Standard Operating Procedure (SOP)

Management of Amendments for Studies Sponsored by St George's

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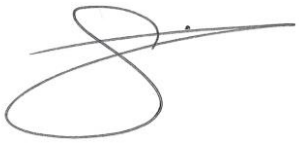
Signature of Authoriser:			

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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	Priscilla Aryee
V2.0	The SOP was updated to ensure that study CIs are aware of their responsibility to sign the approved study protocol following amendment approval from the main REC and MHRA prior to R&D approval being issued.	Ira Jakupovic
V3.0	SOP template updated and version number corrected in line with true document history. Process of amendment approval updated to reflect the new process	Debbie Rolfe
V4.0	Typos corrected and the correct indexing used	Lucy Parker

V5.0	Corrections to process & New logo and name change to FT Trust and change of title to Head of Research Governance	Lucy Parker
V6.0	Reference to JRESWPD0004 MHRA submission format added	Lucy Parker
V7.0	Reviewed and updated to include HRA changes	Anika Kadchha
V8.0	Amendment Template log updated.	Debbie Rolfe
V9.0	Studies that are not sponsored by St George's have been removed to facilitate a new and separate SOP	Debbie Rolfe
V10.0	Reflecting changes in JRES and job titles and minor changes to delegations of responsibilities. Also, insertion of associated JRES documents. Update to procedure as per HRA processes.	Georgia Bullock

Associated JRES documents

SOPs	WPDs	Docs	LOGs
JRESGOVSOP0006 Reporting of AEs for CTIMPs JRESGOVSOP0019 Preparation and Maintenance of the TMF	JRESWPD0023 General Research Definitions		JRESLOG0006 Study Amendments Log JRESLOG0016 Study Training Log

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1. Background

The UK Clinical Trials Regulations set out the legal requirements for notification and approval of 'substantial amendments' arising from Clinical Trials of Investigational Medicinal Products (CTIMPs). Studies that are not considered to be 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 (ie: HRA/MHRA) has been given. 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, the Competent Authority (where applicable) and the HRA before they can be implemented. All amendments submitted to REC and/or MHRA will need HRA approval. Once the amendment has been assessed against HRA standards relating to the legal and regulatory aspects of the study, the HRA assessment team will issue a 'Confirmation of Amendment Assessment' letter. After the letter has been issued and relevant REC/MHRA approvals received, the amendment can be implemented.

Non-substantial amendments need to be submitted to the REC only. The REC will then assess and approve the amendment before implementation at sites.

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 –

- Amendment to research that ALL participating NHS organisations are expected to consider – Category A
- Amendment to research that only sites affected by the amendment are expected to consider – Category B

- Amendment to research that participating sites are not expected to consider – Category C

The Sponsor must be aware of all amendments. The JRES, on behalf of St George's (acting as trial Sponsor) reviews and authorises all clinical research that takes place within St George's University Hospital's NHS Foundation Trust (SGHFT) and/or St George's, University of London (SGUL).

The JRES must be notified of all amendments made to a clinical trial and confirmation of the continuity of Research and Development (R&D) approval must be obtained prior to any amendments being implemented for both Sponsored and/or hosted studies.

The requirements have been incorporated into this Standard Operating Procedure (SOP) to define procedures undertaken by the Sponsor at St George's to comply with the UK Regulations.

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 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 management of 'substantial' and 'non-substantial' amendments and Urgent Safety Measures for research where St George's is named as the Sponsor.

It also outlines the submission process to the Research Ethics Committee (REC), Health Research Authority (HRA) and where applicable, the MHRA for approval of substantial amendments and for notification of non-substantial amendments.

This SOP details the process for the Chief Investigator (CI)/Principal Investigator (PI) (or delegated trial personnel) conducting clinical trials Sponsored by St George's when undertaking:

- Classification and submission of CTIMP amendment proposals to the JRES
- Submission of non-CTIMP amendments to the HRA and REC

4. Definitions

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

5. Responsibilities

This SOP is to be followed by the JRES Research Governance and Delivery team; the Head of Research Governance & Delivery (HRGD), Research Development and Governance Manager (RDGM), Research Governance and Facilitation Officer(s) (RGFOs), and the Clinical Research Associates (CRAs).

The assigned Research Governance and Delivery Team member (RGDT) will be responsible for updating the Workflows on EDGE and uploading any documents onto the electronic file.
The RGDT will inform the relevant finance contact of amendment processing to facilitate financial reimbursement where applicable or appropriate.

Study type specific responsibilities are:

5.1 Sponsored CTIMPs – JRES Responsibility

- The RDGM/CRA is responsible for submitting substantial amendments of all CTIMPs sponsored by St George's to the MHRA via the MHRA Submissions Portal, following the initial review of documentation submitted to the JRES. The initial review will be undertaken by both the CRA and RDGM to ensure full knowledge of proposed change and that any change in risk assessment that may affect the monitoring plan is considered.
- It is the responsibility of the CRA/RDGM to assess the proposed amendment against the original risk assessment tool to identify whether risk scores originally assigned would change. In the event of changes, the monitoring plan must be reviewed and adjusted as necessary. This process must be documented and kept in the Sponsor Site file.
- It is the responsibility of the CRA/RDGM to assess whether to forward a copy of the amended documents to the insurance broker depending on the risk impact, to facilitate assurance that insurance conditions, cover and/or premiums have not changed. In the event the insurance assessment does require variation to the cover and/or premiums this must be communicated to the CI and the Research Funding Officer immediately.
- The CRA/RDGM is responsible for informing the CI of the outcome of the MHRA submission.

- The CRA/RDGM is responsible for updating both the electronic and physical (if present) Sponsor files.

5.2 Sponsored CTIMP – Investigator Responsibility

- It is the responsibility of the CI for any St George's clinical trials to notify the JRES of all proposed trial amendments throughout the life cycle of a clinical trial. One or more members of the Investigator research team should be named on the study Delegation Log filed in the Trial Master File (TMF) as being responsible for the management and submission of substantial and/or non-substantial amendments to the JRES. The individual responsible for management and submission of amendments must ensure that all amended documents, tracked and proof read, are submitted to JRES for initial review and subsequent continuity of R&D approval.
- The CI is responsible for finalising, uploading and submitting the completed Amendment Tool and associated amendment documents to the REC and the HRA through IRAS.
- The CI is responsible for ensuring any financial and resource impact of the proposed amendment is taken into consideration and mitigated against. This should be outlined within the amendment.
- The CI is responsible for ensuring that all PIs and trials sites are informed of the outcome and that they all receive amended documents and any MHRA/HRA/REC decision/approval documents. Upon receipt of the HRA categorisation email circulate the amended documents to participating site R&D teams to enable assessment of the amendment to commence.
- The PIs (which includes CI if they are acting as PI) are responsible for providing all amended documents and approval documents to site support departments (*i.e.* Pharmacy, Clinical Research Facility (CRF) and Laboratory) and for obtaining the necessary R&D approvals at their respective sites.

5.3 Sponsored non-CTIMP – JRES Responsibility

- It is the assigned RGDT's responsibility to review & approve amendments before they are submitted to REC & HRA for approval and subsequently for R&D approval.

5.4 Sponsored non-CTIMP – Investigator Responsibility

- It is the CI's responsibility to ensure that non-CTIMP amendments are submitted to JRES for review, to the REC & HRA for approval and subsequently for R&D approval. The CI is responsible for ensuring any financial and resource impact of the proposed

amendment is taken into consideration and mitigated against. This should be outlined within the amendment.

6. Procedure

6.1 Management of amendments to CTIMPs sponsored by St George's

6.1.1 Investigator Procedure

a) It is the responsibility of the CI or delegate to complete the Amendment Tool, which can be accessed on the IRAS website:

https://www.myresearchproject.org.uk/help/hlpamendments.aspx#June

Correct completion of Sections 1 and 2 of the Amendment Tool will categorise the amendment as either substantial or non-substantial, based on the information entered and this should be sent to the responsible CRA in JRES for review along with accompanying trial documentation including;

- Any trial document that has been amended e.g. Protocol, Patient Information Sheet (PIS), and Informed Consent Form (ICF). Documents should show both the previous and new wording (Tracked change) and must be version-controlled (i.e. version number and date should be modified)
- A covering letter detailing the amendment and the rationale to support it
- Supporting data for the amendment, including where applicable:
    - summaries of data
    - updated overall risk benefit assessment
    - possible consequences for subjects already in the trial
    - possible consequences for the evaluation of results

The CRA will check the Amendment Form and associated documentation to ensure that all required information has been input into Sections 1 and 2 of the Tool, which generates the corresponding HRA amendment classification, categorisation, information on notification to participating sites (if relevant) and flags other review bodies to be notified on the 'Submissions Guidance Tab'.

If there are financial implications as a result of the amendment, the CRA will discuss this with the JRES Funding Team prior to approval.

The RDGM/HRGD will complete Section 3 of the Amendment Tool (Sponsor Declaration), which will lock the form for submission.

The CI or delegate will follow the appropriate guidance on the 'Submissions Guidance' tab and will submit the final Amendment Tool to the relevant review bodies (REC and/or HRA depending on classification) using the Online Submission Tool via IRAS.

The PDF of the *locked* Amendment form should be filed in the TMF and sent to the CRA/RDGM to be saved electronically and/or physically in the Sponsor Site File (SSF).

MHRA approval required

Submission to MHRA is delegated to the CRA/RDGM in the JRES. The Amendment tool and supporting documents should be uploaded via the MHRA Submissions Portal.

Portal upload and acceptance emails should be filed upon receipt together with amendment documentation in the TMF and sponsor file.

The CRA/RDGM may request further information from the CI. The CI should respond to queries as soon as possible to avoid delays in both processing the submission and the review of an amendment by the relevant review body.

The CI delegate should file the completed Study Amendments Log JRESLOG0006 upon receipt by the CRA/RDGM in the TMF and ISF.

6.1.2 JRES Procedure for amendments to CTIMPs Sponsored by St George's

Once the JRES receives all of the above documents, the amendment must be reviewed against the original risk assessment undertaken for the study to ensure that risk score has not changed. Should there be any changes then the risk assessment findings must be documented by endorsing the current monitoring plan with date and 'no change' if relevant, or date and begin work on new monitoring plan.

The CRA/RDGM should review the amendment documentation prior to processing further. Once this review has been completed, then the Amendment Tool can be signed. The CRA/RDGM will submit the Amendment Tool and supporting documents to the MHRA in the following manner:

- If MHRA approval is required; the CRA/RDGM will convert all documents to PDF versions to submit to the MHRA..

- The CRA/RDGM will request Insurance broker assessment in circumstances where the proposed amendment has altered the study risk profile and may affect premium or cover.
- The CRA/RDGM will email the CI a copy of all the documents submitted to the MHRA for filing in the TMF (JRESGOVSOP0019) including the covering letter.
- The CI should be instructed to circulate the Amendment submission package to any participating sites to facilitate R&D assessments to commence.
- The CRA/RDGM will ensure a copy of all documents submitted are both filed in the Sponsor Site File and also sent to Research Pharmacy for retention in the Pharmacy Site File (PSF).
- Upon receipt, a copy of the MHRA approval should be sent to the HRA via email to facilitate HRA approval.
- Once the REC, HRA and MHRA approve the amendment, the CRA/RDGM will notify the CI to implement the amendment by providing him/her with a copy of the appropriate approval letters e.g. REC, HRA and MHRA along with confirmation of JRES R&D approval in the form of an email. No physical letters will be issued for amendments for studies taking place at St George's. The JRES R&D approval email should include all support departments.
- Ensure the amendment log is updated with the relevant approval requirements and dates of approval and a copy is forwarded to the CI, any key staff identified on EDGE and the lead Research Pharmacist for their files. For multi-site studies or where a CTU/CRO is involved ensure a copy of the completed log and document approval set is sent.
- Ensure EDGE workflows are updated with Amendment type, date, summary and approvals (where applicable).

6.1.3 What to expect from REC, HRA and MHRA

- The REC will write within 5 working days to confirm if the notice of amendment is valid. It is anticipated that an ethical opinion will be issued within a maximum of 35 working days from the date of receipt of a valid notice of amendment. The Sponsor may submit a modified amendment if an unfavourable ethics opinion is received. Modified amendments will be addressed within 14 days.
- The MHRA will also write within 5 days to acknowledge receipt of a valid amendment notification. MHRA will also review the amendment and issue their opinion within 35 working days from the receipt of an acknowledgement letter.

- Once the amendment has been submitted to REC, REC will share the documents with the HRA. The HRA Assessment Team will categorise the amendment according to the UK amendments process and inform the CI within national timeframe. If there are participating NHS/HSC sites in other UK nations, the HRA will share the amendment and categorisation with the other participating UK nations.
- The CI or delegate can then send the amendment and the categorisation information to participating NHS organisations so that, where necessary, arrangements can be put in place to continue the site's capacity and capability to deliver the study. It is the CI's responsibility to communicate the categorisation and the amendment to UK sites. HRA email templates for site correspondence/dissemination can be found at https://www.hra.nhs.uk/approvals-amendments/amending-approval/. Contact details of R&D offices can be found on the NHS R&D Forum website: http://www.rdforum.nhs.uk/content/contact-details/

6.1.4 Investigator procedure for dissemination of information following approval of an amendment

Following receipt of the amendment approval letter the CI will ensure that:

- Actions required by the REC, HRA and MHRA in the approval letter are undertaken (*i.e.* re-consenting patients);
- The JRES amendment approval email and supporting documentation are filed in the appropriate section of the TMF. Old versions of the amended documents should be filed in the superseded section of the TMF dated and marked as 'superseded'.
- The ISF should be furnished with any newly approved documents. A single copy clearly marked as superseded with date removed from circulation should be added to documents that should no longer be used.

For a multi-centre trial, the CI must ensure that:
All trial sites, PIs and support departments (if relevant) receive the approval letters and the supporting amended documents and that they are all prepared to abide by the changes.

The CI or delegate ensure collaborating PIs inform their respective R&D departments of all amendments and that where required, the host site confirms continuity of host site approval. HRA email templates for site correspondence/dissemination can be found at https://www.hra.nhs.uk/approvals-amendments/amending-approval/. Contact details of R&D offices can be found on the NHS R&D Forum website http://www.rdforum.nhs.uk/content/contact-details/

Staff involved in the study conduct and/or study management are aware of any amendments to the clinical trial and comply with amendments. If the amendment pertains to the protocol, it might be necessary to re-train the trial staff to the protocol. The CI/PI must carefully document that such training is required/has taken place.

Although it is the CI's responsibility, the CRA/RDGM may assist (where feasible) the CI with the training on any changes in the protocol or study related documentation to study personnel upon request.

Any training conducted or received will be documented on the training log JRESLOG0016 and filed in the TMF/ISF as appropriate.

Should an R&D department raise objection to the proposed amendment within 35 days an urgent discussion with the CI should take place to establish if any facilitative actions can take place to improve acceptability.

6.2 Management of amendments to non-CTIMPs sponsored by St George's

a) It is the responsibility of the CI or delegate to complete the Amendment Tool, which can be accessed on the IRAS website:

https://www.myresearchproject.org.uk/help/hlpamendments.aspx#June

Correct completion of Sections 1 and 2 of the Amendment Tool will categorise the amendment as either substantial or non-substantial, based on the information entered and this should be sent to the responsible RGFO in JRES along with:

- Any trial documents that have been amended (e.g. Protocol, PIS). All documents should show both the previous and new wording via Tracked changes and must show version control (see Section 6.2.1)
- A covering letter detailing the amendment and the rationale to support it

The RGFO will check the Amendment Form and associated documentation to ensure that all required information has been input into Sections 1 and 2 of the Tool, which generates the corresponding HRA amendment classification, categorisation, information on notification to participating sites (if relevant) and flags other review bodies to be notified on the 'Submissions Guidance Tab'.

If there are financial implications as a result of the amendment, the RGFO will discuss this with the JRES Funding Team prior to approval

The RGFO will completed Section 3 of the Amendment Tool (Sponsor Declaration), which will lock the form for submission.

The CI or delegate will follow the appropriate guidance on the 'Submissions Guidance' tab and will submit the final Amendment Tool to the relevant review bodies (REC and/or HRA depending on classification) using the Online Submission Tool

The RGFO must forward the amendment package and categorisation email to the study co-ordinator to forward onto any participating site research teams and their respective R&D offices. HRA email templates for site correspondence/dissemination can be found at https://www.hra.nhs.uk/approvals- HYPERLINK "https://www.hra.nhs.uk/approvals-amendments/amending-approval/"amendments/amending-approval/. Contact details of R&D offices can be found on the NHS R&D Forum website http://www.rdforum.nhs.uk/content/contact-details/

For any amendments categorised by the Amendment Tool as 'A' or 'B', participating site R&D offices have 35 days from receipt of the amendment notification and categorisation to raise a written objection- (to reject proposed amendment) or the amendment is implemented in line with details in the categorisation email.

Once REC has issued favourable opinion of the amendment (only for substantial amendments), and HRA approval is received (for all amendments), JRES approval should not be delayed and must be provided by the responsible RGFO before implementation of the proposed changes at site.

The RGFO should provide confirmation of acceptance of the amendment within 5 working days upon receipt of HRA approval for any amendments effecting study delivery within St George's hospital.

This completed updated Log of amendments JRESLOG0006 and all modified documents highlighting non-substantial changes should be kept in the Investigator Site File (ISF) and the Trial Master File (TMF) and must be made available upon request for the purposes of monitoring, audit or inspection.

6.2.1 Reporting amendments for Research Tissue Banks and Research Databases

Research Tissue Banks and Research Databases will continue to use the IRAS-generated Notification of Non-Substantial Amendment (NoSA) forms. The CI or delegate should generate and complete these forms and send them to JRES for review and authorisation as per section 6.3.

Once the responsible RGFO in JRES has approved the amendment, the CI or delegate should counter-sign the NoSA and submit for REC review using the electronic submission in IRAS.

6.2.2 Amendments to add the involvement of Adults Lacking Capacity for the first time

Research studies involving adults who lack capacity must be reviewed by specialist RECs before this patient population can be included in research.

If the inclusion of adults lacking capacity has not previously been described in an approved research project, this requires review by a specialist REC and such an amendment cannot be submitted through the Online Submission Portal.

The CI or delegate should contact the responsible RGFO in the JRES, who will contact the REC which issued the original Favourable Opinion to provide further guidance.

6.3 Investigator procedure for reporting Urgent Safety Measures

It is recommended that the CI/PI contacts the JRES within 24 hours, should they plan to implement or have already implemented any urgent safety measures as defined in, for CTIMPS in JRESGOVSOP0006 Reporting of AE for CTIMPs, and for non-CTIMPs see Section 4 above.

Once an urgent safety measure has taken place on site the following procedure must be followed by the **CI/PI**:

- Immediately telephone the MHRA Clinical Trials Unit and discuss the issue with a medical assessor.

- Submit a written summary of the MHRA conversation and an agreed action plan within 3 days along with any relevant supporting documentation to notify the REC, MHRA and JRES of the urgent safety measure.
- CI must ensure all participating sites and support departments especially Research Pharmacy and Clinical Research Facility are kept informed of the urgent safety measure and ongoing study participant's medical management.
- File the notification in the ISF or TMF along with all the other documents submitted above.
- Log the event in the Log of Amendments clearly marking it as an urgent safety measure.
- Ensure that acknowledgements from all of the above organisations are received and if in doubt telephone the REC, MHRA, and JRES to request acknowledgement of receipt of the event notification.
- Ensure that any acknowledgements (and/or any other correspondence related to the event reported above) from the REC and MHRA, are forwarded to the JRES.
- The JRES will ensure that such notifications/acknowledgements are filed in the Sponsor Site Files
- The JRES will ensure, where applicable, that EDGE is updated with details of the Urgent Safety Measure
- Ensure a full amendment is prepared and submitted together with any supporting documentation as described in section 6.2

7. References

Examples of Substantial and Non-Substantial Amendments:
https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-substantial-amendments/

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

MHRA
www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/ManagingyourCTA/Amendments/Whattosend/index.htm

https://www.hra.nhs.uk/approvals-amendments/amending-approval/

NHS R&D Forum http://www.rdforum.nhs.uk/content/contact-details/

8. Appendices

None associated with this SOP.