Standard Operating Procedure (SOP)

Reporting of Serious Breaches of Good Clinical Practice or The Trial Protocol

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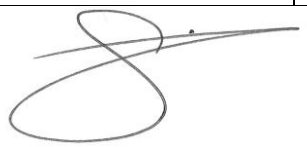
Signature of Authoriser:			

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The master document is posted on the JRES website and any print-off will be classed as uncontrolled.

Researchers and their teams are responsible for checking the JRES website for the most recent version.
They may print off this document for training and reference purposes.

SOP Chronology

SOP Version Number:	Reason for Change:	Author:
V1.0	Original Version	Lucy H Parker
V2.0	Change in version number, updated logo and trust name, change from CRGM to HRG	Mallikarjuna Rao Vemula (Arjun)
V3.0	Add clarity of action to be taken upon receipt of notification of a Serious Breach that has occurred on a study that is hosted by St George's University Hospitals NHS Foundation Trust.	Debbie Rolfe
V4.0	Reflecting changes in JREO to JRES and job titles and minor changes to delegations of responsibilities. Also, insertion of associated JRES documents.	Ali Alshukry/Georgia Bullock

Associated JRES documents

SOPs	WPDs	Docs	LOGs
JRESGOVSOP0006 Reporting of Adverse Events for CTIMPs Sponsored by St George's	JRESWPD0023 General Research Definitions	JRESDOC0061 Deviation Reporting Form JRESDOC0106 Notification of Serious Breach Timeline and Action Taken	

Contents

1. Background

The Clinical Trials Regulations state that Sponsors of clinical trials must notify the licensing authority in writing of any serious breach of Good Clinical Practice (GCP) in connection to that trial or of the protocol relating to that trial. Serious breaches must be reported within **7 days** of becoming aware of the breach.

A 'serious breach' is defined as:

A breach which is likely to affect 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.

More information on serious breaches, examples of possible serious breaches, the reasons behind the requirement to report these to the MHRA and the reporting process is available here: MHRA Guidance on Serious Breaches.

Not every deviation from the protocol needs to be reported to the MHRA as a serious breach. Deviations from clinical trial protocols and GCP occur commonly in clinical trials. The majority of these instances are 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 should be documented using the Deviation Reporting Form (JRESDOC0061) and added to the Deviations spreadsheet for the trial, in order for appropriate corrective and preventative actions (CAPA) to be taken. In addition, these deviations should be included and considered at the end of the study, as they may have an impact on the analysis of the data.

Deviations which are classified as serious must be reported to the MHRA.

2. Joint Research and Enterprise Services (JRES) Policy

All JRES SOPs will be produced and approved in accordance with the JRES SOP on SOPs and must be used in conjunction with local NHS Trust and University policies and procedures.

The JRES acts as the Sponsor representative of both St George's University of London (SGUL) and St George's University Hospitals NHS Foundation Trust (SGHFT). St George's will be the official name used on all SOPs to represent both institutions acting as Sponsor.

3. Scope

This SOP will describe the process for notification of serious breaches of GCP or the approved trial protocol to the JRES in their remit as Sponsor and to the MHRA.

This SOP will describe the process that the JRES will undertake upon receipt of notification of a serious breach of a clinical trial.

This SOP will not cover safety reporting for CTIMPs, this is covered by JRESGOVSOP0006.

4. Definitions

For general research-related acronyms used in this SOP, refer to General Research Definitions Working Practice Document JRESWPD0023.

5. Responsibilities

This SOP is to be followed by the Chief Investigator (CI) / Principal Investigator (PI) and their delegates and also the JRES Governance team.

If a researcher is unsure as to whether a breach has occurred, they must contact the JRES to discuss the event and to see whether the breach should be classified as serious.

It is the responsibility of the Sponsor to assess the impact of a breach on the scientific value of the trial. This will depend 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 and the impact of excluding the data from the analysis.

6. Procedure

The procedure for the notification of serious breaches of GCP or the trial protocol can be divided into 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 and preventative actions (CAPA).

6.1 Identifying a Serious Breach and Notifying the Sponsor

It is the responsibility of the CI and PIs to continually monitor the conduct of a clinical trial. This may be delegated to a suitably qualified/experienced member of the research team or sub-contracted to an appropriately qualified party such as a Clinical Research Organisation (CRO). However, the ultimate responsibility for the conduct of the trial remains with the CI.

St George's may audit a trial as part of their Quality Assurance procedures and Audit Programme which may identify serious breaches of the protocol or GCP.

Breaches identified by any means must be reported to the assigned Clinical Research Associate (CRA) and the Research Development and Governance Manager (RDGM) or the Head of Research Governance and Delivery (HRGD), within **24 hours** of the breach being identified.

Initial reporting of a breach should be carried out via telephone, email or in person, and should include:

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

If the CRA, RDMG, or HRGD are unavailable, then the report should be made to one of the JRES Research Governance and Facilitation Officers.

6.2 Assessment of a Serious Breach

Upon receipt of an initial breach report, the CRA/RDGM will discuss the issue with the CI/PI to identify which area/section of GCP or the protocol has been breached and how the breach impacts on patient safety and/or the scientific integrity of the trial.

The CRA/RDGM will meet with the CI/PI and the study team to discuss the breach and compile evidence to support notification to the MHRA.

The CRA/RDGM will work with the CI/PI to identify the extent of the breach and to initiate any Urgent Safety Measures that may be required.

The CRA/RDGM will confirm classification of the breach through analysis of the event, in accordance with the MHRA guidelines on serious breaches. The impact of the serious breach on

the scientific value of the trial must be assessed and also a formal plan for CAPA which can be provided to the MHRA.

Where required, the breach will be escalated to the HRGD for review and advice on its potential impact and management.

All serious breaches reported to the JRES and/or investigated by the JRES must be reported to the St George's Research Governance Committee (RGC) or sub-committee.

If the JRES is unclear about the potential for a breach to have significant impact on the scientific value of the trial, the JRES will contact the MHRA Inspectorate to discuss the issue.

The JRES will contact the Investigator within **48 hours** to:

- Inform them of the outcome of the assessment.
- Agree on the appropriate CAPA to be taken.
- Provide further instruction in accordance with the final decision within 48 hours via email or other means of communication during the provision of the initial report.

6.3 Initial Notification of Breach to MHRA

The CRA/RDGM will collate all available information and complete the MHRA Notification of Serious Breaches of GCP or the Trial Protocol form (https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#report-a-serious-breach).

The form will be submitted via e-mail by the JRES to the MHRA within the required **7-day reporting period**. The completed form must be sent to GCP.SeriousBreaches@mhra.gov.uk.

A copy of the completed MHRA form must also be submitted to the **Research Ethics Committee** (REC) which approved the trial.

The CRA and/or RDGM will be the contact person for all correspondence with the MHRA.

It is **not** necessary to wait to report to the MHRA until all the information has been collected. Updates are acceptable. If investigations or corrective and preventative actions are on-going at the time of reporting the serious breach, it is acceptable to outline the plans in the initial report, indicating when they are expected to be completed and what follow-up reports will be provided to the MHRA and when. Follow-up reports should be made in writing (the same reporting form can also be used for this) and must:

- Be clearly identified as a follow-up report.

- Identify the unique GCP identification allocated when the initial report was acknowledged (if aware of this information).
- Be forwarded to the inspector dealing with the initial notification directly and copying GCP.SeriousBreaches@mhra.gov.uk (unless instructed not to).

6.4 Provision of Additional Information to the MHRA

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

The CI/PI 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.
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).
10. Any other related study.

The CRA or RDGM will review the project report and submit it to the MHRA.

The MHRA may request additional information such as a copy of the protocol, ethics application, SOPs etc. The CRA or RDGM will liaise with the study team to obtain additional documents and submit them to the MHRA via email, quoting the GCP reference number.

6.5 Planning and Implementing Corrective Action

The JRES will work with the study team to devise a formal plan of corrective and preventative action (also known as a CAPA) to address the breach. The action plan will be submitted to the MHRA on their request.

Depending on the initial assessment of impact, the JRES may carry out a full audit of the trial and general trial management systems and procedures. The JRES will complete the Notification of a Serious Breach Timelines and Actions Taken form (JRESDOC0106).

The JRES will notify the Investigator's line-manager of the notification of a serious breach having been sent to the MHRA. The line-manager of the Investigator will also be informed of what CAPA plan was agreed, to ensure that the Investigator and their research team implement the plan.

The Research and Development (R&D) department of the site where a serious breach occurred (if at a different site to St George's) will also be informed.

It is good practice to inform other CIs conducting CTIMPs sponsored by St George's in an anonymised manner to prevent such breaches from recurring on other trials.

It is important that all members of the JRES Governance team are aware of all serious breaches and have details of sites where those occurred, so that it is taken into consideration when considering the site participation on other CTIMPs sponsored by St George's.

6.6 Receipt of a Serious Breach Notification on a Hosted Clinical Trial

The serious breach notification should be acknowledged in writing (via email) to the sender, ensuring that all relevant personnel are cc'd to make them immediately aware that a notification has been received.

The Sponsor, CI and the site PI must be notified via email that a Serious Breach notification has been received and it will be reviewed and investigated. Contact details for any correspondence must be clearly provided to facilitate onward and timely communications.

The CRA or RDGM must review the outline of the breach notification and assess both actual and potential impact to patient safety and/or data credibility.

For actual impact and potential impact to patient safety or data integrity - information should be sought via the governance database and the research team (or clinical area) implicated within the serious breach notification immediately. Depending on the nature of the serious breach it may be required to immediately halt recruitment into the affected study **and** any other studies that the Investigator or research team supporting the Investigator are working on until it is deemed safe following satisfactory investigations.

For participants already receiving study treatment or an intervention, an independent assessment by a suitably qualified individual (in accordance with the nature of the condition) should be requested, with the support and knowledge of the Sponsor, to ensure the safety and ongoing management of affected patients is appropriate.

The Sponsor medical advisor and/or the CI should be contacted to enquire of any immediate suggested management plans for ongoing participants and any actions taken thus far by the JRES.

The CRA or RDGM must complete a 'Notification of Serious Breach Timeline and Actions Taken' form and maintain up to date information.

An electronic folder for Serious Breaches should be created on the shared JRES drive for the trial and all documentation and correspondence should be saved throughout the investigation.

The PI, research team members and relative support departments (e.g. Research Pharmacy and/or Clinical Research Facility) must be informed of the immediate and ongoing patient management, affected study(s) status and request cooperation with any investigation of the serious breach and resulting CAPA.

If further studies or research activities are implicated, the Sponsor(s) and/or head of support department(s) affected must be informed that a serious breach has been reported and will be under investigation by the JRES. Confidentiality must be respected at all times.

Any findings, conclusions and/or actions must be documented clearly and communicated with the Sponsor, CI, PI and relevant research committees. Where requested a copy may be required to be provided to the MHRA.

Where a CAPA has been implemented, regular updates should be provided at agreed timepoints to all parties involved until all points on the CAPA have been completed.

7. References

ICH GCP and Clinical Trials Regulations.

https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#report-a-serious-breach

MHRA Guidance on Serious Breaches

8. Appendices

None associated with this SOP.