St George's University of London

St George's University Hospitals NHS
NHS Foundation Trust

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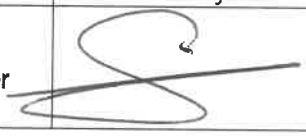
Signature of Authoriser			

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

Standard Operating Procedure (SOP)

Management and recording of Protocol Deviations

SOP Chronology

SOP Version Number:	Reason for Change:	Author:
V1	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

V6	Removal of the term protocol violation in accordance with ICH E3 - EMA Q&A Document Revised (rev1) July 2012 and addition of the definition of different categories of deviation based on "Classification and analysis of the GCP inspection findings of GCP inspections conducted at the request of the CHMP EMA/INS/GCP/46309/2012" Addition of Definition of Personal Data and EMA 45/2001	Godwill Iheagwaram

Table of Contents	**Page**

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 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 (SGFT). 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 Clinical Trials of Investigational Medicinal Products (CTIMPs) and non-CTIMPs sponsored by St George's to report protocol deviations 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 REC to ensure that legal reporting requirements are met.

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

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. 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 change, divergence or departure from the study design or procedures as defined in the protocol.. An example of this would be undertaking a procedure in a slightly different way to that documented in the protocol.

Protocol deviations will be assigned to one of three groups:

Critical

- Conditions, practices or processes that **adversely affect** the rights, safety or well-being of trial subjects and/or the quality and integrity of data
- Critical observations are considered totally unacceptable

All critical protocol deviations must be reported to the JREO immediately, since they may be reclassified as a serious breach.

Remarks: Observations classified as critical may include a pattern of deviations classified as major, bad quality data and/or absence of source documents. Manipulation and intentional misrepresentation of data are considered to be critical deviations.

Major

- Conditions, practices or processes that **might adversely affect** the rights, safety or well-being of trial subjects and/or the quality and integrity of data
- Major observations are serious findings and are direct breaches of GCP principals

Remarks: Observations classified as major may include a pattern of minor deviations and/or numerous minor observations

Other (minor)

- Conditions, practices or processes that **would not be expected to** adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data

- Observations classified as minor indicate the need for improvement of conditions, practices or processes

Remarks: Many minor observations may be grouped and categorised as a major finding.

It is important to record 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 /Urgent Safety Measures and Serious Breaches (JREOLOG0005). The Log is then sent to the JREO on request.

The JREO recognises that deviations may be identified

i) **Prospectively** e.g. a patient is unable to attend a planned protocol defined visit in the future

ii) **Retrospectively** e.g. a monitoring visit identifies that a protocol defined assessment was not performed.

4.2 Personal data

Any information relating to an identified or identifiable person. An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his or her physical, physiological, mental, economic, cultural or social identity.

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, and urgent safety measures that occur for the duration of the trial

c) The Investigator should record all protocol deviations, and urgent Safety measures on the JREOLOG0005 within timelines agreed within the protocol and section 6 of this SOP to facilitate timely action and response by the JREO regulatory support team

d) Subject confidentiality must be met at all times and participants' names or other direct identifiers (e.g. hospital or NHS numbers) must not be included in any correspondence sent to the JREO

e) The Chief Investigator (CI) is responsible for setting up and managing the Data Monitoring Committee (DMC) if required. The CI will inform JREO of all significant findings and recommendation by the DMC.

f) Clinical Trial participants must be protected at all times and the Site Investigator/Principal Investigator (PI) must undertake appropriate urgent safety measures immediately. Following such measures, the Investigator must report his/her action(s) to JREO immediately. The CI must summarise the discussion/agreement with the MHRA in writing and submit the discussion summary to the MHRA and REC within 3 days.

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 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

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 may be:

1. Reported directly by the Investigator or member of the clinical trial research team
2. Identified during monitoring visits by the Regulatory Support Officer (RSO)or auditor
3. Result from whistle-blowing by another source (contractors, medical staff and PIs) or indirectly *via* the JREO

Significant impact of the protocol deviation 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 must be reported to the JREO. Critical deviations should be reported 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) Complete a Deviation Reporting Form JREODOC0061 for each critical or major deviation. Each deviation must be allocated an individual deviation number in sequential order starting at 001 (refer to the deviation log JREOLOG0005 – see below). Any follow up report must also contain the allocated deviation number which should remain the same throughout the reporting process.

   The initial report to inform the JREO of the protocol deviation 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 JREOLOG0005. Each deviation recorded on the log must be given a number in sequential order starting at 001. The completed log, reporting form, any Urgent Safety Measures and/or Serious Breaches should be faxed to the JREO on **0208 725 0794** or via an e-mail sent to adverseevents@sgul.ac.uk

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*

All potential deviations identified either by a member of the JREO governance team during a scheduled monitoring visit; or when auditing or reviewing amendments and/or Self-Monitoring Reports) or directly/indirectly reported by the Investigator or their research team will be assessed in the following manner:

a) Must be assessed 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 of the deviation to the level of major or critical.
d) The JREO assessor should discuss findings and evidence with the CI to highlight any possible reason and suggest a Corrective and preventative Action Plan (CAPA)
e) The JREO assessor and the Investigator will make an initial assessment of the protocol deviation and assess the grading according to the perceived effect on either the trial subjects or scientific data for the trial.
f) The deviation log should be uploaded onto study specific e-folder on W drive in 'reports' sub-folder for "Hosted studies" or '8. Protocol deviation violation' sub-folder for StG sponsored CTIMPS so that the Regulatory Assurance team can review prior to a monitoring visit. For Multi-site studies a sub-folder can be set up for each site. A physical copy should also be printed and filed in the JREO SSF
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 for further information in order for the JREO to meet their governance obligationsTherefore it is a requirement that the Investigator and/or the person that identified the protocol deviation to the above request within agreed timelines outlined in the 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 Regulatory Assurance Team for inclusion in the Sponsor Site File (SSF) and for use at future monitoring visits:

- Mark the form as a 'follow up report' to deviation number XXX 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 deviation(s) occurred may also be informed if the deviation is considered Critical in nature

b) It is good practice to inform other Cis/PIs conducting CTIMPs sponsored by St George's in an anonymised manner to prevent such deviations from recurring on other trials. This may be presented as a Case Study

c) It is important that all members of the JREO Governance team are aware of all critical protocol deviations 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.

d) All Protocol deviation logs, subsequent CAPA, assessments, follow ups and related correspondence must be filed in the SSF and TMF and uploaded electronically into the eTMF. This is to ensure availability to all relevant JREO team members for monitoring, audit / inspection , consideration for inclusion into Annual reports (for the Regulatory authorities) and or escalation to the Research Governance Committee (if required).

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. The CI/PI must contact the MHRA immediately and disclose the incident in full detail to allow for a consensus to be agreed in action going forward. A written summary of the incident and agreed actions/ Urgent safety measure(s) must be received by the MHRA within 3 days of the conversation. A copy must also be provided to the JREO via the adverseevents@sgul.ac.uk. The JREO will contact the CI/PI and discuss onward site and participant management going forward until an official amendment has been constructed for submission to the MHRA and REC.

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 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.

Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18th December 2000 on the protection of individuals with regards to the processing of personal data by the community institutions and bodies on the free movement of such data

JREODOC0061 Deviation Reporting Form

JREOLOG0005 Protocol Deviation Log

JREOSOP0032 Reporting of Serious Breaches

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