St George's University of London

St George's University Hospitals NHS
NHS Foundation Trust

Standard Operating Procedure (SOP)
Routine Monitoring of CTIMPs Sponsored by St George's

SOP ID number:	JREOSOP0009	**Effective Date:**	02/01/2018
Version number and date:	Final Version 6.0 15/12/17	**Review Date:**	02/01/2018
Author:	Debs Rolfe	**Title:**	Regulatory Assurance Manager
Approved by:	Subhir Bedi	**Date:**	22/12/17
Signature of Authorisor			

This is a controlled document.

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

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

List of SOP Chronology

SOP Version Number:	Reason for Change:	Author:
V1.0	Original Version	Alisa Withers
V2.0	To update the previous original version in line with new procedures implemented by the JRO.	Ira Jakupovic Caroline Corbett
V3.0	To include reference to clinical trials in non CE marked medical devices	Harshani Hettiararchi
V4.0	New JREO Template and SOP numbering. Amendments to reflect new JREO process.	Ekugbe Onoge Mallikarjuna Rao Vemula (Arjun)
V5.0	Logo and Trust name updated, reference to HRA and background of SOP, refined definitions, reference Monitoring WPD	Debs Rolfe
V6.0	New SOP format and minor adjustments	Godwill Iheagwaram, Sue Cromarty, Debs Rolfe

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.

To breach these requirements constitutes a breach in criminal law. The requirements have been incorporated into this Standard Operating Procedure (SOP) to define procedures undertaken by the Sponsor (St George's, University of London (SGUL) and/or St George's University Hospitals NHS Foundation Trust (SGHFT) to comply with the UK Regulations.

In order to meet the requirements of the UK regulations, the Joint Research and Enterprise Office (JREO) must have monitoring procedures to ensure Clinical Trials of Investigational Medicinal Products (CTIMPs) sponsored by St George's and Clinical Investigations which include a CE marked device used/applied outside the scope of the technical information or a non-CE marked device are conducted in accordance with the principles of Good Clinical Practice (GCP) (R2).

In accordance with the Medical Devices Regulations and subsequent Guidance Notes produced by the MHRA and HRA guidance for clinical trials involving non-CE marked medical devices, monitoring activities will be carried out by the JREO for all Clinical Trials in Medical Devices (CTMD) as akin to CTIMPs.

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 Hospitals NHS Foundation Trust (SGHFT). St George's will be the official name used on all SOPs to represent either institution acting as Sponsor.

3. Scope

This SOP outlines the role of the Regulatory Support Officer (RSO) in the monitoring of clinical trials Sponsored by St George's. This SOP applies to CTIMPs and clinical investigations of a medical device (CTMD) sponsored by St George's.

4. Definitions

For general research management related acronyms used in this SOP refer to "General Research Definitions" working practice document JREOWPD0020

5. Responsibilities

5.1 Investigator Responsibilities

a) The Investigator must update the JREO with patient recruitment status by communicating this information directly to the RSO or entering recruitment figures on EDGE regularly to ensure compliance with the monitoring plan.
b) The Investigator must inform their assigned RSO of any staff changes during the lifetime of the trial to facilitate documentation of training on Sponsor SOPs, the protocol and any study related procedures.
c) The Investigator must ensure all staff members with any trial related duties are fully trained on the protocol and competent to carry out those tasks.
d) The Investigator must make themselves and their team available for monitoring visits.
e) The Investigator must ensure that the study site files and any requested Case Report Forms together with respective source data is available for the monitoring visit.

5.2 Regulatory Support Officer Responsibilities

a) The RSO is responsible for verifying that the study is being conducted according to the study protocol and in compliance with GCP, UK Regulations and any other applicable requirements.
b) The RSO will share all monitoring reports for investigator-led studies with the investigator team and (where relevant, the JREO research governance team) to ensure that the Investigator team understands the findings of the report in order to act upon them.
c) The RSO is responsible for ensuring training is provided by an appropriate research team member for all new trial staff members on all JREO SOPs and associated documents and logs appropriate for the protocol.

5.3 Subcontracted Clinical Trials Monitor Responsibilities

In addition to 5.2 a-c above the following are applicable:

a) The SuM is responsible for reading, understanding and complying with the JREO SOPs for CTIMP studies.
b) The SuM is responsible for ensuring that monitoring visit reports are copied to the Regulatory Assurance Manager for review and approval prior to circulating to the site Investigator team unless otherwise stipulated.
c) The role and responsibilities of the SuM will be stipulated in the Monitoring Plan.

6 Procedure

All CTIMPs Sponsored by St George's will be monitored. The RSO will produce a Monitoring Plan (JREODOC030) to document monitoring requirements for each individual trial based on a risk assessment conducted in accordance with JREOSOP0005 Risk Assessment for CTIMP studies.

The Monitoring Plan should be viewed as a guidance document that can be re-assessed and appropriately modified as the trial progresses. The monitoring plan will document the activities to be undertaken for the duration of the trial as well as the frequency and nature of the visits (*i.e.* initiation, routine, close-out visit *etc.*). All previous versions of the monitoring plan must be retained in the Trial Master File (TMF). Reasons for amendments or changes must be clearly documented in the updated version of the plan. The agreed Monitoring Plan will also be discussed with the Chief Investigator (CI) and the research team during the trial Initiation Visit (JREOSOP0013) and after any amendments or change has been made.

Every visit will always include a detailed review of the Investigator Site File (ISF) including 100% verification of Informed Consent Forms. For CTIMP studies visits to the pharmacy department to review the Pharmacy Site File (PSF) and procedures will be conducted regularly during the course of the study. It is anticipated that the first monitoring visit will normally be arranged and/or conducted, where reasonably practical after the first patient being recruited to the study.

6.1 Procedure undertaken by the CTM prior to monitoring visit

a) The RSO will contact the CI and/or PI by email prior to the planned visit to discuss the current status of the trial. The RSO will send the CI and/or PI 'intent to monitor letter' (JREODOC0036) to confirm the CI/PI is available on a mutually agreed date. The CI/PI may nominate appropriate team members to host the visit and for the RSO to liaise with (e.g. main research nurse) during the monitoring visit.
b) The RSO will also confirm (where relevant) the availability of the Lead Research Pharmacist (LRP) for the visit and confirm by letter (as above) a visit to the pharmacy department and, laboratory or other departments based on trial requirements.
c) The intent to monitor letter will inform the CI/PI and LRP of the purpose of the forthcoming visit and request that they make available appropriate source documents (*i.e.* patient medical records) Case Report Forms (CRFs), the ISF and/or the PSF for review during the visit.
d) The RSO will need to ensure that the study specific Patient Tracker has been prepared in accordance with protocol patient scheduled events (to assist in tracking study visit CRFs monitored) for each site

6.2 Procedure during the monitoring visit

The RSO will perform the monitoring visit in line with the current approved monitoring plan. The monitoring plan is typically designed to check the following aspects of the TMF and/or ISF: Also refer to JREOWPD0008

a) ***Status of the Investigator Site File (ISF)*** *–Is the ISF in good order? Is it stored in a confidential location with strict access? Is the ISF index/review (JREODOC004/JREODOC0035) tool present?*

b) ***Trial Master File (TMF)***- *Check the file against the appropriate TMF index and ensure that essential documentation is filed appropriately and kept up to date. Is it stored in a secure area with restricted access?*

c) ***TMF/ISF Essential Documents*** *–Are all essential documents as per appropriate Index present? Are documents appropriately version controlled? Comment on presence/absence of any old approved version. If any documents are absent, locate document and file appropriately.*

d) ***Standard Operating Procedures (SOPs)*** *– Are trial specific SOPs in the TMF/ISF? Is there an up to date training Log present to document that the trial staff have read and understood SOPs, especially trial specific SOPs (if applicable)? Does the team require any additional training?*

e) ***Amendments*** *– Is there a Log in place to document all amendments ideally in chronological order, both substantial and non-substantial? Evidence of R&D approvals in place for ALL substantial amendments and / acknowledgement for non-substantial amendments.*

f) ***Subject Recruitment*** *– Ensure that the trial team understands how to record information on and has been maintaining the following logs: Subject Screening Log (JREOLOG0001), Subject ID Log (JREOLOG0002) and Subject Tracking Log.(JREOLOG0003)*

g) ***MHRA remarks/REC conditions/R&D Department conditions/Funding conditions*** *– Ensure that all conditions have been addressed prior to any amendment related procedures/documentation being used.*

h) ***Delegation of Responsibilities and Signature Log (JREOLOG0004)***–*Ensure that all trial staff have completed and signed the Log and the CI/PI has signed off each member of staff. For each member of staff on the Log, a copy of the signed and dated CV current within 2 years is filed in the ISF and a current GCP training certificate is also filed (training attended within last 3 years). Any CVs and GCP certificates that are updated throughout the duration of the study should also be filed. Remind the Investigator to enter end dates for team members who cease to work on the trial. New staff members should provide a recent signed and dated CV along with GCP certificate for the file. Training logs present for new members? Do they require training on the study protocol – must be documented once completed.*

i) ***Trial specific meeting and training*** *–Ask about the frequency of team meetings to discuss any trial related duties. Advise the team to keep a record of all meetings with names of personnel present and minutes of the discussion.*

j) ***Pharmacovigilance (PVG) and Drug Safety*** *(or Device Safety) – Ensure that the team understands what needs to be recorded and that this is routinely done. Discuss the PV section of the protocol with the trial team and explain recording/reporting requirements in detail if necessary. Check source data against CRFs, AE forms and SAE forms to ensure protocol PV reporting requirements are being adhered to. Ensure that the team understands and has been adhering to external reporting requirements if required (e.g. IMP supplier/manufacturer and/or funding organisations etc.) If applicable, compare patient diaries for any AEs entered by patient to CRF and AE log – do any qualify as SAEs? Remind the CI of the DSUR*

anniversary date. Remind the trial team of their obligation to ensure IB/SmPC/RSI is checked and updated periodically and at least annually. NB Research Pharmacy regularly check for SmPC updates. For blinded trials verify with the trial team that the procedure for un-blinding in an emergency situation has been tested and validated and that this procedure has been documented (this is also undertaken during the risk assessment and initiation procedure)

k) ***Laboratory(ies)*** *– Ensure that the trial team, in particular the personnel dealing with data, have access to all the normal range(s) of all the tests carried out on their samples in order to make a judgement of any possibility of AE/R (this is also undertaken during the initiation procedure). Ensure that all laboratories involved in the analysis of samples have the appropriate certification in place e.g. GLP certification, validation of protocol specific assay? Investigator should sign and date all the reports generated during the trial and complete with statement as to whether it is 'clinically significant' or 'not clinically significant'. Ensure that any samples are stored in line with GCP guidance and the study protocol requirements. Encourage use of Sample Collection log and Sample Storage Box map*

l) ***IMP/Device management*** *– Remind the trial team to use the Research Pharmacy approved Clinical Trial Prescription Form (cross check version numbers with original approved copy kept in PSF at each site). Check the prescription was written up after patient consent taken. Prescriptions must be signed by delegated qualified team member (approved prescribers as per delegation log retained in PSF) and a copy of the prescription form present in the medical notes.*

m) ***IMP/Device handling*** *- Who is handling the IMP/device? Personal Protective Equipment (PPE) required? Do they fully understand their responsibilities (i.e. they must not change the source of IMP, or the formula, or the dose or schedule without a substantial amendment)? Are the IMP/device(s) securely stored, according to the correct temperature/storage conditions? Note the correct storage conditions in the report. Are temperature logs kept? Is there a calibration or revalidation certificate on file for the thermometer? Have any temperature excursions occurred? Document the date range for the temperature records and state "no excursions" where none have occurred. However if temperature excursions have occurred – what action was taken? Review related documentation for completeness and check if reported as protocol deviation. How is IMP transported to patient? When does administration take place? Is there a chain of custody? Did administration take place prior to the expiration date of the product? How many doses/ IMP containers are expected in relation to physical findings?*

n) ***CRFs and Source Data Verification (SDV)*** *– Ensure that any trial related activity has been performed only after informed consent has been taken and in accordance with the procedure as defined in the protocol. Have CRFs been recently amended? Is data for each subject recorded using CRFs? Are CRFs stored separately to the signed Informed Consent e.g. in a separate folder? Verify information collected in CRFs by cross checking with medical records? Are Clinical Trial Alert stickers evident on the outside of the patient medical notes? If electronic patient records, has their inclusion into a Clinical Trial been flagged?*

o) ***Protocol Deviations, Serious Breaches & Urgent Safety Measures*** – *Ensure that all Protocol Deviations, Serious Breaches, Urgent Safety Measures (if any) are recorded and reported in accordance with the JREO SOPs (JREOSOP0012 & JREOSOP0032).*

p) ***Maintenance of equipment***- *request to see service and maintenance records and machine validation checks*

The above is not intended to be a definitive or exhaustive list of checks but represents a guide which can be used when developing the monitoring plan. Further checks will be performed in order to demonstrate that the study is being conducted in line with the current approved protocol and all sponsor requirements . Conversely lower risk studies will have fewer checks.

6.3 Procedure after the monitoring visit

a) The RSO should ensure that a close-out meeting for the visit is arranged, to enable the RSO to discuss any findings from the visit, resolve as many issues as possible (e.g. Signing off lab reports, CRFs etc.) and make suitable recommendations prior to issuing a formal monitoring report. Timelines for completing findings/data queries must be agreed at this meeting and re-iterated on the monitoring visit report.

b) The RSO needs to make sure that the Monitoring Visit Log (JREOLOG0008) is signed during the close-out meeting. A copy will exist both in the ISF and PSF (these may be specific to each department). Take a copy of/scan the Log and file a copy in the Study Sponsor File (SSF). Alternatively for multi-site studies a note to file may be created stating that the monitoring logs are in the ISF and will be sent to the SSF at the end of the study.

c) The RSO should complete the monitoring visit report (JREODOC0031) within 2 weeks of the visit to document recommendations, actions undertaken and actions required resulting from the visit. Actions required will be accompanied by timelines for completion of the actions. The report should be discussed, reviewed and signed by the Regulatory Assurance Manager (RAM). The finalised report will be sent to the CI/PI, relevant study team members and LRP (if applicable). Copies of the monitoring visit report will be retained in the TMF, ISF, PSF (if applicable) and SSF.

d) If required, the RSO may arrange a follow-up visit to check that any issues requiring resolution have been addressed as recommended in the monitoring report.

e) The RSO will update the study specific 'Monitoring visit log' with details of the monitoring visit. The RSO will also upload the monitoring report and protocol deviation log (if relevant) to the e-SSF.

f) The RSO will follow JREOWPD0016 to record any study related expenses and update the patient visits on the Patient tracker under the site specific tab

6.4 Triggers for monitoring visits

a) The PI at each site is responsible for completing the Self-Monitoring form JREODOC0040. The frequency of completing the form will be detailed in the study monitoring plan. The

PI may delegate this responsibility to another member of the team. However, the PI's signature is still required to confirm that he/she has agreed with the information provided to the Sponsor.

b) PI and/or Trial Coordinator/Data Manager will be asked to send a copy of the completed form to the RSO or RAM. The RSO and/or the RAM will review the questionnaire once received.

c) Any potential issues identified during the review of the questionnaire will be discussed with the RAM in the first instance. The RAM will escalate issues to the Head of Research Governance & Delivery (HRGD) where necessary.

d) The monitoring plan will specify triggers that will initiate a monitoring visit. The following are some of the JREO examples that may trigger extra monitoring or monitoring of a non-CTIMP study:
   - Identification of a Serious Breach
   - Poor data quality
   - Persistent non-compliance with GCP

e) Triggered monitoring visits will be arranged and conducted as described in Sections 6.1 - 6.3 of this SOP.

7. References

The Medicines for Human Use (Clinical Trials) Regulations 2004 SI 1031 www.legislation.gov.uk/uksi/2004/1031/contents/made

The Medicines for Human Use (Clinical Trials) Regulations 2006 SI 1928 www.legislation.gov.uk/uksi/2006/1928/contents/made

ICH GCP: Note for Guidance CPMP/ICH/135 http://www.ich.org/

CT Tool Kit: Management and monitoring www.ct-toolkit.ac.uk

MHRA Clinical Investigations for Medical Devices:

https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device

8. Appendices

There are no Appendices associated with this Standard Operating Procedure