St George's University of London

St George's University Hospitals NHS
NHS Foundation Trust

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Standard Operating Procedure (SOP) Initiation of Clinical trials of Investigational Medicinal Products (CTIMPs) Sponsored by St George's

SOP Chronology

SOP Version Number:	Reason for Change:	Author:
V1.	Original Version – The procedure outlined in this SOP was drafted in March 2010 (Appendix 2). When the position of CTM was filled by Caroline Corbett (new CTM) the SOP was reviewed, updated and finalised in September 2010.	Ira Jakupovic Caroline Corbett
V2.	Minor clarifications in text upon review of the Original Version.	Harshani Hettiarachchi ira Jakupovic

V3.0	New template and numbering and minor clarifications	Mallikarjuna Rao Vemula (Arjun) Ekugbe Onoge
V4.0	New Trust name/logo and SOP update to reflect current practice	Debs Rolfe
V5.0	New HRA process and documentation in England	Mallikarjuna Rao Vemula (Arjun)
V6.0	Deputy PI to be checked on Delegation log	Debbie Rolfe
V7.0	Processes updated to reflect JREO change and SOP template update	Debs Rolfe, Sue Cromarty, Godwill Iheagwaram

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 (SGUL and/or SGHFT) to comply with the UK Regulations.

It is the GCP requirement under Schedule 1 Part 2 of the Regulation, that:

- The Investigator and Sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial – (Principle 8);
- Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits outweigh the risks – (Principle 10);
- A trial shall be initiated only if Ethics Committee, the Competent Authority (MHRA for UK) come to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored – (Principle 12).

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 (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 covers the procedure set up by the JREO to ensure that a trial site is initiated prior to the screening and/ or recruitment of any trial subject, any trial procedures taking place, and following the local site Confirmation of Capacity and Capability (in England) and NHS Permission (R&D approval) in Scotland, Wales and Northern Ireland along with issuing 'open to recruitment letter (JREODOC0043)'. The SOP also outlines the procedure the Regulatory Support Officer (RSO) and/or Regulatory Assurance Manager (RAM) will follow when initiating site(s) that wish to participate in single and/or multicentre trials 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

This SOP is to be followed by the JREO Governance team (*i.e.* the Regulatory Assurance Manager (RAM), and Regulatory Support Officers (RSO)). It is the responsibility of the HRGD to ensure that the SOP is updated and audited when necessary.

RAM is responsible for:

- Set up of the Sponsor Site File (SSF) in accordance with the JREO CTIMP Index (JREODOC0066) for CTIMP studies, JREODOC0082 for Device studies
- Provide Research pharmacy (CTIMP studies) with copies of the MHRA clinical trial application form, Copy of MIA IMP License if applicable, Approved CTIMP labels, MHRA authorisation letter, REC and HRA approvals.
- Ensuring that all approvals are evidenced and in place and request any outstanding documents e.g. Research Pharmacy Green light
- Signing the Site Registration and activation form (JREODOC0010) to ensure all documents are in place prior to the site initiation;
- Working with the CI to ensure that the list of sites highlighted in the IRAS application form completed by the CI is still current;
- Create an electronic (Sponsor) Trial Management File (eTMF)
- Liaising with the RAM /RSO/ Contracts manager to ensure that all clinical trial agreements (*i.e.* IMP supply agreement, Technical Agreement, Clinical Trial Site Agreements (CTSAs)) are finalised;
- Liaising with the RSO to inform him/her that when local host site (R&D) Approval/Confirmation of capacity and capability is issued and to organise the initiation visit with the Investigator.
- Issue the CI with the TMF index e.g. JREODOC0003 for CTIMPs with instruction to start populating with correspondence and essential documents. *NB There will be an opportunity where Sponsor Site file and Trial Master file will be compared to ensure duplication.*

The RSO is responsible for:

- Signing off the Site Registration and activation form (JREODOC0010);
- Liaising with the RAM and the Investigator (study management team where applicable) to organise the Initiation Visit;
- Preparing the initiation visit slides (*i.e.* update trial specific information, add contact details, investigator name, trial details *etc.*);for approval by the RAM
- Generating the Site Initiation Pack (SIP) – see Appendix 1;
- Producing/populating ISF & TMF with available documents within the JREO for the Investigators

- Conducting the initiation visit
- Generating the Initiation Visit Report (IVR) Monitoring visit report Template JREODOC0031

6. Procedure for St George's

6.1 *Pre-Initiation Procedure*

The RAM/RSO will:

1. Ensure that all essential documents listed in the Site Registration and activation form (JREODOC0010) are in place and that all agreements/contracts are signed off and finalised. Follow-up with the Investigator to obtain any outstanding documentation (if any);

Please note, the SSF should contain documents already provided/received during the trial set up process (i.e . Letters from the REC, MHRA, HRA, Sponsorship approval letter etc.) These documents will still be placed in the JREO SSF & eISF to be issued to external sites if applicable.

2. Issue an email confirming capacity and capability in accordance with JREOSOP0017.

3. Review the SSF (Sponsor Site File) located in the JREO and highlight all outstanding documents to enable the RSO to obtain those documents pre and/or during the initiation visit.

4. Inform the RSO that the site is ready for initiation to enable the RSO to:

    - Check the eISF and Pharmacy file as per the Site Registration and activation form and Pharmacy File Index (List of documents provided) along with associated SOPs;
    - Customise the SIP by completing the information requested on the cover page of the initiation visit slides.

The RSO will:

5. Generate the Initiation visit letter (JREODOC0036) for both the Investigator and the pharmacy;

6. Issue the letter to the CI and the Lead Research pharmacist (LRP) along with the SIP,and for external sites, ISF Index and ensure that:

    - The PI is aware that the TMF/ISF should be made available during the visit along with any central files that may contain CVs, GCP training certificates *etc.*;
    - The PI provides you with a list of all attendees of the initiation meeting;
    - The location of the TIV (Trial initiation visit) is suitable to accommodate all attendees and that the RSO has access to a laptop and, if possible, projector (if a projector is not available, provide site with printouts of the SIV slides).
    - That the LRP is available to attend the meeting (please note the pharmacy initiation visit may have to take place separately);

- Ensure that Pharmacy has issued pharmacy Green light for the study (This may follow on from SIV).

7. Ensure that the PI and Pharmacy have confirmed their availability

8. The RSO must ensure that they have a thorough understanding of the approved protocol, esssential documents set (including the CRFs), trial procedures/assessments before conducting the initiation.

6.2 *JREO Initiation Procedure*

1. The RSO will present the initiation slides to the Investigator team and a copy of the presentation will be retained in the TMF/ISF.

2. Contact LRP and get a copy of the Pharmacy approved Clinical Trial Prescription template and any other IMP related paperwork, external pharmacy site packs etc – place a copy in the SSF. Request a ePDF copy to be provided by Research Pharmacy to Investigators (cc RSO/RAM to facilitate saving in e-TMF)

3. Where appropriate the Case Report Form (CRF) will be discussed page-by-page with the study staff to ensure all staff are aware of the completion requirements. A source document memo should be agreed and discussed with the study team. The RSO will construct this and forward it to the team following the initiation visit for retention in the ISF. A copy must be retained in the e-TMF.

4. The ISF will be reviewed in detail by the RSO and he/she will discuss all forms/log (Appendix 1) which are to be completed during the trial with the study staff. Any essential documents in addition to those required for site activation not previously collected will also be discussed and collected.

5. The following procedures will be discussed with the Investigator and study staff during the initiation meeting:

   - Reporting of AEs and SAEs including pregnancy reporting as documented in the Sponsor's PV (Pharmacovigilance) procedure for Investigators; AE log (JREOLOG0007). Ensure training log is filed in the ISF and signed by all staff present.
   - Documentation of subjects / patients, who have been screened, randomised or discontinued from the trial and communication to the RSO according to the monitoring plan.
   - The need to notify the subject's GP of inclusion in the study using the current REC approved version of the GP letter (if applicable) and enter the details in GP letter log (JREOLOG0014).
   - Opening a study randomisation code for a patient in an emergency, (code break envelopes should be on site by the time IMP is at site) and out of hours access will be provided for code breaking as the primary concern is patient safety. Check 24 hour access IS available- cross check location of code-break access and whether there

could be a problem over a weekend. Is there a backup arrangement?

- Investigator responsibilities during the trial.
- Storage and temperature monitoring (using calibrated/ certificated temperature monitors) of study drug/device/samples, and the importance of reporting of any temperature excursions that occur.
- Process for prescribing drug orders and re-labelling (if anticipated).
- Product re-call procedure.
- Delegation of responsibilities to study staff by the Investigator. JREOLOG0004 'Staff Delegation of Duties Log' will be completed. A named deputy PI must be evident on the delegation of duties log that can undertake all clinical decisions for the upkeep of participant safety in the absence of the main PI. Updated copies of the log to be held where appropriate to allow cross-reference of designated responsibilities (e.g. Pharmacy). **Pharmacy must have a copy in the pharmacy file detailing authorised prescribers.**
- CVs and GCP certificates will be collected for any personnel signing the 'Staff Delegation of Duties Log'. Where possible these CVs will be current and signed and dated within the past year, or in accordance with local SOPs. GCP training should be within last 3 years and renewed every 3 years throughout the life of the study.
- Monitoring Plan prepared by the RSO and/or RAM.
- Regular update (Send screening logs) of patient recruitment activity must be provided to the JREO at agreed intervals appropriate to predicted recruitment target.
- Importance of reporting of first patient recruited to JREO via RSO or RAM.
- Importance of ensuring recruitment is uploaded into EDGE database by the delegated member of the research team

6. The procedure for storage, ordering, handling, dispensing and accountability of the study medication will be discussed with the study staff/pharmacy, together with the procedure to be followed in the event of a product re-call and the reporting of temperature excursions. If required, a separate initiation meeting will be held with the pharmacy staff responsible for the study. A full inventory of the study medication sent to site will be made and storage conditions checked and noted (for future reference on monitoring visit reports). A copy of the Delivery note and batch certification, i.e. QP release certificate, will be taken for retention in the SSF.

7. Where the IMP is shipped to the site prior to initiation (but post completion of the Site Activation Form) Pharmacy will be requested to confirm quarantine of IMP until receipt of the 'open to recruitment' letter from the JREO (JREODOC0043)

8. All Investigator Site team members attending the meeting will be asked to sign a training log JREOLOG0016 and Initiation Training Session Attendance log JREOLOG0010 to document their presence and training received during the initiation visit.

9. Where appropriate, copies of any nursing guidelines/study plans prepared by the Investigator site staff will be collected for review by the RSO / RAM to ensure that they are

consistent with the protocol.

10. The Monitoring Visit Record Log JREOLOG0008 will be signed and a copy filed in the relevant site file.

6.3 Procedure for external sites

1. Undertake the pre-initiation procedure as described in Section 6.1 of this SOP; Feasibility form (JREODOC0083).

2. Prepare three copies of the Clinical Trial Site Agreement (CTSA) if indicated in use on HRA Statement of Activities form and send to the site for signature (along with copies of any other relevant agreements/contracts if applicable);

3. Upon receipt of all local approvals/ Confirmation of Capacity and capability (as documented in the Site Activation/Registration Form) including a copy of the completed Site Activation/Registration Form and the signed CTSA the site will be contacted to arrange a visit with the site team for the initiation;

4. Ensure that the site is sent confirmation details of the initiation visit

5. Follow the process outlined in Section 6.2 of this SOP

6. Ensure the site PI has returned the following:

    - A copy of the Delegation of responsibilities Log for a copy to be placed in the dispensing pharmacy file
    - Receipt/Acknowledgement of the ISF and/Pharmacy File
    - Any other relevant outstanding documents.

6.4 Post initiation visit procedure

1. The RSO will complete the Initiation Visit Report (IVR) within 10 calendar days of the visit. This report will be reviewed and signed off by the RAM within 14 calendar days of the visit. The report will summarise all discussions held, any materials delivered and documentation collected.

2. Once all outstanding actions are completed (if applicable) the 'open to recruitment' letter is issued to each individual site by the RSO/RAM and a copy sent to pharmacy.

3. The site is now open to screening/recruitment

4. Ensure that all site initiation documents are filed in the Monitoring section of the ISF and TMF (copies will also be retained in Sponsor Site file retained in JREO).

5. Ensure that EDGE is updated with site status- Open to Recruitment

7. References

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended http://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf

EU Clinical Trials Directive 2001/20/EC http://ec.europa.eu/health/human-use/clinical-trials/directive/index_en.htm

http://www.hra.nhs.uk/resources/hra-approval-guidance-for-sponsorschief-investigators-working-collaboratively-with-nhs-organisations-in-england/

8 Appendices

Appendix 8.1 Site Initiation Pack (SIP)
Appendix 8.2 Trial Initiation Procedure for St George's sponsored and hosted CTIMP

Appendix 8.1

Site Initiation Pack (SIP) Preparation List

Listed below are the documents that must be put together to generate the SIP:

1. Initiation Visit Slides prepared by the RSO
2. Initiation Visit Letter confirmed appointment with the site PI or CI
3. Site Registration/Activation Form
4. Investigator Site File Index & Trial Master File index, files populated with required documentation
5. Investigator Site File Index Review
6. Sponsor's Trial management/conduct Logs:
    - Subject Screening Log (JREOLOG0001)
    - Subject ID Log (JREOLOG0002)
    - Subject Withdrawal, Enrolment and Completion Log (JREOLOG0003)
    - GP letter log (JREOLOG0014)
    - Staff Delegation of Duties Log (JREOLOG0004)
    - Protocol Violations and Deviations Log (JREOLOG0005)
    - Study Amendments Log (JREOLOG0006)
    - AE Log (JREOLOG0007)
    - Monitoring Visit Log (JREOLOG0008)
7. Sponsor's Standard Operating Procedures (SOPs)for trial management/conduct (ZIP file – JREO sponsored CTIMP studies)
8. Associated pharmacy documents –liaise with LRP
9. Monitoring Plan

Appendix 8.2

Trial Initiation Procedure for St George's sponsored and externally hosted CTIMPs

1. Purpose of the procedure:

- Set up and maintenance of the Investigator Site File (ISF)
- Research Team awareness of Investigator/Sponsor responsibilities
- Research Team awareness of GCP compliance requirements
- Discuss Sponsor's internal procedures to ensure compliance with GCP
- Distribute Sponsor's Logs and advice on completion and purpose

2. When is it conducted?

- JREO issued **final sponsorship** (subject to MHRA/REC/HRA approval)
- All **contract** with external vendors are agreed
- Pharmacy is ready to issue **'green light'**
- **Support Departments** approvals in place
- **Case Report Forms (CRFs)** approved by Sponsor representative

3. Procedure

BEFORE the INITIATION MEETING:

Single site CTIMP **sponsored** and **hosted** by **St George's** (SGUL or SGHFT):

- **'Intent to Initiate email** sent to the CI & study team
- 3 dates proposed to ensure **availability** of the **entire study team**
- Review the content of the **ISF**
- **Read** and understand the study **protocol**
- Make 'Initiation Meeting **Slides**' and 'Sponsor's **Logs**' **trial specific –RAM to approve**
- Meeting date confirmed: **Book** a meeting room with **AV** facility
- **Confirm** the exact **time** and **location** with the study team
- Issue **'Monitoring Plan'**
- Ensure **all contracts** are signed

DURING the INITIATION MEETING

- **Present** slides
- Present **Logs** in relation to JREO **trial management** -Advice on **Log purpose** and **completion**
- Ensure **Delegation of Duties Log** is **signed** by the team
- **ISF** review: Discuss all missing documents
- Discuss any **outstanding contracts**
- Summarise the visit and findings if any
- Discuss monitoring plan (frequency of monitoring)
- Explain 'Open to Recruitment Letter'
- Ensure 'Monitoring Log' is signed
- Ensure Training & Attendance logs signed by all present

AFTER the INITIATION MEETING:

- Prepare the **'Initiation Meeting Report'**
- Ensure all **outstanding actions** are mentioned and **timelines** are given
- Issue **'Site confirmation of Capacity and Capability**
- Liaise with Pharmacy to confirm **'green light'** is given
- Issue **'Open to Recruitment Letter'**

Multi-centre CTIMP **sponsored** and **hosted** by St George's (SGUL or SGHFT) and other sites:

- Initiate St George's site as described on left
- Site feasibility form (JREODOC0083)
- Send the Site Registration/Activation Form to each site listed in the protocol

Include the following documents:

Study approvals (MHRA/REC/HRA), Sponsorship and Insurance Letter, Approved Documents (Protocol, Patient/Subject Information Sheet, Consent Form (ICF), GP Letter), Sponsor's Logs and final CRFs, Investigator Site File Index, Trial Specific SOPs, Clinical Trial Site Agreement and any other applicable agreements.

- Site Self-Monitoring Form (JREODOC0040)
- Instructions of Trial Management and Participation
- Request - Site confirmation of capacity and capability/ Host site approval

Request the following documents back: and file in SSF or TMF

- Signed and dated study protocol; PIS, ICF and GP Letter on local headed paper; Investigator CV and GCP certificates, study team contact details
- Signed and dated agreements
- Completed Delegation of Duties Log
- Completed Site Registration/Activation Form

Upon receipt of the above:

- Review for ambiguity
- Contact site to obtain missing information
- Ensure all documents are in place as requested
- Issue 'Open to Recruitment Letter'