Standard Operating Procedure (SOP)
Management and Recording of Protocol and GCP Deviations

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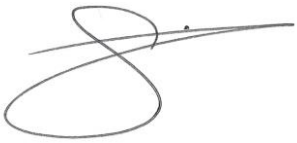
Signature of Authoriser			

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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	Ailsa Withers
V2.0	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
V3.0	Review of V2.0	Ira Jakupovic
V4.0	New numbering and SOP format. Removal of reference to Serious Breach and Safety measures as covered in separate SOPs	Debbie Rolfe
V5.0	New logo and Trust name	Lucy Parker

V6.0	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"	Godwill Iheagwaram
V7.0	Reflecting changes in JREO to JRES and job titles and minor changes to delegations of responsibilities. Also, insertion of Associated JRES documents table.	Georgia Bullock

Associated JRES documents

SOPs	WPDs	Docs	LOGs
JRESGOVSOP0011 Management of Amendments StG Sponsored JRESGOVSOP0032 Reporting of Serious Breaches	JRESWPD0023 General Research Definitions	JRESDOC0061 Deviation Reporting Form	

Contents

1. Background

A study protocol that has received HRA/REC approval and, where applicable, MHRA approval, must be strictly adhered to, in order to ensure patient safety and data integrity. This is particularly important for Clinical Trials of Investigational Medicinal Products (CTIMPs), in order to be compliant with the current Clinical Trials Regulations.

Deviations from clinical trial protocols and Good Clinical Practice (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.

Occasionally it may be necessary to deviate from the requirements of a protocol to protect the safety of a research participant and this is known as an Urgent Safety Measure. For CTIMPs, these need to be reported according to defined reporting requirements.

The recording of all deviations from the protocol is essential to facilitate the assessment of their effect, either singularly or collectively, on the wellbeing, rights and safety of the trial subjects or on the data generated for the study.

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 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 clinical trials Sponsor.

3. Scope

This SOP outlines the process for recording, reporting and assessing deviations, which is to be followed by the JRES and all Investigators undertaking CTIMPs and non-CTIMPs sponsored by St George's. Deviations may need to be upgraded as 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 to the JRES and where applicable, to the REC and MHRA.

This SOP does **not** cover the management of Serious Breaches - please refer to JRESGOVSOP0032.

4. Definitions

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

Protocol/GCP Deviation:

A deviation is any change, divergence or departure from GCP or from the study design/procedures defined in the protocol. An example would be undertaking a procedure in a slightly different way to that documented in the protocol.

Deviations will be assigned to one of three groups:

a. **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 deviations must be reported to the JRES immediately, since they may be reclassified as a serious breach.

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

b. **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 principles.

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

c. **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.

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.

The JRES recognises that deviations may be identified:

i) **Prospectively** eg: a patient is unable to attend a planned protocol-defined visit in the future. The Sponsor reserves the right to refuse the implementation of a prospectively identified deviation.

ii) **Retrospectively** eg: a monitoring visit identifies that a protocol-defined assessment was not performed.

Urgent Safety Measure:

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 the JRES, 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 CI/PI can choose to delegate the responsibilities outlined below to other members of their team:

- The PI must ensure that other research team members are trained in the JRES procedure outlined in this SOP, prior to being delegated any related responsibilities.
- The PI must record and report all deviations and urgent safety measures that occur, for the duration of the trial.
- Subject confidentiality must always be met and participants' names or other direct identifiers (e.g. hospital or NHS numbers) must not be included in any correspondence sent to the JRES.
- The CI is responsible for setting up and managing the Data Monitoring Committee (DMC) if required. The CI will inform JRES of all significant findings and recommendations by the DMC.

- The PI must implement any required urgent safety measures immediately. Following such measures, the Investigator must report the action(s) taken to JRES immediately. The CI must summarise the discussion/agreement with the MHRA in writing and submit to the MHRA, REC, and JRES within 3 days.
- The CI and PI have a responsibility to follow this SOP in detail.

5.2 The Joint Research and Enterprise Services (JRES)

The JRES' Research and Development Governance Team (RDGT), upon notification of a deviation, will assess the information provided and suggest corrective/preventative actions immediately.

The JRES will record all protocol deviations, and urgent safety measures on a Deviation spreadsheet for each individual study, within the timelines agreed within the protocol and section 6 of this SOP.
The procedure outlined below will enable the JRES to assess the impact of deviations considering the definition outlined above.

6. Procedure

6.1 Deviation

All deviations from the protocol and/or GCP should be documented in the CRF or by a file note in the TMF, in order for appropriate corrective and preventative actions (CAPA) to be taken. These deviations may also need to be included and considered when the clinical study report is produced, as they may have an impact on data analysis.

It is important to inform the JRES of deviations at the time they are identified. This will enable the JRES to help classify the deviation and devise a formal CAPA plan to be put in place if appropriate.

Deviations may be:

1. Reported directly by the Investigator or member of the research team.
2. Identified during monitoring visits/audits, by the Clinical Research Associate (CRA) or auditor.
3. Result from whistle-blowing by another source (contractors, medical staff and PIs) or indirectly via the JRES.

The impact of the deviation on the scientific value of the trial depends on a variety of factors (ie: the design of the trial, any impact on data and type of data affected, the impact of data being excluded, etc.).

6.2 Notifying the JRES of a Deviation

- All deviations must be reported to the JRES. Critical deviations should be reported immediately after being identified to ensure that the JRES 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 JRESGOVSOP0032).
- Complete a Deviation Reporting Form (JRESDOC0061) for each deviation. Each deviation must be allocated an individual deviation number in sequential order starting at 001 and a code from the list given on the form. 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 JRES of the deviation should contain enough information for the initial assessment and impact of the event to take place, both as a standalone report or where previous reports have been received collectively.
- The completed reporting form, any Urgent Safety Measures and/or Serious Breaches should be e-mailed to adverseevents@sgul.ac.uk.
- The information will be added to the relevant Deviations spreadsheet by the JRES.
- The JRES will undertake an assessment of the event as outlined in Section 6.3 of this SOP.

6.3 JRES Assessment of Deviations

All potential deviations will be assessed in the following manner:

- Critical or major deviations must be assessed within 24 hours of receipt.
- If the report of a deviation is isolated and would not qualify as a persistent occurrence at a site, then the report can be simply filed in the Sponsor Site File (SSF).
- If however, upon reviewing previously received logs held in the SSF, the deviation has occurred frequently this could collectively require upgrading of the deviation to the level of major or critical.
- The JRES assessor should discuss findings and evidence with the CI to highlight any possible reason and suggest a Corrective and Preventative Action Plan (CAPA).

- The JRES assessor and the Investigator will make an initial assessment of the deviation and assess the grading according to the perceived effect on either the trial subjects or scientific data for the trial.
- The deviation log should be uploaded into the SSF so that the CRA can review it prior to a monitoring visit. For multi-site studies a sub-folder can be set up for each site.
- The outcome of any assessment and CAPA will also be documented in the Trial Master File (TMF).

6.4 Procedure for Investigators Following JRES Assessment

It is important that the Investigator promptly responds to the any requests for further information, in order for the JRES to meet their governance obligations. The Investigator and/or the person that identified the deviation must respond to requests within 48 hours from when the Investigator is informed of the JRES assessment.

6.5 Follow-up Reports

It is recommended that all follow-up reports, including CAPA and resulting changes in practice, are forwarded to the Governance Team at the JRES for inclusion in the SSF and for use at future monitoring visits. The follow-up form should be marked as a 'follow up report' to deviation number XXX for XXX trial reported on dd/mm/yyyy.

6.6 Additional Actions Taken by the JRES

- The Research and Development (R&D) department of the site where the deviation(s) occurred may also be informed if the deviation is considered 'critical'.
- It is good practice to inform other CIs 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.
- It is important that all members of the JRES' RDGT are aware of all critical 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.
- All deviation forms and logs, subsequent CAPA, assessments, follow-ups and related correspondence must be filed in the TMF and SSF to ensure availability to all relevant JRES team members for monitoring, audit and inspection and for 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 a temporarily halting of the trial may be taken without prior authorisation from the REC and/or MHRA. The CI/PI must immediately notify the JRES 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 JRES via adverseevents@sgul.ac.uk. The JRES will contact the CI/PI and discuss site and participant management going forward until an official amendment has been constructed for submission to the MHRA and REC.

Please note:

When the Sponsor halts a clinical trial (i.e. stops the recruitment of new subjects and/or interrupts the treatment of subjects already included), 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 JRES SOP on amendments (JRESGOVSOP0011) fully describes the procedures on reporting Urgent Safety Measures to the REC, MHRA, and JRES.

7. References

ICH GCP

http://www.ct-toolkit.ac.uk/routemap/urgent-safety-measures/

8. Appendices

None associated with this SOP.