Standard Operating Procedure (SOP)

Site Initiation, Monitoring and Close-Out for CTIMPs Sponsored by St George's

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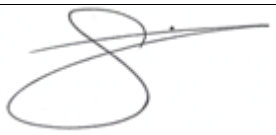
Signature of Authorisor			

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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
V7.0	**Updated to incorporate JREOSOP0013 and JREOSOP0014 into this SOP.** Amendments to JREO to JRES. Updated Associated JRES documents table. Updated references and links. Minor administrative amendments to original text.	Georgia Bullock

SOPs	WPDs	Docs	LOGs
JRESGOVSOP0012 Protocol and GCP Deviations JRESGOVSOP0032 Reporting of Serious Breaches	JRESWPD0008 Monitoring JRESWPD0023 General Research Definitions	JRESDOC0003 TMF Index JRESDOC0004 ISF Index JRESDOC0031 Monitoring Visit Report Template JRESDOC0040 Self-Monitoring Form	JRESLOG0001 Screening and Enrolment Log JRESLOG0002 Subject ID Log JRESLOG0004 Staff Delegation of Duties Log JRESLOG0008 Monitoring Visit Log

Contents

1. Background

In order to meet the requirements of the UK Clinical Trials Regulations and the principles of Good Clinical Practice (GCP), the Joint Research and Enterprise Service (JRES) must have procedures in place for the initiation, monitoring and close-out of study sites participating in Clinical Trials of Investigational Medicinal Products (CTIMPs), which are sponsored by St George's. This includes Medical Device trials where approval by the UK regulatory authority is required.

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 either institution acting as Sponsor.

3. Scope

This SOP outlines the procedure for the monitoring of sites participating in CTIMPs sponsored by St George's, including the Site Initiation Visit (SIV) and the Close-out Visit. It also outlines the role of the JRES Clinical Research Associates (CRAs) in the monitoring of clinical trials sponsored by St George's.

4. Definitions

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

Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and the applicable regulatory requirement(s). (ICH GCP).

Monitoring plan: a formal, trial-specific document which clearly identifies the elements of monitoring to be covered and how it will be conducted. The monitoring plan will include frequency of visits, any triggers or escalations, the type of monitoring to be used (on-site or remote), percentage of source data verification and on what data. Key standards and procedures may be referenced including query management and the expected communications. The document will be agreed between the Sponsor and the Investigator and will be provided by the assigned CTA at the SIV.

Site Initiation Visit (SIV): a monitoring visit which occurs prior to patient recruitment to prepare and set up a research site, to ensure that the site is ready to start enrolling patients.

Close-out Visit: the final monitoring visit which ensures that the investigator has a complete and independent record of the trial at their site and that all trial-related activities are appropriately reconciled and documented. The close out visit may also include a review of the archiving arrangements and facilities.

5. Responsibilities

This SOP is to be followed by all investigators conducting St George's sponsored CTIMPs and the JRES Governance team, including the CRAs and Research Development and Governance Manager (RDGM).

5.1 Investigator Responsibilities

a) The Investigator must update the JRES with patient recruitment status by communicating this information directly to the CRA or entering recruitment figures on EDGE regularly to ensure compliance with the monitoring plan.
b) The Investigator must inform the assigned CRA of any staff changes during the lifetime of the trial to facilitate 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 their assigned tasks.
d) The Investigator must make themselves and relevant members of the trial team available for monitoring visits, including the SIV and Close-out visit.
e) The Investigator must ensure the completeness of all trial site files (eg: Investigator Site File/Trial Master File, Pharmacy Site File) and Case Report Forms (CRFs) and must ensure that these are available for monitoring visits as requested, together with the related source data.
f) The Investigator is responsible for the resolution of any outstanding issues raised at monitoring visits and as listed on the monitoring report.
g) The Investigator must notify the CRA of the Last Patient Last Visit (LPLV) for the Close-out Visit.

5.2 Clinical Research Associate (CRA) Responsibilities

a) The CRA 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 CRA is responsible for producing a monitoring plan for their assigned trials, based on the individual risk assessment, and reviewing/modifying the monitoring plan as necessary as the trial progresses.
c) The CRA is responsible for liaising with the trial site to arrange monitoring visits in accordance with the trial-specific monitoring plan.

d) The CRA will conduct all monitoring visits.
e) The CRA will write all monitoring visit reports and share these with the investigator and their team and where relevant, the JRES research governance team.
f) The CRA is responsible for ensuring training is provided by an appropriate research team member for all new trial staff members on all JRES SOPs and associated documents and logs appropriate for the protocol.

6. Procedure

For detailed instructions on each procedure, refer to the current version of Working Practice Document JRESWPD0008.

Site Initiation Visit (SIV)

a) The CI should confirm that the list of sites highlighted in the IRAS application form is still current.
b) External sites will be sent copies of any Trial Agreements/Contracts for signing. This will include the PI Responsibilities Agreement – CTIMPs (JRESDOC0128) which must be signed by the PI before the Sponsor will issue greenlight for recruitment. They must also provide all local approvals and acknowledge the receipt of the ISF and Pharmacy File.
c) The CRA should liaise with the trial site to arrange the SIV and will prepare the JRES Initiation Slides and Site Initiation Pack (see Appendix 8.1). The CRA/study team will prepare the study specific SIV slides.
d) The CRA will produce/populate the ISF for all sites (and the TMF if this is under JRES management) with the available documents for the Investigator.
e) The CRA will generate and issue an Initiation Visit letter for both the Investigator and the Lead Research Pharmacist at the site. The Site Initiation Pack and the ISF Index (for external sites) will also be issued. If the SIV is to be conducted remotely, the external site will be provided with the ISF index and will be expected to prepare the ISF on site.
f) The CRA will ensure that they have a good understanding of the protocol, CRFs, trial procedures and essential documents prior to conducting an SIV.
g) The Investigator/Site must ensure that:
    - The TMF/ISF is available during the SIV along with any central files that may contain CVs, GCP training certificates etc.
    - A list of all attendees of the initiation meeting is provided.
    - The location of the SIV is suitable to accommodate all attendees and that the CRA has access to a laptop and projector. If a projector is not available, then the SIV slides should be printed for the attendees.
    - The Lead Research Pharmacist is available to attend the SIV or the visit can be arranged separately /remotely.
    - The Research Development and Governance Team/CRA will ensure that the Site Registration and Activation form (JRESDOC0010) is signed to confirm that all documents are in place after the SIV. This includes all approvals, trial site

files, Sponsor site files and Clinical Trial Agreements which must be in place prior to start of recruitment

h) **Remote SIVs:** there may be occasions where an SIV can be conducted remotely via telephone or via an audio/video platform (e.g. Skype) between the CRA and the site, and/or a Site Initiation Pack sent to the site containing instructions with forms to complete and return. The SIV may not be required at all, for example, where there is familiarity with the site; the site has previously received training in similar trials; the simplicity of the trial is such that training is considered unnecessary. However, any such decisions must be clearly documented and justified in the risk assessment and/or monitoring plan. If conducted remotely, the method (Skype, teleconference etc.) must be accsessible for all. If possible, a recording of remote meeting should be taken and retained in the eTMF.

i) The CRA/study team will present the slides at the SIV and the following procedures will be discussed with the site team:
    - Investigator responsibilities during the trial.
    - Delegation of tasks/responsibilities to trial staff by the investigator on the Delegation of Duties log.
    - The ISF requirements and the collection of any outstanding documents, including signed CVs and current GCP certificates for all staff on the Delegation of Duties log.
    - Overview of the CRF, including instructions on how to complete each page.
    - Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs) using the appropriate forms/logs.
    - Documentation of all patients screened, randomised and withdrawn and the reporting of these to the CRA.
    - Notification of an individual's enrolment to the trial to their GP using the appropriate letter/log.
    - The emergency code break procedure for randomised trials including out-of-hours procedures.
    - The storage and temperature monitoring for trial drugs and biological samples, where applicable and the procure for reporting any deviations.
    - Management and dispensing of the trial medication, including product re-call procedures.
    - Provision of recruitment updates to the JRES.

j) After the SIV, the CRA will complete the Initiation Visit Report (IVR) within 10 working days of the visit. This report will be reviewed and signed off by the RDGM within 14 working days of the visit. The report will summarise all discussions held, any materials delivered and documentation collected.

k) Once all outstanding actions are completed (if applicable) the 'Open to Recruitment' letter will be issued to each individual site by the CRA/RDGM and a copy sent to pharmacy.

l) The site will then be open to screening/recruitment.

m) All SIV documentation must be filed in the ISF and TMF and in the Sponsor Site File at the JRES. EDGE should also be updated to show the site status as 'Open to Recruitment'.

Monitoring

a) All CTIMPs sponsored by St George's will be monitored as per the trial-specific Monitoring Plan produced by the assigned CRA based on the risk assessment.
b) The monitoring plan should be viewed as a guidance document that can be re-assessed and appropriately modified as the trial progresses.
c) 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 (eg: initiation, routine, close-out visit). All previous versions of the monitoring plan must be retained in the TMF. Reasons for amendments or changes must be clearly documented in the updated version of the plan. The agreed plan will also be discussed with the CI and the research team during the SIV and after any amendments or changes have been made.
d) All monitoring visits should include a review of the ISF and 100% verification of the Informed Consent Forms (if this is not done, the reason will need to be documented and justified in the monitoring report).
e) Regular visits to the Pharmacy will be made to review the Pharmacy Site File and related documentation.
f) The first monitoring visit after the SIV will usually be after the first patient has been recruited to the trial.
g) Prior to a planned visit, the CRA will send the CI/PI an email with an Intent to Monitor letter, and will agree a mutually convenient date with the Investigator or an appropriate nominated member of the trial team who will host the visit (eg: a Research Nurse). The CRA will also contact the Pharmacy and, if applicable, other departments (eg; laboratory) to confirm the visit and the availability of the relevant staff.
h) The letter will inform the trial team of the purpose of the visit and which documents need to be made available for the visit, for example: CRFs; patient medical records and other source documents; the ISF and the Pharmacy File.
i) Once at the site, the CRA will perform the visit according to the current monitoring plan.
j) The following aspects (list not exhaustive) will be checked/verified **(see JRESWPD008 for more detail):**
    - Status of the ISF/TMF and presence of all essential documents.
    - Trial-specific SOPs and evidence of training on these.
    - Amendments and their approvals and any conditions that should have been met.
    - Patient recruitment logs.
    - Delegation of Duties log and CVs/training certificates.
    - Trial meetings/training.
    - Pharmacovigilance/ Recording and reporting of AEs and SAEs.
    - Laboratory/Sample analysis/ Laboratory reports.
    - IMP management/storage/dispensing/administration.

- CRFs/Informed Consent/Source Data Verification (SDV).
- Protocol deviations/Serious Breaches/Urgent Safety Measures.
- Equipment maintenance.

k) After the monitoring visit, the CRA will meet with the trial team to resolve as many issues as possible and make recommendations before the formal monitoring report is issued. The CRA will also ensure that the Monitoring Visit Log (JRESLOG0008) is signed.

l) Within 2 weeks of the visit, the CRA will complete the Monitoring Visit Report (JRESDOC0031). Any actions will have timelines for completion. The report will be reviewed and signed by the RDGM. The final report will be sent to the CI/PI and other relevant trial team members and to the Pharmacist, if necessary. Copies of the report and any protocol deviations must be filed in the TMF, ISF, Sponsor Site File and in the Pharmacy Site File if applicable.

m) A follow-up visit may be needed to check that any actions/recommendations have been addressed.

n) The CRA will update any JRES spreadsheets with details of the completed monitoring visit.

o) The PI at each site is responsible for completing the Self-Monitoring Form (JRESDOC0040) as per the monitoring plan for the trial. The CRA/RDGM will review this and highlight any concerns which may trigger a monitoring visit.

p) Additional monitoring visits may be triggered by:
   - Identification of a Serious Breach.
   - Poor data quality.
   - Persistent non-compliance with GCP.

Close-out Visit

a) The CRA will arrange the Close-Out visit as for other monitoring visits.

b) The CRA should prepare for the visit by cross-checking essential documentation versions and presence in the physical and electronic Sponsor Files. Previous monitoring reports should be carefully checked for any unresolved issues.

c) At the visit, the CRA will check the ISF/TMF for completeness and will ensure that the following documents are present:
   - Monitoring visit log for ISF, pharmacy file and laboratory file.
   - Staff delegation of duties log completed with start and finish dates and signed off by the PI.
   - Patient Screening log and other supporting logs as applicable.
   - Drug accountability and dispensing logs including receipt and dispensation to subjects.
   - All prescriptions are in the Pharmacy File.
   - Documentation of IMP destruction.
   - Treatment allocation and decoding documentation.
   - Code break envelope accountability/tracking form.
   - Audit certificate, if applicable.

- Financial agreement (all versions).
- A reminder that final invoices need to be raised to cover any activity.

d) The CRA will also check/verify that:
   - A reason for any early closure of a site is documented in the TMF/ISF. If a site is closed early, the CRA will need to inform the REC and the MHRA.
   - All SAEs for the site have been reported to the Sponsor and have been resolved. Any unresolved SAEs at site closure must be followed up.
   - All outstanding data queries and issues from previous monitoring visits have been resolved/documented.
   - Any loaned equipment has been returned, if applicable.
   - A timeline for database lock has been determined by the CI followed by sign-off of the final CRF.
   - The archiving procedure has been discussed with the site.
   - The Monitoring Visit Log has been signed by all present during the visit.
   - The drug accountability is complete.
   - The destruction or return of any unused IMP has been completed and documented.
   - The Pharmacy File documentation is complete and present.
   - Arrangements are in place for the destruction or ongoing storage of biological samples as agreed.
   - The Site Status on EDGE has been changed to reflect the fact that the site is closed.
   - The CI is aware of their responsibility to submit the End of Trial Notification form to the Sponsor within the required timelines. The CRA will submit this to the REC/MHRA as per regulatory and Sponsor requirements.
   - The CI has been reminded when the Final Study Report is due to be submitted to the Sponsor.

e) The CRA will complete a report within 5 days of the visit and will follow-up any issues identified at the visit.

7. References

ICH GCP and Clinical Trials Regulations:
https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/

CT Tool Kit: https://www.ct-toolkit.ac.uk/routemap/trial-management-and-monitoring/

8. Appendices

Appendix 8.1 Site Initiation Pack

Appendix 8.2 Trial Initiation Procedure for St George's sponsored and hosted CTIMPs

Appendix 8.1

Site Initiation Pack Preparation List

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

1. Initiation Visit Slides prepared by the CRA/study team
2. Initiation Visit Letter confirmed appointment with the site PI or CI
3. PI Responsibilities Agreement - CTIMPs
4. Site Registration/Activation Form
5. Investigator Site File Index & Trial Master File index, files populated with required documentation

6. Sponsor's Trial management/conduct Logs:
    - Subject Screening and Enrolment Log (JRESLOG0001)
    - Subject ID Log (JRESLOG0002)
    - Subject Withdrawal Log (JRESLOG0024)
    - GP letter log (JRESLOG0014)
    - Staff Delegation of Duties Log (JRESLOG0004)
    - Study Amendments Log (JRESLOG0006)
    - AE Log (JRESLOG0007)
    - Monitoring Visit Log (JRESLOG0008)
    - Study Training Log (JRESLOG0016)
    - Reconsenting Log (JRESLOG0023)
    - File Note Log (JRESLOG0022)
    - SOP Reading Log (JRESLOG0009)
    - Sample Collection Log (JRESLOG0012)
    - CVs and GCP Certs Log (JRESLOG0018)
7. Sponsor's Standard Operating Procedures (SOPs) for trial management/conduct (ZIP file – JRES 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?

- JRES 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 –RDGM 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 JRES **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 (JRESD0C0083)
- 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 (JRESDOC0040)
- 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'