St George's University Hospitals NHS
NHS Foundation Trust

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Standard Operating Procedure (SOP)

Management and recording of Protocol Deviations and Violations

SOP Chronology		
SOP Version Number:	**Reason for Change:**	**Author:**
v.10	Original Version	Ailsa Withers
V2	To update the above SOP with the new procedure for Sponsor's management of protocol violations, deviation, urgent safety measures and potential serious breaches. To apply the new SOP numbering system	Ira Jakupovic
V3	Review of V2.0	Ira Jakupovic
V4	New numbering and SOP format. Removal of reference to Serious Breach and Safety measures as covered in separate SOPs	Debbie Rolfe
V5	New logo and Trust name	Lucy Parker

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1. Background

The European Clinical Trials Directive (EUCTD) 2001/20/EC was transposed into UK Regulations by the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) on the 1st May 2004. UK regulations will be the term used to cover the UK legislation and the EUCTD in this document. The UK regulations set out the legal requirements for the recording of protocol deviations and/or protocol violations to facilitate the assessment of their effect either singularly or collectively on the wellbeing, rights and integrity of the trial subjects or data generated for the clinical trial. Forward management and where necessary following assessment, escalation to Sponsor and/or regulatory approval bodies will be covered in this SOP

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 representative of both St George's University of London (SGUL) and St George's University Hospital's NHS Foundation Trust (SGHT). St George's will be the official name used on all SOPs to represent both institutions acting as clinical trials Sponsor.

3. Scope

This SOP outlines the overall process and procedures to be followed by the JREO and all Investigators undertaking CTIMPs and non-CTIMPs sponsored by St George's to report protocol deviations and violations that may also need to be assessed and graded individually or collectively and upgraded as appropriate if potential serious breaches of GCP and/or the trial protocol. The purpose of this SOP is to outline practical arrangements for notification, and provide advice on classification as well as what must be reported.

The SOP describes the reporting procedure to the JREO, and where appropriate the MHRA, and the main REC to ensure that legal reporting requirements are met.

This SOP does not cover the management of Serious Breaches- please refer to JREOSOP0032

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4. Definitions

The following definitions and background information will help readers understand the purpose of this SOP and enable them to understand the importance of recording and reporting protocol deviations and violations (minor and major). Please ensure that you understand definitions in this section prior to following the procedure outlined in Section 6 of this SOP.

4.1 Protocol Deviations

A Protocol Deviation is any alteration/modification of the information relating to the conduct of the trial that has been approved by the main REC and MHRA. This also relates to any of the approved trial documents (i.e. Protocol, Patient Information Sheet (PIS), Informed Consent Form (ISF), etc.). 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.

It is important to record such deviations continually in the Case Report Forms (CRFs) and/or source data (patient's notes). It is the responsibility of the CI/PI to train the research team on the trial protocol to avoid repeated deviations to the study protocol. The CI/PI must ensure that all deviations are recorded using the Sponsor's Log of Deviations/Violations/Urgent Safety Measures and Serious Breaches (Appendix 1) and that the Log is sent to the JREO on request.

4.2 Protocol Violations

A Protocol Violation is any protocol deviation that is <u>not</u> approved by the REC/MHRA prior to its implementation. Repeated wilful occurrence of a protocol deviation may also be assessed as a protocol violation. A collection of protocol violations may collectively be reclassified as a serious breach. A protocol violation is often described as a <u>serious non-compliance</u> resulting in error, fraud or misconduct and may require reporting to the JREO, REC, <u>and MHRA</u> within agreed timeframes. All protocol violations must be reported to the JREO immediately, since they may sometimes constitute a potential serious breach (see 4.4).

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 JREOSOP0032). Examples of this maybe;

- Failure to obtain informed consent (i.e. no documentation)

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- Enrolment of participant that does not meet the inclusion criteria (previous approval not sought)
- Undertaking trial procedures not approved by the REC/Competent Authority (CA)
- Failure to report SAE to Sponsor/REC/CA within defined timelines
- IMP dispensing/dosing error

Minor Violation - a violation that does not impact on participant's safety or compromise the integrity of study data. Examples of this may be;

- Missing original signed consent form (only photocopy present)
- Use of invalid/unapproved consent form (out of date version)
- Failure to follow trial procedures but in the opinion of the Investigator does not affect subject safety or integrity of data

4.3 Urgent Safety Measures

An urgent safety measure is a procedure not defined by the protocol that is put in place prior to authorisation by the MHRA, REC and JREO in order to protect clinical trial participants from any immediate hazard to their health and safety.

5 Responsibilities

5.1 Chief Investigator (CI)/Principal Investigator (PI)

The Investigator can choose to delegate the responsibilities outlined below to other members of his/her team:

a) The Investigator must ensure that other research team members are trained in the JREO procedure outlined in this SOP, prior to being delegated responsibilities outlined in Section 6
b) The Investigator has a responsibility to record and report all protocol deviations, violations (minor and major), and urgent safety measures that occur for the duration of the trial
c) The Investigator should record all protocol deviations, violations and urgent Safety measures on the JREOLOG005 (Appendix 1) within timelines agreed within the protocol and section 6 of this SOP to facilitate timely action and response by the JREO governance team
d) Subject confidentiality must be met at all times and participants' names must not be included in any correspondence sent to the JREO

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e) The Chief Investigator (CI) is responsible for setting up and managing the Data Safety Monitoring Board (DSMB) if required. The CI will inform JREO of all significant findings and recommendation by the DSMB
f) Clinical Trial participants must be protected at all times and the Investigator must sometimes undertake appropriate urgent safety measures immediately. Following such measures, the Investigator must report his/her action(s) to JREO immediately to enable JREO to inform the MHRA and REC within 3 days of any Urgent Safety Measure taken
g) The Investigator must therefore follow this SOP in detail

5.2 The Joint Research and Enterprise Office (JREO)

The JREO governance team upon notification of a protocol deviation/violation will assess the information provided and suggest corrective/preventative actions immediately.
The procedure outlined below will enable the JREO to assess the impact of deviations in light of the definition outlined above.

6 Procedure

6.1 Deviation or Violation?

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 participants or significantly affect the scientific value of the reported results of the trial. These cases should be documented, i.e. in the CRF or file note in the TMF, in order for appropriate corrective and preventative actions (CAPA) to be taken and/or to ensure that these deviations are included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data.
It is important to inform the JREO of deviations at the time they are identified. This will enable the JREO to help you classify that particular deviation and devise a formal CAPA plan to be put in place if appropriate.
Protocol deviations or violations of the trial protocol may be:

1. Reported directly by the Investigator
2. Identified during monitoring visits by the Clinical Trials Monitor (CTM) or auditor
3. Result from whistle-blowing by another source (contractors, medical staff and PIs) or indirectly *via* the JREO

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Significant impact of the protocol deviation or violation on the scientific value of the trial depends on a variety of factors (*i.e.* the design of the trial, any impact on data and type of data affected, the impact of data being excluded, *etc.*).

6.2 Procedure to notify JREO of a protocol violation or deviation

a) All protocol deviations or violations must be reported to the JREO immediately after being identified to ensure that the JREO is allowed enough time to:
   - conduct an appropriate assessment
   - notify the MHRA within 7 calendar days of the Sponsor becoming aware, should the event be confirmed a 'serious breach' (refer to JREOSOP0032)
b) The initial report to inform the JREO of the protocol deviation/violation should contain enough information for the initial assessment and impact of the event to take place both as a stand alone report or where previous reports have been received collectively.
c) The information must be transcribed onto the Sponsor's Log of Deviations/Violations/Urgent Safety Measures and Serious Breaches and fax to the JREO on 0208 725 0794 or via an e-mail sent to the lead Research Governance Officer (RGO) and Clinical Trials Monitor
d) The JREO will undertake an assessment of the event as outlined in Section 6.3 of this SOP.

6.3 JREO assessment of protocol deviations or violations

All potential deviations or violations identified either by a member of the JREO governance team (*i.e.* Clinical Trial Monitor (CTM) during a scheduled monitoring visit; Clinical Research Governance Officer (RGO) when auditing or reviewing amendments and/or Self-Monitoring Reports) or directly/indirectly reported by the Investigator will be assessed in the following manner:

a) Must be assessed by the lead RGO and CTM within 24hrs of receipt
b) If the report of a protocol deviation is isolated and would not qualify as a persistent occurrence at a site then simply file the report in the trial SSF
c) If however upon interrogating previously received logs held in the trial SSF the deviation has occurred frequently this could collectively require upgrading to a protocol violation.
d) The RGO and/or CTM should discuss findings and evidence with the CI to highlight any possible reason and suggest a Corrective and preventative Action Plan (CAPA)
e) The RGO and/or CTM and the Investigator will make an initial assessment of the protocol violation and assess the grading major or minor according to the perceived effect on either the trial subjects or scientific data for the trial.

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f) The deviation/violation log should be uploaded onto ReDA so that the CTM can review prior to a monitoring visit.
g) The outcome of any assessment and CAPA will also be documented in the Trial Master File (TMF).

6.4 Procedure for Investigators following JREO's assessment

It is important that the Investigator promptly responds to the JREO request of further information in order for the JREO to meet their governance obligations. Please comply with the following procedure:

- The Investigator and/or the person that identified the protocol violation must respond to the above request within agreed timelines when the Investigator is informed of the JREO assessment (usually 24-48 hrs).

6.5 Follow up reports

It is recommended that all follow up reports including CAPA and resulting change in practice are forwarded to the JREO RGO and/or CTM for inclusion in the Sponsor Site File (SSF) and for use by CTM at future monitoring visits:

- Mark the form as a 'follow up report' to Violation for NNnnn Trial reported on dd/mm/yyyy

6.6 Additional actions taken by the JREO

a) The R&D department of the site where the protocol deviations occured may also be informed if considered Major in nature
b) It is good practice to inform other CIs conducting CTIMPs sponsored by St George's in an anonymised manner to prevent such violations from recurring on other trials. This may be presented as a Case Study
c) It is important that all members of the JREO Governance and Approvals team are aware of all major protocol violations and have details of sites where those occured, so that careful consideration is given to those sites when considering their participation on other CTIMPs to be sponsored by St George's.
d) All Protocol deviation logs, subsequent CAPA, assessments, follow ups and related correspondance must be filed in the SSF and uploaded electronically into the eTMF to ensure availability to all relevant JREO team members for monitoring, audit and inspection and for

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consideration and where appropriate inclusion of Annual reports for the Regulatory authorities or where required escalation to the Research Governance Committee

6.7 Urgent Safety Measures

Urgent Safety Measures may be undertaken by the Sponsor and/or the Investigator in order to protect the subjects of a clinical trial against any immediate hazard to their health. Safety measures such as temporarily halting the trial may be taken without prior authorisation from the REC and/or MHRA. The CI/PI must immediately notify the JREO and provide reasons for and justification of the urgent safety measure, along with plans for further action. This may be done by telephone in the first instance followed by a written report. The JREO must inform the REC and the Competent Authority (CA) in writing within 3 days of the measure being taken.

NB:

When the Sponsor halts a clinical trial (i.e. stops recruitment of new subjects and/or interrupts the treatment of subjects already included in trials), the MHRA and the REC concerned should be notified as soon as possible and not later than 15 days as a substantial amendment. They may not recommence the trial until they have notified a substantial amendment to restart the trial and the REC has given a favourable opinion and the MHRA has not raised grounds for non-acceptance of recommencement.

The JREO SOP on amendments JREOSOP0011 fully describes the procedures on reporting Urgent Safety Measures to the main REC, MHRA, and JREO.

7. References

Directive 2001/20/EC of the European Parliament and of the Council of 4th April 2001 on the approximation of the laws, regulations and the administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

The Medicines for Human Use (Clinical Trials) Regulation 2004 (SI 2004/1031) and amended regulations.

JREOLOG0005 Protocol Deviation/Violations log

JREOSOP0032 Reporting of Serious breaches

JREOSOP0011 Management of Amendments for CTIMPs and non-CTIMP studies Sponsored and/or hosted by St George's

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8. Appendices

8.1 Protocol deviation/violation log

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Appendix 1 Deviations/Violations/Serious Breaches Recording Log

St George's University of London	Protocol Deviations/Violations Log	St George's University Hospitals 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					
			Major		Yes					

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[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 participant 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 subject'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

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