co-Sponsored and hosted by NHS Greater Glasgow and Clyde (NHSGGC) and staff involved in this activity.

2. Purpose

The purpose of this SOP is to describe the process for identifying, documenting and reporting serious breaches of Good Clinical Practice (GCP) or the trial protocol to the Medicine and Healthcare products Regulatory Agency (MHRA) in compliance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004/1031) and as amended.

3. Procedures

3.1. Definition of Serious Breach

It is a legal requirement in the UK (Regulation 29A of SI 2004/1031) for the sponsor of a clinical trial of an investigational medicinal product to report to the Medicines and Healthcare products Regulatory Agency within 7 days of becoming aware of any serious breach of:

a) The conditions and principles of good clinical practice as defined in the UK legislation in connection with that study; or
b) The protocol relating to that study, as amended from time to time in accordance with regulations 22 and 25

For the purposes of this regulation, a "serious breach" is a breach that is likely to affect to a significant degree:

i. The safety or physical or mental integrity of the subjects of the trial; or
ii. The scientific value of the trial

In order to meet the definition of a Serious Breach, one of the above criteria (a or b) must be fulfilled. The event in question must then also be serious through virtue of negatively impacting the safety, physical or mental integrity of participants of a trial or the scientific value of the trial itself (i or ii).

3.1.1. Determining if a Breach has occurred

The determination of whether or not a breach of factors (a) or (b) mentioned in 3.1 is generally a straight forward matter as there are a number of conditions against which the suspected non-compliance can be compared. By reviewing the incident in comparison to both the protocol and the principles of GCP a decision can be made as to whether either have been breached.

3.1.2. Determining Impact of Breach

The judgement on whether a breach has a significant impact on the factors outlined in i or ii can be addressed by reviewing the MHRA guidance document:

https://assets.publishing.service.gov.uk/media/5f22f594e90e071a603d33f4/Guidance_for_the_Notification_of_Serious_Breaches_of_GCP_or_the_Trial_Protocol_Version_6__08_Jul_2020.pdf

- Safety of Trial Subject
  If it is the determination that the safety of a trial subject has been impacted or is at risk of being impacted then this would be sufficient for a breach to be classed as serious. By its nature, this does not require that the patient has been harmed, but that they were put at risk of harm.
- Mental or Physical Integrity of Trial Subject
  This covers both the physical and mental well-being of a patient. Example of physical impacts include physical injury, administered incorrect IMP or incorrect dose which could be viewed as harmful. In addition, the mental aspect must be considered - eg, has anything been done which could cause the patient concern or worry? Have they been given incorrect information? Have they been given cause to be worried for their safety or privacy?
- The scientific value of the trial
  The judgment on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors, i.e. the trial design, the phase 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.

3.1.3. Examples of a serious breach:

Below are some examples of Serious Breaches, this list is not exhaustive:

- Proof of fraud relating to clinical trial records or data if the fraud is likely to have a significant impact on the integrity of the trial subjects or the scientific value of the data
- A breach of GCP or the protocol leading to the death, hospitalisation or permanent disability of a trial subject in the UK
- Failure to report adverse events, serious adverse events or SUSARS in accordance with the UK legislation such that the trial subjects or the public are put at significant risk
- Persistent or systematic non-compliance with GCP or the trial protocol that has a significant impact on the integrity of trial subjects or on the scientific value of the trial

Further examples and information on Serious Breaches can be found on the MHRA's website and in the following blog: GCP Serious Breaches - the 2018 Edition - MHRA Inspectorate (blog.gov.uk)

3.2. Identifying and reporting Serious Breaches

Any employee with concerns over the conduct or quality of a clinical trial must report these concerns immediately, they may report them through any appropriate means which result in the information being delivered to any of the following as soon as possible:

- Research Governance Manager
- Lead Clinical Trials/R&I Pharmacist

Note: All concerns relating to safety and quality will be managed by the Lead Pharmacist Clinical Trials/R&I and/or Research Governance Manager for further assessment and reporting, where appropriate.

3.3. Trials Sponsored or Co-Sponsored by NHSGGC

Any issues with regard to patient safety, conduct of the trial or quality must immediately be escalated to R&I for resolution. The Research Governance Manager and/or the Lead Clinical Trials/R&I Pharmacist are responsible for overseeing the assessment and follow-up process for the information that is received.

Any issues escalated to R&I for resolution will be logged on Q-Pulse in line with SOP 51.008. If required, NHSGGC may need to perform some degree of investigation and assessment in order to confirm that a serious breach is likely to have occurred.

If a serious breach is a possible or likely outcome, the Research Governance Manager and/or the Lead Clinical Trials/R&I Pharmacist shall facilitate a systematic evaluation of the issue with a Breach Assessment Group (BAG). The determination of who will lead on the issue is assessed by the nature of the issue, if the breach relates to an issue with IMP or a laboratory then the Lead Pharmacist Clinical Trials/R&I will lead. For all other issues the Research Governance Manager will lead. On occasion another Senior R&I member of staff or nominated Governance or Pharmacist may lead under the direction of any of those listed in 3.2, such as:

- R&I QA Manager
- Sponsor Pharmacist
- Lead Monitor
- PV Manager

3.3.1. Breach Assessment Group (BAG)

A breach assessment group is formed at the earliest opportunity but within the 7 day Regulatory timeline to ensure reporting to the MHRA, if required. The clock for the 7 day timeline starts when the Sponsor becomes aware of the existence of a potential Serious Breach. A BAG is not formed for all escalated non-compliances, it is only those which are deemed likely or possible to result in a Serious Breach by the Lead Pharmacist Clinical Trials/R&I and/or Research Governance Manager through their initial review. The intention of the group is to review the evidence provided by the Lead Pharmacist Clinical Trials/R&I or Research Governance Manager and to confirm the decision if a Serious Breach is likely to have occurred. Further investigation by the relevant lead may be required prior to and following the formation of the BAG. This can involve contacting the PI/CI, site, monitors, project managers (as team representative and not Sponsor) , pharmacy teams, data management centre, laboratory or external organisation for information relating to impact to participants and/or statisticians for impact to scientific integrity of the trial.

The BAG will be comprised of:

- the CI or PI, if appropriate, to provide additional information
- Physician(s) to represent the Sponsor(s)
- key experts, depending on the type of event, from within the Sponsor organisation(s) (**For example, monitor, pharmacovigilance , project management, data management, statistician) or external parties as required

NOTE: It is vital to form the BAG in a timely manner as the requirement to report a serious breach to the MHRA within 7 days of the Sponsor first becoming aware must be adhered to.

Not all staff members listed that work within the Sponsoring Organisation(s) will act as Sponsor Representatives, as defined in 3.3.2.1.

The BAG will be chaired by someone that is independent of the research group/CI. Evidence and expert opinion will be provided by the Research Governance Manager and/or the Lead Clinical Trials/R&I Pharmacist based on who is leading on the issue.

The assessment made by the BAG shall:

- Confirm whether the potential Serious Breach is considered likely to be a Serious Breach or not. Consensus is not required and erring on the side of caution may be required to ensure compliance to legislation – see 3.3.2.
- Identify the impacts on trial participants and/or the scientific integrity of the research.
- Determine if there is a potential systematic issue which may impact on other studies

The BAG may be in person or virtual to ensure that if a serious breach has occurred, NHSGGC will meet the deadline to notify the MHRA within 7 days of becoming aware of the potential Serious Breach. The outcome of the BAG will be recorded using Form 51.009A, this will act as the evidence of the decision of the BAG and be attached to the Non-Compliance record held in Q-Pulse. This will act as a summary and therefore minutes will not be required for the BAG given the time constraints.

3.3.2. Definition of Aware of Breach

The requirement to report a potential Serious Breach to the MHRA stipulates that this must be done within 7 calendar days of becoming aware of the breach. In the blog posted by the MHRA on their website, GCP Serious Breaches - the 2018 Edition - MHRA Inspectorate (blog.gov.uk), this is further detailed as awareness of the event in question and the Sponsor should not wait until they determine if the event is in fact a breach or not before reporting. Awareness of the event is not linked to the occurrence of the event. For example, if the event was not reported to the Sponsor until 5 days after its occurrence then the 7 day clock only starts from the moment it was reported to the Sponsor and would not include the 5 day gap. For avoidance of doubt, the Sponsor being made aware is defined as the moment in which any of the Sponsor Representatives detailed in 3.3.2.1 are made aware that the event in question has taken place. This does not cover when other NHSGGC staff are made aware as they are not considered Sponsor Representatives, not does it require for the Sponsor to have reviewed and determined that it is in fact a Serious Breach before it can be considered that they are aware.

3.3.2.1. Sponsor Representative

A Sponsor Representative is any member of staff working within the Sponsor function of NHSGG&C or Glasgow University for Co-Sponsored Trials. This includes roles such as:

- R&I Director
- R&I Senior Manager
- Research Governance Manager
- Lead Pharmacist Clinical Trials/R&I
- Sponsor Pharmacy
- PV Staff
- Monitoring Staff
- R&I QA Staff
- R&I Systems & Operations Manager
- R&I Sponsor Co-Ordinator
- Research Regulation & Compliance Manager
- Head of Research Regulation and Compliance

Notable exclusions of staff who do not act in a Sponsor role are:

- GCRF & BCRF staff
- CRUK CTU Staff
- Project Managers
- Data Centre Staff

3.3.3. Submitting a Suspected Serious Breach

The relevant lead will complete a notification of serious breach of Good Clinical Practice of the trial protocol form (available from the MHRA website) and report to the MHRA. The form must be sent to GCP.SeriousBreaches@mhra.gov.uk and to the relevant REC.

In the event that neither the Research Governance Manager nor Lead Pharmacist Clinical Trials/R&I are available to submit the form then either the R&I Director or chair of GHSP RAG will submit the form to the MHRA. The form must be quality assured by the members of the BAG to ensure that all contact details, dates and relevant information are correct prior to submission.

If a response is not obtained within two weeks then the relevant lead will contact the MHRA for an update and will continue to follow up with the MHRA until closed out by the inspector allocated.

Updates, follow up reports and new or additional information will be forwarded to the MHRA when made available and as required. This will be recorded on the notification form indicating that it is a follow up report. There is no Regulatory timeline for submitting a follow up report but this should be timely and in line with the requirements specified by the MHRA.

The internal Corrective and Preventable Action plan will be closed on Q-pulse.

3.4. Externally Sponsored Trials

If the potential serious breach relates to an externally sponsored trial, relevant management must be notified as per section 3.2. In addition, the trial Sponsor, if not already aware, must be notified of the potential serious breach immediately by the trial team, as that Sponsor has the legal responsibility for reporting the breach to the MHRA. If agreed with the Sponsor, the procedures listed in section 3.3 may be followed where appropriate. SOP 51.008 will still be followed to manage non-compliances as it relates to hosted activity while the Sponsor will carry the responsibility to report as a Serious Breach.

In exceptional circumstances, where staff deem it is not appropriate to report potential serious breach through the reporting lines defined in this SOP, they can make representation directly to the MHRA.

3.5. Logging of serious breaches on the Non-compliance register

If evidence suggests a serious breach is likely to have occurred "Escalated >Serious Breach" will be selected as the Source within the CAPA record in Q-Pulse. The CAPA record in Q-Pulse will capture the following information:

- **ID**- unique number given to each issue, each will have the prefix of "ESC" to identify as an escalated non-compliance.
- **Trial** – This will capture the title, whether hosted or sponsored and the R&I Ref.
- **R&D ref -** local R&D reference number for the trial
- **CI-** Investigator taking responsibility for overall management of trial on all sites
- **Source** – This will be used to identify as a serious breach
- **Fault Category**- Select from the list one of the predefined categories that best applies.
- **Sponsor** – name the organization taking legal responsibility for the trial
- **Raised By-** indicate staff type who reported the issue
- **Name Sponsor rep dealing with issue (Lead Pharmacist Clinical Trials/R&I or Research Governance Manager)**
- **Raised Date-** Date issue was first reported to Sponsor.
- **Details-** describes the issue in more detail.
- **Workflow Stages-** describes actions taken for each appropriate stage, each will be completed over the duration of the non-compliance.
- **Raised Against-** indicate which site the issue relates to
- **Severity-** indicates which category of non-compliance the issue refers to. Select from Category 1, 2 3 or 4, Serious Breaches will only be a Category 3 or 4.
- **MHRA GCP reference number**
- **Properties**- this can be used to add notes or attach documents, for example the non-compliance form or the e-mail in which the event is first raised to the Research Governance Manager or Lead Pharmacist Clinical Trials R&I and any relevant correspondence.
- **Status**- indicate whether open or closed
- **Follow up report dates**
- **Date closed by MHRA**
- **Date closed by Sponsor-** once corrective and preventative actions are complete
- **Closed by-** indicate who closed the issue

In addition to recording Serious Breaches in Q-Pulse, they may continue to be recorded on an excel log held on the common drive. All updates to the MHRA will be attached to the Q-Pulse record as an attachment, records of communication relating to the serious breach will be retain in E-Mails by the relevant lead and the records updated to reflect the outcomes of the discussions.

A member of the Quality Assurance Team or the Research Governance Facilitator will assist with the entry of records on to Q-Pulse.

Routine reviews of the contents of Q-Pulse and the excel log will be carried out to ensure they are aligned in terms of content until the process is fully transitioned to Q-Pulse. The Research Governance Manager and Lead Pharmacist Clinical Trials R&I can update the Q-Pulse records directly or notify those mentioned above to update Q-Pulse on their behalf.

Categories

Category 1:

Issues of non-compliance of an administrative or technical nature are detected that do not compromise patient safety or the integrity of the data.

Category 2:

Issues are detected that could affect the conduct of the study but do not constitute a serious breach of GCP or the protocol. Category 2 may include issues that have minor impact but no impact on patient safety and/or the integrity of the data. However, it is still important to record Category 2 issues as a reasonable volume of the same issue can lead to a Category 3 issue.

Category 3:

Issues are detected that may impact on patient safety and/or integrity of the data. It may also impact on other trials or indicate issues with Sponsor processes. This may include potential serious breaches of GCP and/or the trial protocol.

Category 4:

Issues are detected that have a significant and/or immediate impact on patient safety and/or integrity of the data. This may include life threatening patient safety issues and potential serious breaches of GCP and/or the trial protocol.

4. Referenced documents

- Form 51.009A – Record of Breach Assessment Group
- Statutory Instrument 2004/1031**:** The Medicines for Human Use (Clinical Trials) Amendment Regulations 2004
- Guidance for the notification of serious breaches of GCP or the trial protocol: https://mhrainspectorate.blog.gov.uk/2019/05/24/gcp-serious-breaches-the-2018-edition/
- SOP 51.008 - Handling non-compliance with Good Clinical Practice (GCP) and/or the trial protocol in clinical research
- SOP 51.031 - Corrective and Preventive Action Plan Management

5. Related documents

- SOP 53.001 - Handling urgent safety measures for clinical trials of investigational medicinal products
- SOP 53.002 - The Handling of Poor Quality and Fraud in Clinical Research
- SOP 53.003 - Temporary halt or early termination of clinical trials of investigational medicinal products
- Glasgow Health Science Partnership Regulatory Affairs Group Terms of Reference

6. Document History

Version	Date	Description
1.0	18/06/09	Release of Version 1.0
1.1	15/10/13	Minor administrative changes Reporting structure changes
1.2	13/02/15	Type of serious breach classified as part of 2013 MHRA inspection findings
2.0	14/07/2016	Update to template 1.4 and renumber
3.0	02/10/2018	Addition of Breach Assessment Group Addition of staff categories
4.0	17/12/2018	Clarification as to the role of the BAG group Need to QA the form prior to submission Need to follow up within a month if no response from the MHRA Reference to CAPA breach SOP Non –compliance log: source data defined; need for a unique ID for each issue Clarification of date of notification & event; date closed should include MHRA and sponsor dates for closure
5.0	25/11/2024	Update to include use of Q-Pulse, inclusion of RACI, restructure of headings and expansion of definitions for Serious Breach, BAG and awareness.