Standard Operating Procedure (SOP)

Management of Amendments for Studies Hosted by St George's

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Approved by:	Subhir Bedi	**Date:**	11/01/2022
Signature of Authorisor			

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

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	Subhir Bedi
V2.0	Updates to JRES processes on appointment of new staff and update to REC/HRA Amendment review process	Joe Montebello / Chantelle Simpson

Contents

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. UK Regulations and subsequent amendments thereto set out the legal requirements for notification and approval of 'substantial amendments' arising from Clinical Trials of Investigational Medicinal Products (CTIMPs). To breach these requirements constitutes a breach in criminal law.

Studies that are not considered CTIMPS must still apply for formal approval of any substantial amendments under the terms of the UK Policy Framework for Health and Social Care Research.

Amendments are changes made to a clinical trial after a favourable ethical opinion and/or approval by a Competent Authority (*i.e.* HRA/MHRA in UK) has been given (1). Amendments can be made to any information relating to a trial. An amendment to a clinical trial can be either substantial or non-substantial in nature.

Substantial Amendments require favourable opinion from the REC that granted a favourable opinion for the trial (and from the Competent Authority if a CTIMP/Device trial) before they can be implemented. Substantial amendments will also need HRA approval. Upon submission of the amendment package to the relevant REC, the Sponsor/CRO will receive a "Amendment confirmation of REC Validation, categorisation and implementation information" email from the REC. This email contains a REC validation letter, which outlines the documents to be reviewed and states that the REC will issue an ethical opinion on the amendment within a maximum of 35 days from the date of receipt. The email also provides the status of HRA assessment (approval is either given from the date of the email or specified as pending assessment) and the HRA categorisation (see Table 1.). The implementation date is defined as 35 days from date amendment information together with the categorisation email, is supplied to participating organisations (provided HRA Approval for the amendment is in place and conditions are met).

Within 35 days of receipt of the amendment submission, the Sponsor/CRO will receive the REC opinion. If this is approved, the REC will provide a "Favourable Opinion of a Substantial Amendment Letter", listing the documents that have been approved with the corresponding version numbers and dates. This letter is usually attached to the email confirming HRA approval, which provides the amendment number, date and type and instructions to implement the amendment at sites by the date given in the categorisation email.

Non-substantial amendments require assessment and approval by the HRA only, prior to implementation at site

For multi-site studies conducted in the UK, the amendments are further categorised and a presumed implementation following regulatory approval has been adopted. Unless an objection to the amendment within a reasonable time ~ (35 days) is raised the amendment will be implemented.

Amendments have been grouped into 3 different categories –

Table 1. HRA Categorisation of Amendments

Category	Definition	Explanation
A	Amendment to research that ALL participating NHS organisations are expected to consider	Includes any amendment to a research study that has implications for, or affects, ALL participating NHS organisations hosting the research study. All participating NHS organisations will be informed of, and have access to the amendment, for example, additional trial related procedures to be performed onsite.
B	Amendment to research that only affect certain/specific sites	Includes any amendment to a research study that has implications for, or affects, SPECIFIC participating NHS organisations hosting the research study. Only those participating NHS organisations affected by the amendment will be informed of the amendment. However, all participating NHS organisations will have access to the amendment through the relevant national coordinating function. Only those participating NHS organisations affected by the amendment are expected to consider the amendment to determine whether they are able to continue to confirm capacity and capability.
C	Amendment to research that participating sites are **not** expected to consider	Includes any amendment to a research study that has no implications that require management or oversight by the participating NHS organisations hosting the research study, but the amendment should still be provided for information. All participating NHS organisations will have access to the

		amendment. Participating NHS organisations are NOT expected to consider the amendment or give continued confirmation for these amendments.

The Sponsor categorises the amendment as substantial or non-substantial, however for the purpose of this SOP, and for studies not sponsored by St George's, the primary consideration is the categorisation of the amendment by the HRA. The JRES, on behalf of St George's, should be sent all amendment notifications and documents for clinical research that takes place within St George's University Hospital's NHS Foundation Trust (SGHT) and/or St George's, University of London (SGUL). The JRES Amendments inbox, researchamendments@sgul.ac.uk, should be used for this purpose.

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 covers the management of amendments and Urgent Safety Measures for hosted clinical research studies.

4. Definitions

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

5. Responsibilities

JRES

This SOP is to be followed by members of the JRES.

It is the responsibility of the Head of Research Governance and Delivery within the JRES to ensure that the SOP is updated when necessary. This responsibility can be delegated.

The Clinical Research Auditor will be responsible for reviewing the amendment, updating the electronic JRES file and issuing R&D approval for the amendment, by the implementation date specified in the HRA categorisation email.

Investigator

It is the Principal Investigator's responsibility to ensure that amendments for hosted studies are submitted to the JRES for approval (**if not done by the sponsor**). The amendment pack and associated correspondence should be sent electronically to the JRES Amendments inbox: researchamendments@sgul.ac.uk. It is the responsibility of the Principal Investigator to ensure that the changes are not implemented for Category A and or B (relevant to St Georges) prior to JRES confirmation.

Research Teams & Support Departments

Research teams should ensure that amendments are reviewed carefully. If there is any aspect of an amendment that the team are unsure about, they should liaise directly with the study Sponsor and the PI.

The Clinical Research Auditor should notify Research Pharmacy of any amendments to hosted CTIMPs by sending the amendment package to research.pharmacy@stgeorges.nhs.uk and obtaining approval from the department before implementation.

If other support departments are involved in the study, such as Radiology and Pathology, the Clinical Research Auditor should send the amendment package to the nominated research contact in the department for review and approval, prior to implementation.

6. Procedure

Is the amendment substantial?

The CI/ Sponsor should determine whether the amendment is substantial or non-substantial and are responsible for submissions to the regulatory bodies and local sites.

Management amendments to studies hosted by St George's

Upon notification of an amendment by the Sponsor/CRO, Principal Investigator or RGFO, the Clinical Research Auditor will update the project files on EDGE and review the amendment documents.

The JRES will require the following documents (where relevant):

- REC Validation, Amendment Categorisation and Implementation Email – The Clinical Research Auditor will ensure that the amendment has been categorised by the HRA and will aim to issue R&D approval for the amendment in line with the implementation date specified.
- REC Amendment Approval Letter – The Clinical Research Auditor will ensure that the documentation submitted has been approved by REC and that the correct versions have been submitted.
- HRA Amendment Approval-The Clinical Research Auditor will ensure that the documentation submitted has been approved by the HRA and that the correct versions have been submitted.
- MHRA Approval (if applicable) – The Clinical Research Auditor will ensure that all Substantial Amendments for CTIMP/Device studies hosted by St George's received MHRA approval of the amendment.
- Amendment Tool- The Clinical Research Auditor will review the Amendment Tool to ensure that the information has been captured properly and reflects the proposed changes.
- Updated SOECAT (Non-Commercial) or Costing Template (Commercial) – This is only required if the amendment has financial implications for the participating site and should be provided by the Sponsor/CRO. This should be reviewed and approved by the JRES Finance Team prior to implementation.
- Draft addendum to Clinical Trials Agreement – This is generally only required if the amendment has financial implications for the participating site and should be provided by the Sponsor/CRO. This should be flagged to the RGFO for review and approval prior to implementation.

Where the HRA categorisation confirmation labels the amendment as a Category **"C" or "B" (not relevant to St George's)** the Clinical Research Auditor only needs to acknowledge receipt of the amendment. No formal review or ongoing confirmation is required. The Clinical Research Auditor

should update the electronic study file on EDGE with the documents and correspondence provided and acknowledgement sent.

Where the HRA categorisation confirmation label the amendment as Category **"A" or "B" (relevant to St Georges)** formal review of the amendment implication is required. The Clinical Research Auditor should review details of the amendment submission documentation to determine the effect it may have on the study locally. The Clinical Research Auditor should identify any/all support departments approvals that will be required and work with local study team to ensure the changes can be accommodated on site. This could include Pharmacy, Pathology, Radiology, and Clinical Research Facility, Finance and Contracts as well as other departments.

If the amendment cannot be reviewed fully **within 35 days of notification** from the sponsor and or cannot be accommodated locally, the Clinical Research Auditor should notify the sponsor at the earliest opportunity.

If the amendment cannot be accommodated within St George's, the Clinical Research Auditor will notify the lead RGFO, who will inform the PI and Sponsor within a reasonable timeframe by e-mail. If no resolution can be reached, St Georges will be unable to confirm the amendment and host confirmation may be suspended or withdrawn. Physical letters will not be issued for amendments.

Investigator procedure for reporting Urgent Safety Measures

In the event that a Sponsor or Investigator feels it necessary to take emergency measures to protect a research participant from a perceived immediate hazard to their health or safety, they may do so without prior authorisation from a regulatory body. It is the Sponsor's responsibility to make a Substantial Amendment to notify the REC within 3 days of the urgent safety measure, outlining the rationale and steps taken.

The CI/PI/sponsor must contact the JRES within 24 hours, should they plan to implement or have already implemented any urgent safety measures as defined in Section 4.

Urgent Safety Measures can be implemented on site without prior JRES confirmation however a review of the ongoing implications may be required, and Principal Investigators and Research Teams must ensure they keep their dedicated RGFO updated to ensure oversight of the situation.

The Clinical Research Auditor will be responsible for reviewing and implementing the corresponding Substantial Amendment as outlined in section 6.

7. References

NIHR Clinical Trials Toolkit www.ct-toolkit.ac.uk

HRA https://www.hra.nhs.uk/approvals-amendments/amending-approval/
https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

IRAS https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx

8. Appendices

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'

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 (JRESDOC0083)
- 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'

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'**

Appendix 8.3

Confirmation of amendment notification email template:

From: St Georges JRES

To: Sponsor representative, Chief Investigator, Clinical Trial Unit/Study Manager/Study Coordinator (where applicable),

Cc: Principal Investigator or Local Collaborator, Lead Research Nurse/Coordinator, Support Departments, LCRN London South (NIHR CRN studies), Lead RGFO

Subject: IRAS xxxxxx. Amendment Confirmation at **St Georges Healthcare NHS Foundation Trust/ St Georges, University of London**

Attachment: updated Signed agreement as appropriate

Dear Sponsor Representative,

RE: IRAS xxxxxx. Amendment (Number and or Date) Confirmation at **St Georges Healthcare NHS Foundation Trust / St Georges, University of London.**

Full Study Title:	
Site PI/LC	
Amendment Number and Date	
Current Protocol version:	
HRA Approval date:	

This email confirms that **St Georges Healthcare NHS Foundation Trust / St Georges, University of London** confirms the subjected amendment.

If you wish to discuss further, please do not hesitate to contact us and local team (cc-ed above).

Kind regards

INSERT PERSONAL SIGNATURE

Appendix 8.4

HRA Flowchart