St George's University Hospitals NHS
NHS Foundation Trust

St George's University of London

Standard Operating Procedure (SOP)

SOP ID number:	JREOSOP0032	**Effective Date:**	28th February 2017
Version number and date:	Version 3.0 22nd February 2017	**Review Date:**	27th February 2019
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Approved by:	Mark Cranmer	**Date:**	27th February 2017
Signature of Authorisor			

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They may print off this document for training and reference purposes.

Standard Operating Procedure (SOP)

Reporting of Serious Breaches of Good Clinical Practice or Trial Protocol

SOP Chronology

SOP Version Number:	Reason for Change:	Author:
V0.1	Original Version	Lucy H 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

1. Background

The EU GCP Directive 2005/28/EC was transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928 and contains a requirement for the notification of "serious breaches" of GCP or the trial protocol:

"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".

The requirement was implemented in UK legislation in order 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 Sponsor to assess the impact of the breach on the scientific value of the trial. If a researcher is unsure as to whether a breach has occurred, he/she must contact either the Regulatory Assurance Manager (RAM) or the Head of Research Governance (HRG) to discuss the event and to see whether the breach should be classified as serious (examples of possible serious breaches can be found in appendix 2).

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.

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 (for example, in the trial Case Report Form (CRF) or the Trial Master File (TMF) by completion of the protocol violation and deviation log JREOLOG0005) in order for appropriate corrective and preventative actions 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. However, not every deviation from the protocol needs to be reported to the MHRA as a serious breach.

2. Joint Research and Enterprise Office (JREO) Policy

All JREO SOPs will be produced and approved in accordance with the JREO SOP on SOPs and must be used in conjunction with local NHS Trust and St George's policies and procedures.
The JREO acts as the Sponsor representative of both St George's University of London (SGUL) and St George's University Hospitals NHS Foundation Trust (SGHT). 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 JREO in their remit as Sponsor and to the MHRA.
This SOP will describe the process that the JREO will undertake upon receipt of notification of a serious breach of a Clinical Trial that is hosted by St Georges University Hospitals NHS Foundation Trust.
This SOP will not cover safety reporting for CTIMPS or non CTIMP sponsored studies. These topics are covered by JREOSOP0006 and JREOSOP0032 respectively.

4. Definitions

4.1 Serious 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; or
(b) The scientific value of the trial".

4.2 CAPA

A formal plan of corrective and preventative action (also known as a CAPA) example Appendix 8.5

5 Responsibilities

This SOP is to be followed by the JREO governance section and the Chief Investigator (CI) of the proposed study.

6 Procedure

The procedure for 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 action

6.1 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 such as a Clinical Research Organisation. However the ultimate responsibility for the conduct of the study still remains with the Chief Investigator.

In addition St George's may audit the trial as part of their Quality Assurance procedures through their Audit Programme. Any breaches identified either through monitoring, audit or by other means must be reported to either the Regulatory Assurance Manager (RAM) or the Head of Research Governance (HRG) within 24 hours of the breach being identified.

Initial reporting to the RAM or HRG should be carried out via telephone, email or in person, and should inform of:

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 both the RAM and the HRG are unavailable, the report should be made to one of the JREO Research Governance Officers.

6.2 Assessment of a Serious Breach

Upon receipt of an initial breach report the RAM or HRG will notify the Chair of the Serious Breaches sub-Committee Troika or the Vice-Chair in his/her absence, of a potential 'serious breach' of GCP and/or the study protocol via email.
The RAM or HRG 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 impact on Subject/ participant safety and/or the scientific integrity of the trial.

The RAM or HRG will meet with the Chief/Principal Investigator and the study team to discuss the breach and compile evidence to support notification to the MHRA.

The RAM or HRG 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.

The RAM or HRG and the Chair of the TROIKA will confirm classification of the breach through analysis of the event in accordance with the MHRA Guidelines on serious breaches.

The RAM or HRG, Clinical Trial Monitor (CTM) and the Investigator will meet the Chair if deemed necessary to:

- assess the impact of the breach on the scientific value of the trial and
- Devise a formal plan for CAPA to facilitate notification to the MHRA.

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

The JREO will contact the Investigator within 24-48hrs to:

- Inform him/her of the outcome of the assessment
- Agree on the appropriate CAPA to be taken

- Provide further instruction in accordance with the final decision within 24-48 hours via email or other means of communication during the provision of the initial report

6.3 Initial Notification of Breach to MHRA

The RAM or HRG will collate all available information and complete the Notification of Serious Breaches of GCP or the Trial Protocol form (appendix 1).

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

GCP.SeriousBreaches@mhra.gsi.gov.uk

The RAM or HRG 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 investigation or corrective and preventative action(s) are on-going at the time of reporting the serious breach, it is acceptable to indicate the plans with projected timelines for completion. In such case, this should be indicated in the initial report when they are expected to be completed and what follow-up reports will be provided to the Inspectorate and when. Follow-up reports should be made in writing (the serious breaches form can also be used for this) and should ideally:

- 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 or via the mailbox.

6.4 Provision of additional information to the MHRA

Once the initial notification has been submitted to the MHRA, the JREO will review the breach in full to identify the extent of the breach and the RAM 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)
10. Any other related study

The RAM 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 RAM will liaise with the study team to obtain additional documents and submit them to the MHRA via email still quoting the GCP reference number

6.5 Planning and Implementing Corrective Action

The JREO will work with the study team and the TROIKA to devise a formal plan of corrective action (also known as a CAPA) to address the breach. The corrective action plan will be submitted to the MHRA on their request. Refer to Appendix 8.5 as an example.

Depending on the initial assessment of seriousness and impact, the JREO may carry out a full audit of the trial and general trial management systems and procedures according to the JREO audit SOP (JREOSOP0035). The JREO is to complete the Notification of a Serious Breach timelines and actions taken by the JREO Appendix 8.4

The JREO will notify the Investigator's line manager of the notification of 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 his/her research team implement these actions.

The serious breach, depending on its nature and the decision made by the TROIKA, might also be notified to Research Governance Committee (RGC) and Strategic Planning and Resources Committee (SPARC).

The 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 JREO Governance and Approvals team are aware of all serious breaches and have details of sites where those occurred, so that careful consideration is given to those sites when considering their participation on other CTIMPs to be sponsored by St George's.

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

Acknowledge in writing (via email) the Serious Breach notification from the sender, ensure the TROIKA are cc'd to make them immediately aware that a notification has been received in the JREO.

Inform the Sponsor, Chief Investigator and the site Principal Investigator via email that a Serious Breach notification has been received, will be reviewed and investigated. Ensure contact details for any correspondence are clearly provided to facilitate onward and timely communications.

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

Where investigations indicate Research misconduct or fraud refer to JREOSOP0025.

All Serious breaches reported to the JREO and/or investigated by the JREO must be reported to the next Research Governance Committee as a standing agenda item

- **For actual impact and potential impact to patient safety** - intelligence should be sought via the governance database and the research team (or clinical area) implicated within the serious breach notification immediately. Dependent on the nature of the Serious Breach the following actions may be required

Immediately halt further 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 treatment or study intervention request an independent assessment by a suitably qualified individual (in accordance with the nature of the condition) and with the support and knowledge of the Sponsor to assure the safety and ongoing management of affected patients is appropriate.

Telephone the Sponsor medical advisor and/or the Chief Investigator to enquire of any immediate suggested management plans for ongoing participants and any actions taken thus far by the JREO.

JREO HRG &/or RAM are to complete a 'Notification of Serious Breach Timeline and Actions Taken by the JREO' document Appendix 8.4 and maintain up to date information.

An electronic folder should be created W:\Operational\Committees\TROIKA\SERIOUS BREACH INVESTIGATIONS and all documentation and correspondence should be retained throughout the investigation.

Ensure the Principal Investigator, research team members and relative support departments (e.g. Research Pharmacy and/or Clinical Research Facility) are informed of immediate and ongoing patient management, affected study(ies) status and request cooperation with any investigation of the serious breach and resulting CAPA.(Appendix 8.5)

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 JREO. Confidentiality must be respected and will be made available on a need to know basis.

The HRG and/or RAM will conduct a root cause analysis of the issue reported and relative circumstances which led to the serious breach – this may be by examination/audit of the trial essential documentation; study files; patient medical records; Sponsor monitoring reports and communications; equipment maintenance records; staff training records and face to face interviews with person(s) directly involved and or responsible for the serious breach.

Any findings, conclusions and/or actions must be documented clearly and communicated with the Sponsor, Chief Investigator, Principal Investigator and TROIKA. Where requested a copy may be required to be provided to the MHRA.

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

- **For actual impact or potential impact on data credibility** -Intelligence should be sought via the governance database and the research team (or clinical area) implicated within the serious breach notification immediately. Dependent on the nature of the Serious Breach the following actions may be required

Immediately halt further recruitment into the affected study **and** any other studies that the Investigator or Research team supporting the Investigator are working on until satisfactory investigation has been conducted.

Telephone the Sponsor medical advisor and/or the Chief Investigator to enquire of any immediate suggested management plans and any actions taken thus far by the JREO.

Ensure the Principal Investigator, research team members and relative support departments (e.g. Research Pharmacy and/or Clinical Research Facility) are informed of affected study(ies) 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 JREO. Confidentiality must be respected and will be made available on a need to know basis.

The HRG and/or RAM will conduct a root cause analysis of the issue reported and relative circumstances which led to the serious breach – this may be by examination/audit of the trial essential documentation; study files; patient medical records; Sponsor monitoring reports and communications; equipment maintenance records; staff training records and face to face interviews with person(s) directly involved and or responsible for the serious breach.

Any findings, conclusions and/or actions must be documented clearly and communicated with the Sponsor, Chief Investigator, Principal Investigator and TROIKA. Where requested a copy may be required to be provided to the MHRA.

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

7 References

ICH Good Clinical Practice

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 to the MHRA. www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/SeriousBreachesReporting/index.htm

JREOSOP0025 SOP on Research Misconduct or Fraud

JREODOC0106 Notification of Serious Breach Timeline and Actions taken by the JREO

JREODOC0107 Corrective and Preventative Actions Taken/To be Taken

8. Appendices

8. 1 MHRA notification of serious breach of GCP or the trial protocol

FOR MHRA USE ONLY:	
GCP Unique ID:	
Triaging Inspector	

Appendix One: Notification of Serious Breach of Good Clinical Practice or Trial Protocol

(Ref: UK Statutory Instrument 2004/1031 Regulation 29A, as amended by 2006/1928)

Please forward this notification to GCP.SeriousBreaches@mhra.gsi.gov.uk OR GCP Inspectorate, MHRA, 2a Hunter house, 57 Good Ramsgate, York, YO1 7FX.

Your Name:	**Your Organisation:**
Your Contact Details:	**Date Breach Identified by Sponsor:**
	Date Breach Notified to MHRA:
Details of Individual or Organisation committing breach:	**Details of related study** (if applicable): (e.g. EudraCT No, CTA number, study title)

Report: Tick appropriately	**Initial Report**	☐	**Follow-up Report**	☐

Please give details of the breach

Potential impact to patient safety and/or data credibility:

☐ Patient safety	☐ Scientific value / data credibility
☐ Patient confidentiality	☐ NA/None
☐ Approval Issues	☐ Other Non-compliances (specify)
☐ IMP	

Background:

(continue on additional sheets if required)

Other relevant information:

(i.e. study status, site(s), ethics, trust, CRO /sponsor details etc.)

(continue on additional sheets if required)

Please give details of the action taken:
This should include: Any investigations by your organisation, details of investigations by other organisations (e.g. CRO/ethics/trust), the results and outcomes of the investigations (if known or details of when they will be available/submitted), how it will be reported in the final report/publication, the corrective & preventative action implemented to ensure the breach does not occur again. *(continue on additional sheets if required)*

Actual impact to patient safety and/or data credibility:

☐ Patient safety	☐ Scientific value / data credibility
☐ Patient confidentiality	☐ NA/None
☐ Approval Issues	☐ Other Non-compliances (specify)
☐ IMP	

8.2 Examples of breaches to the MHRA (not exhaustive and provided by the MHRA)

Notifier	Details of Breach Reported	Is this a Serious Breach?
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).	**Yes, there was significant potential to** impact the safety or physical or mental integrity of trial subjects.
	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.	**Yes** 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.
	3) One subject was administered 6 additional doses on 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.	**Yes**, there was impact on the safety or physical or mental integrity of trial subjects and on the scientific value of the trial
	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.	**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 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 not unequivocal evidence of fraud at the time of reporting. One of the studies involved paediatric subjects.	**Yes**, this subsequently led to enforcement action against the organisation in question.
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. Follow-up reports sent to MHRA confirmed the Sponsor concerns over consenting and data changes made to source without an adequate written explanation.	**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 and 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	**Yes**, as this had significant potential to harm the subject if unblinding would have affected the course of treatment

	unhappy that the pharmacy was not available in an emergency situation.	
CRO	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**
CRO	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**
Contractor	The Investigator failed to report a single SAE as defined in the protocol (re-training provided).	**No**, if this did not result in other trial subjects being put at risk, and if it was not a systematic or persistent problem. In some circumstances, failure to report a SUSAR could have a significant impact on trial subjects. Sufficient information and context should be provided for the impact to be assessed adequately.
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**
Identified during inspection	A potential serious breach was identified, but not reported (documentation in the Sponsor's TMF identified that there may have been fraud at an investigator site, re-use of previous time point data in later time points). The Sponsor had investigated and the issue was subsequently found to be a genuine error and not fraud.	**No**, on this occasion. *However, had this been identified as fraud impacting on the integrity of the data, then this serious breach would not have been notified within the regulatory timeframe (i.e. 7 day window).*
Sponsor	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*	**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

	on the potential consequences of the delay should have been provided.	was key safety information not relayed to subjects in a timely manner).
Sponsor	Visit date deviation. *A common deviation in clinical trials.*	**No**, a minor protocol deviation, which does not meet the criteria for notification.
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**
NRES	The early destruction of investigator site files (i.e. one study had only been completed a year earlier and one study was still ongoing).	**Yes**
Member of public	A member of public received a named invite to be a volunteer in a clinical trial (no specific trial mentioned). However, this person was not on the organisation's volunteer database and had not participated previously in a study. On further investigation by MHRA, it was revealed that the organisation had contracted the use of a mail shot organisation to send a generic mails hot to a list of people in a specific location, over a certain age. This had been approved by the REC.	**No**

8.3 Protocol Deviations/Violations Log

Protocol Deviations/Violations Log

St George's University of London

St George's University Hospitals NHS
NHS Foundation Trust

Short Study Title:			
Site Name & Number:		**JREO number:**	
Principal Investigator (PI):		**EudraCT Number:**	

Description of Deviation/Violation (include subject number)	Date occurred	**Please tick appropriate box**					Date Investigator informed	**Corrective and Preventative action taken by the Investigator**	Date submitted to Sponsor	Date MHRA informed (for Serious Breaches only)
		Deviation[1]	Violation[2]		Serious Breach[3]					
			Major		Yes					
			Minor		No					

[1]**Protocol Deviation:** is any **alteration/modification** implemented that is **not** in accordance with the approved protocol. This also includes the Patient Information Sheet and Consent Form and any other information relating to the conduct of the trial that has been approved by the REC and CA. A deviation is usually an un-intended departure from the expected conduct of the trial and is often classified as non-serious in nature. An example of this would be undertaking a procedure in a slightly different way to that documented in the protocol whereby there was no risk to subject safety and the integrity of trial data was not affected.

[2]**Protocol Violation:** is any protocol deviation that is not approved by the REC and or CA prior to its implementation. This is often described as a **serious non-compliance** resulting in error, fraud or misconduct and would require reporting to the Sponsor, REC and CA within agreed timeframes. There are two types of violations;

- **Major Violation** - a violation that may impact on the participants' safety or affects the integrity of the study data (this may also constitute a Serious Breach of GCP and will require further reporting in accordance with the Sponsor's SOP) (i.e. Failure to obtain informed consent, enrolment of subject that does not meet the inclusion criteria (previous approval not sought), undertaking trial procedures not approved by REC and/or MHRA, Failure to report an SAE to Sponsor/REC/MHRA, IMP dispensing/dosing error
- **Minor Violation** - a violation that does not impact on participants' safety or compromise the integrity of study data (i.e. missing original signed consent form (only photocopy available), use of invalid/unapproved consent form (out of date version), failure to follow trial procedure without affecting participant's safety)

[3]**Serious Breach** is a breach which is likely to affect to a significant degree: a) the safety or physical or mental integrity of the participants of the trial; or (b) the scientific value of the trial

8.4 Notification of Serious Breach Timeline and Actions Taken by JREO – St George's

Serious Breach Report Received Date:	Study Title: Sponsor: JREO Ref:	CI: Local PI:
Date	Action Taken:	Comments/Ongoing Corrective & Preventative Actions

8.5 Corrective and Preventative Actions Taken/To Be Taken (example- amend as applicable)

JREO – St George's University of London & St George's University Hospitals NHS Foundation Trust		
TRUST R&D (JREO)		Study Title JREO ref:
	Action	Date/Evidence
1		
2		
Research Pharmacy		
	Action	Date/Evidence
1		
2		
Chief Investigator		
	Action	Date/Evidence
1		