St George's University of London

St George's University Hospitals NHS
NHS Foundation Trust

Standard Operating Procedure (SOP)

Management of Amendments for studies Sponsored by St George's

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Signature of Authorisor			

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

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 JREOWPD0004 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 Georges have been removed to facilitate a new and separate SOP	Debbie Rolfe

1. Background

The European Clinical Trials Directive (EUCTD) 2001/20/EC was transposed into UK Regulations by The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) on the 1st May 2004. 'UK Regulations' will be the term used to cover the UK legislation and the EUCTD in this document. 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 Research Governance Framework.

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 , 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 HRA only. The HRA 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 –

A- Amendment to research that ALL participating NHS organisations are expected to consider
B- Amendment to research that only sites affected by the amendment are expected to consider
C- Amendment to research that participating sites are not expected to consider

The Sponsor must be aware of all amendments. The JREO, 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 JREO must be notified of all amendments made to a clinical trial and confirmation of the continuity of 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 St George's to comply with the UK Regulations.

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 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 JREO
- Submission of non-CTIMP amendments to the HRA and REC

4. Definitions

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

5. Responsibilities

This SOP is to be followed by the JREO Research Governance and Delivery team: the Head of Research Governance & Delivery (HRGD), Regulatory Assurance Manager (RAM), Research Governance and facilitation Officer(s) (RGFOs), and the Regulatory Support Officers (RSO). It is the responsibility of the HRGD to ensure that the SOP is updated when necessary.

The assigned Research Governance and Delivery Team member (RGDT) will be responsible for updating the Workflows on EDGE (LPMS) 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 – JREO Responsibility

a) The RAM is responsible for submitting substantial amendments of all CTIMPs sponsored by St George's to the MHRA via CESP, following the initial review of documentation submitted to the JREO. The initial review will be undertaken by both the RSO and RAM to ensure full knowledge of proposed change and that any change in risk assessment that may affect the monitoring plan is considered.

b) It is the responsibility of the RSO and/or RAM 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.

c) It is the responsibility of the RSO/RAM to forward a copy of the amended documents to the insurance broker 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.

d) The RSO/RAM is responsible for informing the CI of the outcome of the MHRA submission and also for providing the CI, Research Pharmacy and relevant support departments with a copy of approved amended documents.

e) The RSO/RAM is responsible for updating the EDGE database and the Sponsor files both physical and electronic.

5.2 Sponsored CTIMP – Investigator Responsibility

a) It is the responsibility of the CI (or delegated personnel) for any St George's clinical trials to notify the JREO of all 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 JREO. The individual responsible for management and submission of amendments must ensure that all documents to be amended are submitted to JREO for initial review and subsequent continuity of R&D approval.

b) The CI (or delegated personnel) is responsible for submitting the substantial amendment documents to the REC and the HRA. This responsibility may be delegated to the Regulatory Assurance Team and documented by a file note retained in the Sponsor Site File. A copy should also be retained in the TMF.

c) The CI (or delegated individual) 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 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 Research and Development (R&D) approvals at their respective sites.

5.3 Sponsored non CTIMP – JREO 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 CIs responsibility to ensure that non-CTIMP amendments are submitted to JREO for review, to the REC & HRA for approval and subsequently for R&D approval.

6. Procedure

6.1 Is the amendment substantial?

The Sponsor should first determine whether the amendment is substantial or non-substantial. Examples of substantial and non-substantial amendments are given in Appendix 8.1 of this SOP. The RAM/RSO will assess the proposal

6.2 Management of substantial amendments to CTIMPs Sponsored by St George's

6.2.1 Investigator Procedure

The procedure outlined in this section should be followed by the CI delegate once a study amendment is confirmed as substantial. Where possible, supporting documents to accompany the amendment to the RAM/RSO should be submitted in MS Word format.

a) The CI delegate will complete the appropriate amendment form (Notice of Substantial Amendment) on IRAS. Each proposed study amendment should be submitted using a new form. The first page of the form should clearly identify if the amendment is a:
   - Request for authorisation to MHRA
   - Request for opinion of the REC
   - Notification for information only to the REC and/or MHRA.

b) The completed form should be either sent to the RAM/RSO and entitled 'Substantial Amendment for review'.

c) The form must be accompanied by all relevant version-controlled supporting documents:
   - 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

d) If the amendment affects the information previously submitted, an updated XML and PDF file of the MHRA medicines (EudraCT) application form.
   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

e) Upon confirmation documentation is ready to submit – the documents should be uploaded onto the IRAS checklist and relevant authorisation signatures requested.

f) The delegate should submit the amendment via IRAS by the e-submission tab on IRAS. The PDF and xml of the *locked* Amendment form should be filed in the TMF

REC approval required

g) The delegate should check on the HRA website for the most up to date email address details for the REC identified on the original study approval letter where relevant for REC submission

h) The delegate should ensure the email includes a covering letter to summarise the amendment details, documents and versions contained within the amendment pack.

i) The email to REC should ensure both the RAM and CI are notified and include the HRA amendment assessment team <hra.amendments@nhs.net>

MHRA approval required

j) Submission to MHRA is delegated to the RAM in the JREO

k) File CESP upload and CESP acceptance emails from RAM upon receipt together with amendment documentation in the TMF

l) The RAM/RSO 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.

m) The delegate should file the completed Study Amendments Log JREOLOG0007 upon receipt by the RAM/RSO in the TMF and ISF

6.2.2 JREO Procedure

Once the JREO 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. Document the risk assessment findings by endorsing the current monitoring plan with date and 'no change' if relevant, or date and begin work on new monitoring plan in accordance with JREOWPD0008.

The RAM/RSO should review the amendment documentation prior to processing further. Once this review has been completed, then the amendment form can be signed electronically within IRAS. The RAM will submit the Amendment Form and supporting documents to the MHRA in the following manner:

a) If MHRA approval required the RAM will convert all documents to PDF versions to submit to the MHRA. The Annex 2 Form must contain an electronic signature of the authorised JREO signatory submitting the amendment in accordance with the JREOWPD0004 MHRA submission format

b) The RAM/RSO will request Insurance broker assessment in circumstances where the proposed amendment has altered the study risk profile and may affect premium or cover.

c) The RAM will email the CI a copy of all the documents submitted to the MHRA for filing in the TMF (JREOSOP0019) including the covering letter.

d) The CI should be instructed to circulate the Amendment submission package together with the HRA categorisation email to any participating sites to facilitate R&D assessments to commence.

e) The RAM 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 PSF..

f) Upon receipt, a copy of the MHRA approval should be sent to the HRA via email to facilitate HRA approval.

g) Once the REC, HRA and MHRA approve the amendment, the RAM 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 JREO 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 JREO R&D approval email should include all support departments and follow immediately upon receipt of HRA approval.

h) 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.

i) Ensure EDGE workflows are updated with Amendment type, date, summary and approvals.

6.2.3 What to expect from REC, HRA and MHRA

a) 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.

b) 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.

c) 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 5 days. If there are participating NHS/HSC sites in other nations, the HRA will share the amendment and categorisation with the other participating nations.

d) 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 English sites.

6.2.4 Investigator procedure for dissemination of information following approval of a substantal amendment

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

a) Actions required by the REC, HRA and MHRA in the approval letter are undertaken (*i.e.* re-consenting patients);

b) The JREO 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 'superceded'.

c) The ISF should be furnished with any newly approved documents. A single copy clearly marked as superceded 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:

a) 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.

b) CI or delegate ensure collaborating PIs inform their respective R&D departments of all amendments at the point of receipt of HRA categorisation email and that where required, the host site confirms continuity of host site approval.

c) 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.

d) The RSO may assist the CI with the training on and/or the dissemination of any changes in the protocol or study related documentation to study personnel upon request.

e) Any training conducted or received will be documented on the training log JREOLOG0016 and filed in the TMF/ISF as appropriate.

f) 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.

6.3 Managment of substantial amendments to non-CTIMPs Sponsored by St George's

a) Once the CI or delegate has classified the amendment as substantial, the delegate will generate the notice of substantial amendment (NOSA) form via IRAS. The CI or delegate will submit the NOSA to the JREO *via* the lead RGFO or RSO before being submitting to REC for review. The NOSA form must be accompanied by all the supporting documentation which includes:

- 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/RSO will assess the documentation and amendment submission package prior to authorisation for REC submission. The submission to REC will be via email and will include the CI, key staff listed on EDGE and the RGFO or RSO as recipients. REC automatically share NOSA with HRA.

b) REC will validate the amendment and confirm categorisation via email to CI and the JREO R&D contact.

c) Upon receipt of validation and categorisation email the RGFO/RSO 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.

d) 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.

e) Once REC has issued favourable opinion of the amendment, and HRA approval is received, R&D approval should not be delayed and must be provided before implementation of the proposed changes at site

f) The RGFO/RSO should provide confirmation of acceptance of the amendment within 5 working days upon receipt of HRA approval.

6.4 Procedure for reporting non-substantial amendments

- Non-substantial amendments should be reported to the HRA & the JREO by email. Non-substantial amendments that do not require REC review should be submitted by email to hra.amendments@nhs.net using the non –substantial amendment form. The non-substantial amendment form can be found at: http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/preparing-amendments/. The form will need to be submitted to the HRA with any modified documents. There should be clean and tracked changes version of the documents submitted.

Details of non-substantial amendments may be requested at any time. Details of any previous non-substantial amendments must be included when a substantial amendment is next submitted for regulatory approval. Where trial documents are modified as a result of non-substantial amendment, version control should apply, and copies of the updated documents should accompany the information to JREO and should be included in the changes made with the next substantial amendment to be submitted for approval.

This completed updated Log of amendments JREOLOG0006 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.

6.6 Investigator procedure for reporting Urgent Safety Measures

It is recommended that the CI/PI contacts the JREO within 24 hours, should they plan to implement or have already implemented any urgent safety measures as defined in Section 4.

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

a) Immediately telephone the MHRA Clinical Trials Unit (CTU) and discuss the issue with a medical assessor.
b) 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 JREO of the urgent safety measure.

c) 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.

d) File the notification in the ISF or TMF along with all the other documents submitted above.

e) Log the event in the Log of Amendments clearly marking it as an urgent safety measure.

f) Ensure that acknowledgements from all of the above organisations are received and if in doubt telephone the REC, MHRA, and JREO to request acknowledgement of receipt of the event notification.

g) Ensure that any acknowledgements (and/or any other correspondence related to the event reported above) from the REC and MHRA, are forwarded to the JREO.

h) The JREO will ensure that such notifications/acknowledgements are filed in the Sponsor Site Files

i) The JREO will ensure that EDGE is updated with details of the Urgent Safety Measure

j) Ensure a full amendment is prepared and submitted together with any supporting documentation as described in section 6.2

7. References

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/

8. Appendices

8.1 Examples of Substantial and Non-substantial amendments

8.2 Flowchart of Amendment Process- Studies Sponsored by St George's

8.3 Flowchart of HRA Amendment Process

Appendix 8.1 Examples of Substantial and non-substantial amendments

Examples of substantial amendments:

- changes to the design or methodology of the study, or to background information affecting its scientific value;
- changes to the procedures undertaken by participants;
- any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study;
- significant changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers;
- a change of sponsor(s) or sponsor's legal representative;
- appointment of a new chief investigator
- a change to the insurance or indemnity arrangements for the study;
- inclusion of a new trial site (not listed in the original application) in a CTIMP;
- appointment of a new principal investigator at a trial site in a CTIMP;
- temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt;
- a change to the definition of the end of the study

any other significant change to the protocol or the terms of the REC application.

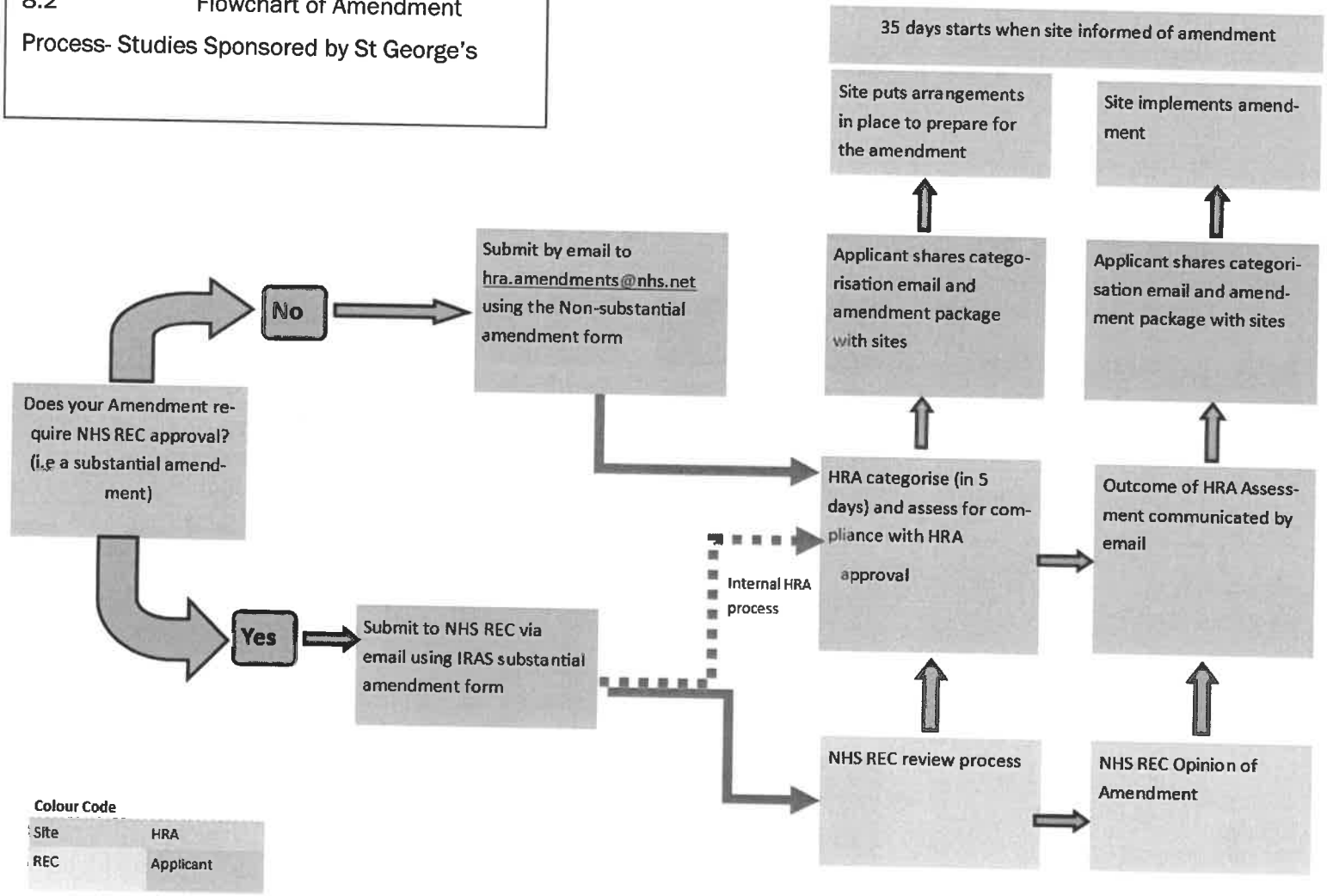
Examples of non-substantial amendments:

minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications;

- updates of the investigator's brochure (unless there is a change to the risk/benefit assessment for the trial);
- changes to the chief investigator's research team
- changes to the research team at particular trial sites (other than appointment of a new principal investigator in a CTIMP);
- changes in funding arrangements;
- changes in the documentation used by the research team for recording study data;
- changes in the logistical arrangements for storing or transporting samples;
- inclusion of new sites and investigators in studies other than CTIMPs;
- Extension of the study beyond the period specified in the application form.

Changes to contact details for the sponsor (or the sponsor's representative), chief investigator or other study staff are minor amendments but should be notified to the REC that approved your original application.

8.2 Flowchart of Amendment Process- Studies Sponsored by St George's



8.3 Flowchart of HRA amendment process