Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

Amendments

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Approved by (name & role)	Dipak Patel R&D Manager	**Date:**	08/07/2021
Signature:			

Standard Operating Procedure: Research Department

Amendments

This SOP has been produced in accordance with **Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, Good Clinical Practice (GCP) &** the UK Policy Framework for Health and Social Care Research (2017). This SOP will outline the procedure for making and reviewing amendments to all clinical research undertaken within Sheffield Teaching Hospitals NHS Foundation Trust.

Background

The STH Research Department reviews and issues Confirmation of Capacity and Capability (CCC) for all research that takes place within the Trust. If changes are made from the original application, the Research Department requires notification of the intended amendment, to enable review and continued confirmation of capacity and capability (cCCC) where applicable.

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Acronyms

CCC	Confirmation of Capacity and Capability
cCCC	Continued Confirmation of Capacity and Capability
CI	Chief Investigator
CRF	Clinical Research Facility
CTIMP	Clinical Trial of an Investigational Medicinal Product
HRA	Health Research Authority
HSC	Health and Social Care
IRAS	Integrated Research Application System
LCRN	Local Clinical Research Network
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PI	Principal Investigator
PIC	Patient Identification Centre
RDB	Research Database
REC	Research Ethics Committee
RMS	Research Management System
RTB	Research Tissue Bank
SGL	Sponsor Green Light

Definitions and National Context

An amendment is any change to the original study application during the life of the study. This includes but is not limited to: protocol amendments, updated study documentation, duration of the study, changes in study management (including sponsorship or funding) or changes to the leads of the research team (CI/PI). Amendments can be classified as Substantial or Non-Substantial, depending on whether they require approval either by the Research Ethics Committee (REC) and/or Medicines and Healthcare products Regulatory Agency (MHRA). Amendments can be classified as requiring study-wide review (notifiable) or not requiring study-wide review (non-notifiable) depending on whether they require approval from the HRA.

Substantial amendment
A substantial amendment is a change to the terms of the REC application (and/or request for clinical trial authorisation in the case of clinical trials of medicines), the protocol or any other document submitted with the application, which significantly affects one or more of the following:

- The safety or physical or mental integrity of study participants
- The conduct or management of the study
- The scientific value of the study
- The quality or safety of any investigational medicinal product used in the study.

Non-substantial amendments
Other changes to the study protocol or any other document submitted with the application to REC/HRA not meeting the above criteria are non-substantial amendments. These amendments may or may not still require HRA review. Non substantial amendments not requiring HRA review are termed ‘non-notifiable’. However, this does not mean that they do not need to be submitted to the HRA and to participating sites.

Amendments for the addition of sites / change of PI at sites

- Addition of sites and change of PI at sites for all studies (including CTIMPs) are non-substantial amendments. These require submission to HRA.
- Addition of PIC sites for a study which already has approval for the use of PIC sites does not need notifying as an amendment for the addition of sites in England. For the addition of PICs in Northern Ireland, Scotland or Wales, the relevant National Coordinating Function will facilitate the setting up of a PIC in their region. In order to initiate this, the addition of the PIC is submitted as a non-substantial amendment to the lead nation for the study.

- Addition of sites and change of PI at sites should be submitted to REC/HRA separately from other study amendments.

Submission of amendments for HRA Approval

Where a study has HRA Approval both substantial and non-substantial amendments must be submitted to the HRA (via IRAS online amendment submission portal) and must be approved by the HRA where the Amendment Tool indicates that study-wide review is required. Amendments must be submitted using the Amendment Tool.

- The Amendment Tool is an MS Excel document which can be downloaded via IRAS. Care should be taken to ensure that the latest version is being used.

The study Sponsor is responsible for determining the substantial or non-substantial nature of the amendment.
Substantial amendments may be substantial with regard to the Research Ethics Committee approval or to the MHRA approval or both.
With the exception of urgent safety measures an amendment may not be implemented until it is approved by the relevant bodies. The relevant bodies are the REC/MHRA where the amendment was substantial for these bodies and also the HRA in the case of both substantial and non-substantial amendments.

Amendment categorisation

The Amendment Tool will generate a categorisation. so that the amendment is handled in a manner that is appropriate to the scale of the amendment and the potential risks to, and the liability of, the NHS/HSC organisation(s) implementing the amendment. The study Sponsor is responsible for ensuring that the appropriate change categories are selected in the Amendment tool to result in the appropriate categorisation - see below table:

Category:	This category includes any amendment to a research project that has:
A	Implications for, or affects, all participating NHS/HSC organisations hosting the research project.
B	Implications for, or affects, specific participating NHS/HSC organisations hosting the research project.
C	No implications that require management or oversight by the participating NHS/HSC organisations hosting the research project. However the amendment should still be provided for information. *Note - Updated Investigator Brochure (IB; Clinical Trials of Investigational Medicinal Products (CTIMPs) only):* Where the IB update, annual or otherwise, constitutes a non-substantial amendment for REC and MHRA and this is the only amendment (e.g. the update to IB does not give rise to updated pharmacy manual or protocol) the updated IB should not be submitted for categorisation. These amendments will always be category C and they will not be assessed by NHS/HSC if submitted. The IB should be provided to each participating NHS/HSC organisation.
New NHS/HSC site	Where the amendment is to add a new NHS/HSC site to the project, the set-up of this new site should proceed according to the process for local study set-up for the nation where the new site is located.

In England (and/or Wales) HRA processes state that once an automated submission email from IRAS online amendment submission is received the Study Manager should share the Amendment Tool and amended documents together with the automated submission email with relevant participating NHS organisations (local research team and NHS R&D Office, together with the LCRN where required locally) using template emails provided on the HRA website.

For category A amendments (and category B amendments where these involve the specific site) NHS organisations in England and/or Wales have 35 calendar days from the day on which the organisation is provided with the Amendment Tool and amended documents to assess the amendment. Following

this time period the amendment may be implemented (ie Sponsor Green Light (SGL) for the amendment may be issued) so long as:

a. HRA and HCRW Approval has been issued for the amendment (if the amendment required study-wide review as per the Amendment Tool).
b. A participating NHS organisation does not request additional time to assess.
c. A participating NHS organisation does not decline to implement the amendment

Sponsors should not expect to receive a letter or email of confirmation from NHS/HSC organisations before implementing the amendment.
Amendments may be implemented earlier than 35 calendar days from the date on which the organisation is provided with the categorisation email where the NHS organisation R&D Office confirms that the amendment may be implemented prior to this date following receipt of Sponsor Green Light for the amendment.

Category C amendments do not require review by participating NHS organisations and may be implemented (i.e. Sponsor Green Light for the amendment may be issued) once HRA approval (either by email if HRA review was required or by automated reply if the amendment was classed as 'non-notifiable') has been received after submission.

Notification of amendments to other approving bodies

Depending on the nature of the study and other existing approvals for the study an amendment may also require submission to other approving bodies (eg CAG/ARSAC). Also please note that arrangements for notification of amendments for medical device trials requiring MHRA approval are different to those for trials of medicinal products. Please refer to the relevant guidance in IRAS and in the guidance available from the relevant approving body for more information

Internal / 'Sponsor only' amendments

Amendments which involve changes only to documents which have not been submitted for external review (e.g. update to case report form only) are sometimes referred to as 'internal' or 'Sponsor only' amendments. These amendments do not require notification to the HRA or other external bodies and do not require R&D review for capacity and capability. The study Sponsor will decide whether they wish to review and approve these amendments.
Except in the case of STH sponsored CTIMPs, where STH is the study Sponsor these amendments do not require Sponsor review and may be handled entirely by the study team, managed by the Study Manager and/or CTRU where one is involved in the study. The process for Sponsor review and approval of internal/Sponsor only amendments for STH sponsored CTIMPs is described in STH R&D SOP C118.

Sponsor Green Light

PI teams should take neither R&D department notification of cCCC nor HRA approval as an indication that an amendment is ready to be implemented at site. HRA processes dictate that study Sponsors are responsible for giving Sponsor Green Light (SGL) for implementation of amendments once all the relevant approvals and documentation and any necessary training for the amendment is in place.

For most single site studies sponsored by STH, STH R&D Department retains responsibility for Sponsor Green Light, except, for example, where a study is managed by a CTRU.

For multicentre studies sponsored by STH, STH R&D Department is not usually directly involved in project management and therefore is not usually directly responsible for Sponsor Green Light. In most cases a delegated CTRU or otherwise delegated Study Manager or sometimes the CI themself is responsible for project management. This responsibility will include ensuring that the amendment is disseminated to the PI teams, local R&D offices and LCRNs at other sites for review and local R&D Confirmation of Capacity and Capability as required, for receiving cCCC from participating sites, and also for notifying those sites of the implementation of amendments. The designated Study Manager (and not STH R&D Department) is therefore responsible for issuing Sponsor Green Light to sites with respect to amendments. STH R&D Department will have responsibility for these tasks for multicentre studies only in exceptional circumstances and by prior arrangement with the STH Research Manager during grant award and study set up.

Study Manager
This is the person appointed by the CI to have overall project management responsibility for the study. For multicentre studies sponsored by STH there must always be a person delegated as Study Manager. This may be a trial manager within a CTRU team or may be the CI themself or may be some other person within the CI team.

Amendments to studies proceeding under NHS Permission (ie studies not requiring HRA approval).
Such studies will always be REC exempt and therefore amendments will always be non-substantial (except where the amendment causes the study to become no longer REC/HRA exempt, in which case a new IRAS application will be required). As such amendments to the protocol which do not affect the status of the study as HRA exempt should be submitted to STH R&D Department for Sponsor review. The STH R&D Coordinator will follow the process for category A amendments where STH is the study Sponsor except that the final cCCC email will be amended to state that it provides continued NHS Permission for the amendment rather than providing cCCC.

Amendments to Research Tissue Banks (RTBs) and Research Databases (RDBs)
Research Tissue Banks (RTBs) and Research Databases (RDBs) continue to use the Notice of Substantial Amendment Form generated in IRAS to notify substantial amendments to REC. This is created from the Amendment tab associated with the RTB/RDB form. The completed Notice of Substantial Amendment form should be electronically authorised by all parties listed on the form's authorisations tab in IRAS. When authorisations are in place, submit the final PDF of the form to the REC, together with all relevant enclosures via IRAS online amendment submission according to the instructions provided on the amendment form's submission tab.

Non-substantial amendments for RTB and RDB projects do not need to be notified to the REC. These can be notified when the next substantial amendment is submitted. Necessary updates to the REC of any minor changes, for example to update key study personnel contact details, can be done by email.

Procedure

1. All amendments where STH is not the study Sponsor (i.e. STH is a participating site)

1.0.1. The STH local research team and/or STH Research Department receives a notification of a study amendment (usually by email) from the study Sponsor or delegate

1.0.1.1. Where the notice of amendment is not copied to STH Research Department the STH local research team forwards the amendment to their R&D Coordinator or to sth.researchadministration@nhs.net

1.0.1.2. On receipt of amendments not directly copied to STH Research Department, in the case of category A/B amendments the R&D Coordinator may email the Sponsor to make them aware of the required HRA process and ask the Sponsor to send the amendment to them directly with a new 35 day deadline.

1.0.2. Where the Amendment Tool is not provided or, in the case of category A/B amendments, where the amendment is otherwise incomplete the STH R&D Coordinator or delegate will email the Sponsor to ask them to re-send the amendment with the additional information and a new 35 day deadline.

1.1. **Process for Cat A and B amendments where STH is not the study Sponsor.** (This section only applies for category B amendments where STH is a site which is specifically affected by the amendment).

1.1.1. The R&D Coordinator or delegate saves the submitted amendment documents in the Amendments under Review section of the study record in Alfresco (section 13) (or in a subfolder of the relevant study folder on the S drive for older studies without Alfresco folders).

1.1.2. The R&D Coordinator or delegate reviews the amendment to identify the main implications.

1.1.3. The R&D Coordinator or delegate starts a new amendment task in RMS. The amendment should be identified by the amendment number / date in the Amendment

Tool. The R&D Coordinator adds a comments field to the task to add an identifying description of the amendment.

1.1.4. Except in cases where the amendment clearly has no impact on the site, the R&D Coordinator or delegate forwards the amendment to the relevant Directorate Research Coordinator or equivalent and/or PI (depending on Directorate practice), summarising the main implications as necessary and requesting confirmation of whether the PI team / Directorate can support the amendment. The R&D Coordinator or delegate may copy in support services as appropriate to alert them to the amendment. For amendments affecting the CRF the R&D Coordinator or delegate starts the process set out in the CRF Amendments Assessment Flowchart (see Appendix 1 for location). Where a study involves pharmacy as a support service all amendments which involve an update to the protocol should be sent to pharmacy regardless of whether any impact on pharmacy is anticipated

1.1.5. The Directorate Research Coordinator and/or PI team confirm to the R&D Coordinator or delegate whether they can accommodate the amendment, highlighting any additional costs / resources as appropriate.

1.1.6. The R&D Coordinator or delegate works with the Directorate Research Coordinator and/or PI team to update the appropriate support service documents as necessary to reflect the amendment and upload amended support service forms to Alfresco (or send by email where Alfresco is not available).

1.1.6.1. Support services (e.g., Pharmacy) may not need their support service documents to be updated and may prefer to receive and consider the amendment via other routes, e.g., email.

1.1.7. The R&D Coordinator or delegate starts any relevant support service tasks within the amendment task on RMS when updated support service forms are available for review on Alfresco or received by email.

1.1.7.1. The relevant support services will review the amendment and updated support service forms and either sign off the amendment in RMS, supplying any costs for additional services in Alfresco or by email or alert the R&D Coordinator or delegate to any issues preventing sign off in RMS as appropriate.

1.1.7.2. Support services (e.g., Pharmacy) may not require support service tasks to be started and may prefer to coordinate review and confirmation of the amendment by email. This can be noted in the diary tab on RMS and/or in the cCCC email.

1.1.8. Where an amendment involves identified additional costs the R&D Coordinator or delegate discusses the amendment with the relevant Directorate Research Finance accountant. The amendment may require a variation to the site agreement/contract or revised statement of activities or a revision to other sources of funding for the study (e.g., excess treatment cost funding).

1.1.8.1. The R&D Coordinator or delegate liaises with the study Sponsor as appropriate following discussion with the Directorate Research Finance accountant.

1.1.8.2. The R&D Coordinator or delegate may revise the finance form and/or start a finance task for the amendment as advised by the Directorate Research Finance accountant.

1.1.8.3. The R&D Coordinator or delegate documents the required actions by email correspondence with the relevant Directorate Research Finance accountant and by making an entry in the diary tab in RMS.

1.1.9. Where the R&D Coordinator or delegate anticipates that confirmation of capacity and capability for the amendment may take longer than 35 calendar days the R&D Coordinator or delegate requests additional time for review by email notification to the Sponsor.

1.1.10. The Sponsor or delegate forwards HRA approval and associated REC/MHRA approval letters to both the PI team and R&D Coordinator

1.1.10.1. Where the Sponsor or delegate does not include relevant REC/MHRA letters the R&D Coordinator requests these.

1.1.11. Where the R&D Coordinator or delegate is otherwise ready to issue cCCC before HRA approval has been received the STH R&D Coordinator or delegate may contact

the Sponsor by email to request the HRA approval (and any relevant REC/MHRA approval letters) and waits until this is received before issuing the cCCC email.

1.1.11.1. If HRA approval is received after 35 day deadline has passed, the R&D Coordinator or delegate may continue to issue the cCCC email to close the loop even though this email is not required to allow the amendment to be implemented at this site. In the case where extra time has been previously requested this cCCC email is required before the amendment may be implemented at this site.

1.1.12. Once HRA approval for the amendment is received and Directorate and Support Service approvals and confirmed funding as applicable are in place, the R&D Coordinator or delegate issues an email to the Sponsor representative, copying in the Directorate Coordinator, PI, support services and other members of the local research team as appropriate confirming continued capacity and capability (cCCC) for the site using the appropriate standard email template, identifying the amendment by its amendment number, date, categorisation, a brief description of the amendment and confirmation of whether the amendment includes an update to the protocol. Support services should always be copied in where the amendment includes an amendment to the protocol or otherwise affects the support service.

1.1.13. The R&D Coordinator or delegate uploads the cCCC email to Alfresco section 5.2 (or in the relevant study folder on the S drive for older studies without Alfresco folders).

1.1.14. The R&D Coordinator or delegate completes the amendment task in RMS (deleting the support service sub-task where no support services are affected by the amendment) and updates the RMS diary page accordingly.

1.1.15. The R&D Coordinator or delegate moves the amendment documents from the Amendments under Review section to the relevant sections in Alfresco, copying the newer version of the document over the top of the previous version to maintain a version control information record. For older studies without Alfresco folders the documents should be filed in the relevant study folder on the S drive.

1.1.16. The cCCC email template will make it clear that this email does not constitute permission to implement the amendment at this site (since as per HRA processes the instruction to implement an amendment must come from the Sponsor or Sponsor delegate).

1.1.17. On receipt of the cCCC email the local PI team contacts the Sponsor or delegate to enquire whether the Sponsor or delegate is ready to issue Sponsor Green Light for the amendment, making it clear that the amendment will not be implemented locally until Sponsor Green Light is received unless the requirement for this has already been explicitly waived by the Sponsor for the amendment concerned.

1.1.18. When Sponsor Green Light for the amendment is received the local research team implements the amendment and updates the local investigator site file according to SOP A116. Where the amendment involves an update to the study protocol the study team should forward the new protocol to the support services involved if the study sponsor has not already done so.

1.2. **Process for Category C amendments where STH is not the study Sponsor.** (This section also applies for category B amendments where STH is a site which is not specifically affected by the amendment).

1.2.2. The R&D Coordinator or delegate confirms the amendment is category C and briefly reviews the amendment to confirm no impact.

1.2.2.1. Where the R&D coordinator or delegate determines that there is an impact to the site the R&D coordinator may suggest to the Sponsor that the amendment may have been incorrectly classified and requests additional time to review the amendment.

1.2.2.2. Where the R&D coordinator or delegate determines that there is an impact to the site the R&D Coordinator or delegate follows the process for category A/B amendments for assessing local capacity and capability at the site as far as possible, whilst not having the ability to delay the implementation of any amendment..

1.2.3. The R&D Coordinator or delegate makes a diary page entry in RMS to note the receipt of the amendment.

1.2.4. The R&D Coordinator or delegate saves the submission email with the submitted documents contained within it in section 3.2 in alfresco (or in the relevant study folder on the S drive for older studies without Alfresco folders) renaming the email with the amendment identifiers and confirmation that it is category C (e.g. NSA01, xxyyyzzzz CAT C amendment).

1.2.5. Where Sponsor Green Light for the amendment is not already given in the submission email, the local PI team waits for further instruction from the Sponsor or delegate before implementing the amendment. PI teams can expect that the Sponsor or delegate will issue Sponsor Green Light to implement the amendment when HRA approval for the amendment is available, if the amendment requires study-wide review as per the Amendment Tool.

1.2.6. Where HRA approval or automated email from the HRA confirming no further review required is already included in the original submission, the Sponsor may also give Sponsor Green Light for the amendment in the submission email. Where this is the case the study team may implement the amendment immediately on receipt as per the Sponsor's Green Light.

1.2.6.1. Where HRA approval for the amendment is already included in the original submission, or the Amendment Tool shows that the amendment does not require study-wide review but Sponsor Green Light to proceed to implementation of the amendment is not explicit PI teams should contact the Sponsor or delegate to enquire whether the Sponsor or delegate is ready to issue Sponsor Green Light for the amendment, making it clear that the amendment will not be implemented locally until Sponsor Green Light is received

1.2.7. When Sponsor Green Light and HRA approval for the amendment is received the local research team implements the amendment and updates the local investigator site file according to SOP A116. Where the amendment involves an update to the study protocol the study team should forward the new protocol to the support services involved if the study sponsor has not already done so.

2. Amendments where STH is the Study Sponsor

2.0. Where STH is the study Sponsor (or UK legal representative) STH R&D Department has responsibility for both confirming capacity and capability for the amendment and for reviewing the amendment as study Sponsor. STH R&D Department may also have responsibility for Sponsor Green Light for amendments depending on the project management set up for the study concerned.

2.0.1. For most single site studies STH R&D Department retains responsibility for Sponsor Green Light, except, for example, where a study is managed by a CTRU.

2.0.2. For multicentre studies STH R&D Department is not usually directly involved in project managing the study. In most cases the CI or a delegated CTRU or otherwise delegated Study Manager is responsible for project management. This responsibility will include ensuring that the amendment is disseminated to the PI teams, local R&D offices and LCRNs at other sites for review and local R&D approval as required and also for notifying those sites of the implementation of amendments. The CI team / Study Manager (and not STH R&D Department) is also therefore responsible for issuing Sponsor Green Light to sites with respect to amendments. STH R&D Department will have responsibility for these tasks for multicentre studies only in exceptional circumstances and by prior arrangement with the STH Research Manager during grant award and study set up.

2.1. **Amendment preparation: All amendments where STH is the study Sponsor. This section applies to both amendments where STH R&D Department retains Sponsor Green Light responsibility and those where it does not.**

2.1.1 The CI or delegate informs the R&D Coordinator of a planned amendment and the R&D Coordinator advises of the below process, along with whether the amendment is substantial or non-substantial for the REC and/or MHRA and the expected categorisation (A, B or C).

2.1.2. Where the study is an STH sponsored CTIMP and STH R&D Department retains project management/Sponsor Green Light responsibility the amendment will undergo additional assessments as per SOP C118.

2.1.3. Where the amendment significantly affects the scientific value of the study the R&D Coordinator determines whether further scientific review is necessary, as per SOP A109. Further statistical advice may also be valuable / necessary, for example in the event of a change in sample size

2.1.4. The CI or delegate drafts updates to study documents as required using tracked changes to make the proposed changes clear and re-versioning the draft updated study documents as per SOP C101

2.1.5. The CI or delegate drafts the Amendment Tool (see Definitions and National Context section) and forwards the draft to the R&D Coordinator for review. The CI or delegate should take note of the below when completing the Amendment Tool:

2.1.5.1 The Amendment Tool should clearly identify the reference number of the amendment. The CI or delegate is responsible for assigning a reference number to each amendment and for keeping a log of amendments as necessary.

2.1.5.2 The amendment date should be left blank; the R&D Coordinator will complete this when adding Sponsor signature.

2.1.5.3 In Section 1, check the pre-selected radio buttons carefully to ensure that the pre-selections are appropriate for your study as these will dictate some of the choices available to you for areas of change in Section 2 and feed into the outcome of the classification of the amendment by the tool in Section 4.

2.1.5.4 Ensure that the correct selections are made in the last two lines of Section 1 as Section 4 will not work unless they are completed.

2.1.5.5 In Section 2, use the smallest number of changes possible to categorise your amendment. Click ‘add another change’ button if amendment is not described by a single set of choices for ‘area of change’ and ‘specific change’. Choices made in this section of the form will determine the type of review the amendment will require; this output is given in Section 4.

2.1.5.6 The CI or delegate should not complete any of Section 3.

2.1.5.7 CI or delegate should check Section 4 to ensure the reviews identified by the Tool are as expected for the amendment (e.g. if amendment is expected to be substantial for REC then ‘changes’ should be selected which result in at least one line in Section 4 being ‘Y’ for full review in the REC column and the overall amendment type should have identified as ‘substantial for review’). CI or delegate should check that the correct categorisation for sites has been identified by the Tool (e.g. if the amendment has implications for the sites involved then the overall category in Section 4 of the tool should be ‘category A’). There is a list of all possible specific changes in the glossary tab but this tab does not specify what category or classification each potential choice would result in.

2.1.5.8 Where the study is a CTIMP and the amendment is substantial, extra fields in the Amendment Tool will be automatically generated and CI or delegate should complete these

2.1.6. The CI or delegate forwards a draft of all study documents, including drafted amendment tool, including a full list of these documents (with updated version number and date of each document) to the R&D Coordinator in either their submission email or in a cover letter if a cover letter has been drafted.

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2.1.7. The R&D Coordinator reviews the Amendment Tool for completeness and against the amended study documents, requesting any revisions from the CI or delegate as necessary. The R&D Coordinator will ensure that the correct classification and categorisation has been identified by the Tool.

2.1.8. Any documents that have been revised should be re-submitted to the R&D Coordinator, along with an updated list of study documents (with updated version number and date).

2.1.9. Once the R&D Coordinator has reviewed the amendment, they will add their name to the Amendment Tool in Section 3 and insert the amendment date into Section 1. The R&D Coordinator will then click ‘lock for submission’ in Section 3. and save the

resulting PDF of the Amendment Tool for return to the CI or delegate as per 2.1.9. The Excel version of the Tool will not be returned.

2.1.10. The R&D Coordinator sends the 'Sponsor pre-submission Approval of Amendment' email to the CI or delegate to confirm that the Amendment Tool and associated documents are acceptable to STH Research Department as study Sponsor. This email will list the documents (and the version/date of these documents) that have been reviewed and will have attached the locked PDF Amendment Tool.

2.1.11. Where project management has been formally delegated (e.g to a CTRU) this may include delegation of the signing of Amendment Tool amendment forms as Sponsor representative to the CTRU/project management team. Where this is the case the R&D Coordinator will send the 'Sponsor pre-submission Approval of Amendment' email The CI or delegate submits the amendment to the REC and/or HRA as per the guidance in IRAS and on the HRA website via the IRAS online amendment submission portal. The CI or delegate ensures that each document associated with the amendment, including the PDF of the locked Amendment Tool and the 'Sponsor pre-submission Approval of Amendment' email is uploaded and that the correct version number and version date of each has been specified.

2.1.12. If the study is an STH sponsored CTIMP and STH R&D Department retains project management/Sponsor Green Light responsibility, where the amendment is substantial for MHRA the R&D coordinator or delegate is responsible for submitting the amendment to the MHRA according to national processes.

2.1.13. The CI or delegate forwards the automated submission email to the R&D coordinator on receipt.

2.1.14. The CI or delegate forwards any subsequent correspondence received from REC, HRA or MHRA to R&D Coordinator.

2.2. STH Sponsored Studies: All Category C or 'Category B with no STH impact' Non-Notifiable amendments for studies where STH R&D Department retains Sponsor Green Light Responsibilities, unless these are STH Sponsored CTIMPs.

2.2.1 Since STH R&D Department is also the study Sponsor and is already aware of the amendment there is no need for notification to STH R&D Department for the amendment and in this case no 35 day deadline for review of the amendment is set.

2.2.2 Since there is no review of these amendments by regulatory bodies, although they do still require submission to the HRA, we will receive no approvals. The HRA will only send an automated email confirming the submission details and that the amendment is 'non-notifiable' and can be implemented immediately.

2.2.3 The 'Sponsor pre-submission Approval of Amendment' email sent to the study team as per Section 2.1 will include the selection of the text 'Please consider this email Sponsor Green Light to implement the amendment once you receive the confirmation email from the HRA after submission'.

2.2.4 Thus once the confirmation email from the HRA is received, where STH are Sponsor and STH R&D Department retains SGL responsibility, the amendment can be implemented immediately.

2.2.5 The local research team implements the amendment and updates the local investigator site file according to SOP A116.

2.2.6 The R&D Coordinator or delegate starts a new amendment task in RMS. The amendment should be identified by the amendment number and date in the Amendment Tool. The R&D Coordinator adds a comments field to the task to add an identifying description of the amendment. The R&D Coordinator signs off the task (deleting the support service sub-task where no support services are affected by the amendment) and updates the RMS diary page.

2.2.7 The R&D Coordinator files all amendment documents in the relevant sections in Alfresco copying the newer version of the document over the top of the previous version to maintain a version control information record. For older studies without Alfresco folders the documents should be filed in the relevant study folder on the S drive.

2.2.8 No further 'cCCC' email will be sent by the R&D Coordinator.

2.3. STH Sponsored Studies: Further local review process for amendments (all categories) for studies where STH R&D Department retains responsibility for Sponsor Green Light, excluding those in 2.2 above.

2.3.1 Since STH R&D Department is also the study Sponsor and is already aware of the amendment there is no need for notification to STH R&D Department for the amendment and in this case no 35 day deadline for review of the amendment is set.

2.3.2. The R&D Coordinator or delegate saves the submitted amendment documents in the Amendments under Review section of the study record in Alfresco (section 13) (or in a subfolder of the relevant study folder on the S drive for older studies without Alfresco folders).

2.3.3. The R&D Coordinator or delegate reviews the amendment to identify the main implications.

2.3.4. The R&D Coordinator or delegate starts a new amendment task in RMS. The amendment should be identified by the amendment number and date in the Amendment Tool. The R&D Coordinator adds a comments field to the task to add an identifying description of the amendment.

2.3.5. Except in cases where the amendment clearly has no impact on the site (including most category C amendments), the R&D Coordinator or delegate corresponds with the relevant Directorate Research Coordinator and/or PI (depending on Directorate practice), requesting confirmation of whether the PI team / Directorate can support the amendment. The R&D Coordinator or delegate may copy in support services as appropriate to alert them to the amendment. This step may be irrelevant in cases where the PI/Directorate team have been involved in the pre-submission work-up of the amendment. For amendments affecting the CRF the R&D Coordinator or delegate starts the process set out in the CRF Amendments Assessment Flowchart. Where a study involves pharmacy as a support service all amendments which involve an update to the protocol should be sent to pharmacy regardless of whether any impact on pharmacy is anticipated.

2.3.6. The Directorate Research Coordinator and/or PI team confirm to the R&D Coordinator or delegate whether they can accommodate the amendment, highlighting any additional costs as appropriate.

2.3.7. The R&D Coordinator or delegate works with the Directorate Research Coordinator and PI team to update the appropriate support service documents as necessary to reflect the amendment and upload amended support service forms to Alfresco (or send by email where Alfresco is not available).

2.3.7.1. Support services (eg Pharmacy) may not need their support service documents to be updated and may prefer to receive and consider the amendment via other routes, eg email.

2.3.8. The R&D Coordinator or delegate starts any relevant support service tasks within the amendment task on RMS when updated support service forms are available for review on Alfresco or received by email

2.3.8.1. The relevant support services will review the amendment and updated support service forms and either sign off the amendment in RMS, supplying any costs for additional services in Alfresco (or by email) or alert the R&D Coordinator or delegate to any issues preventing sign off in RMS as appropriate

2.3.8.2. Support services (eg Pharmacy) may not require support service tasks to be started and may prefer to coordinate review and confirmation of the amendment by email. This can be noted in the diary tab on RMS.

2.3.9. Where an amendment involves identified additional costs the R&D Coordinator or delegate discusses the amendment with the relevant Directorate Research Finance accountant. The amendment may require a variation to the study side letter or funding agreement or a revision to other sources of funding for the study (eg excess treatment cost funding).

2.3.9.1. The R&D Coordinator or delegate may revise the finance form and/or start a finance task for the amendment as advised by the Directorate Research Finance accountant

2.3.9.2. The R&D Coordinator or delegate documents the required actions by email correspondence with the relevant Directorate Research Finance accountant and by making an entry in the diary tab in RMS.

2.3.10. The CI or delegate addresses any requests for further information or further amendment from REC/HRA/MHRA, liaising with the R&D coordinator as appropriate for advice and support.

2.3.11. The CI or delegate forwards the REC, HRA and MHRA approval letters/emails to the R&D Coordinator on receipt.

2.3.12. Once HRA approval for the amendment is received and Directorate and Support Service approvals and confirmed funding as applicable are in place, the R&D Coordinator or delegate issues an email to CI, copying in the Directorate Research Coordinator, PI, support services and other members of the research team as appropriate confirming continued capacity and capability for the site and Sponsor approval for the amendment using the appropriate standard email template, identifying the amendment by its amendment number, date, categorisation, a brief description of the amendment and confirmation of whether the amendment includes an update to the protocol. Support services should always be copied in where the amendment includes an amendment to the protocol or otherwise affects the support service.

2.3.12.1. Where the R&D Coordinator is otherwise ready to issue cCCC before HRA approval has been received the STH R&D Coordinator waits until this is received before issuing the cCCC email

2.3.12.2. Where the study is an STH sponsored CTIMP the appropriate processes for issuing Sponsor Green Light for the amendment are set out in SOP C118.

2.3.12.3. The cCCC / Sponsor approval email will confirm that it constitutes Sponsor Green Light to implement the amendment. The email will confirm the document set approved by reference to the 'Sponsor pre-submission Approval of Amendment' email that was submitted with the Amendment Tool. .

2.3.13. The R&D Coordinator or delegate uploads the cCCC / Sponsor approval email to Alfresco section 5.2 (or in the relevant study folder on the S drive for older studies without Alfresco folders).

2.3.14. The R&D Coordinator or delegate completes the amendment task in RMS (deleting the support service sub-task where no support services are affected by the amendment) and updates the RMS diary page accordingly.

2.3.15. The R&D Coordinator or delegate moves the amendment documents from the Amendments under Review section to the relevant sections in Alfresco copying the newer version of the document over the top of the previous version to maintain a version control information record. For older studies without Alfresco folders the documents should be filed in the relevant study folder on the S drive.

2.3.16. The local research team implements the amendment and updates the local investigator site file according to SOP A116.

2.4. STH Sponsored Studies: Further local review process for category A amendments (and category B amendments where STH is a site which is specifically affected) for studies where STH R&D Department has delegated Sponsor Green Light to the CI team (or CTRU)

2.4.1 Since STH R&D Department is also the study Sponsor and is already aware of the amendment there is no need for notification to STH R&D Department for the amendment and in this case no 35 day deadline for review of the amendment is set. If the project management team's SOPs require it they may submit the amendment to STH R&D Department to fulfil their own processes, in which case any 35 day deadline set will apply.

2.4.2. The R&D Coordinator or delegate saves the submitted amendment documents in the Amendments under Review section of the study record in Alfresco (section 13) (or in a subfolder of the relevant study folder on the S drive for older studies without Alfresco folders)

2.4.3. The R&D Coordinator or delegate reviews the amendment to identify the main implications.

2.4.4. The R&D Coordinator or delegate starts a new amendment task in RMS. The amendment should be identified by the amendment number and date in the Amendment Tool. The R&D Coordinator adds a comments field to the task to add an identifying description of the amendment.

2.4.5. Except in cases where the amendment clearly has no impact on the site, the R&D Coordinator or delegate corresponds with the relevant Directorate Research Coordinator and/or PI (depending on Directorate practice), requesting confirmation of whether the PI team / Directorate can support the amendment. The R&D Coordinator or delegate may copy in support services as appropriate to alert them to the amendment. This step may be irrelevant in cases where the PI/Directorate team have been involved in the pre-submission work-up of the amendment. For amendments affecting the CRF the R&D Coordinator or delegate starts the process set out in the CRF Amendments Assessment Flowchart. Where a study involves pharmacy as a support service all amendments which involve an update to the protocol should be sent to pharmacy regardless of whether any impact on pharmacy is anticipated.

2.4.6. The Directorate Research Coordinator and/or PI team confirm to the R&D Coordinator or delegate whether they can accommodate the amendment, highlighting any additional costs / resources as appropriate.

2.4.7. The R&D Coordinator or delegate works with the Directorate Research Coordinator and PI team to update the appropriate support service documents as necessary to reflect the amendment and upload amended support service forms to Alfresco (or send by email where Alfresco is not available).

2.4.7.1. Support services (eg Pharmacy) may not need their support service documents to be updated and may prefer to receive and consider the amendment via other routes, eg email.

2.4.8. The R&D Coordinator or delegate starts any relevant support service tasks within the amendment task on RMS when updated support service forms are available for review on alfresco or by email.

2.4.8.1. The relevant support services will review the amendment and updated support service forms and either sign off the amendment in RMS, supplying any costs for additional services in Alfresco (or by email) or alert the R&D Coordinator or delegate to any issues preventing sign off in RMS as appropriate.

2.4.8.2. Support services (eg Pharmacy) may not require support service tasks to be started and may prefer to coordinate review and confirmation of the amendment by email. This can be noted in the diary tab on RMS.

2.4.9. Where an amendment involves identified additional costs the R&D Coordinator or delegate discusses the amendment with the relevant Directorate Research Finance accountant. The amendment may require a variation to the study side letter or funding agreement.

2.4.9.1. The R&D Coordinator or delegate may revise the finance form and/or start a finance task for the amendment as advised by the Directorate Research Finance accountant

2.4.9.2. The R&D Coordinator or delegate documents the required actions by email correspondence with the relevant Directorate Research Finance accountant and by making an entry in the diary tab in RMS.

2.4.10. Where a 35 day deadline had been set and the R&D Coordinator or delegate anticipates that confirmation of capability and capacity for the amendment may take longer than 35 calendar days the R&D Coordinator or delegate requests additional time for review by email notification to the CI team / Study Manager.

2.4.11. The CI team / Study Manager addresses any requests for further information or further amendment from REC/HRA/MHRA, liaising with the R&D coordinator as appropriate for advice and support.

2.4.12. The CI team / Study Manager forwards the REC, HRA and MHRA approval letters/emails to the R&D Coordinator on receipt.

2.4.13. Once HRA approval for the amendment is received and Directorate and Support Service approvals and confirmed funding as applicable are in place, the R&D Coordinator or delegate issues an email to CI/Study Manager, copying in the Directorate Research Coordinator, PI, support services and other members of the research team as

appropriate confirming continued capacity and capability for the site using the appropriate standard email template, identifying the amendment by its amendment number, date, categorisation, a brief description of the amendment and confirmation of whether the amendment includes an update to the protocol. Support services should always be copied in where the amendment includes an amendment to the protocol or otherwise affects the support service.

2.4.13.1. Where the R&D Coordinator is otherwise ready to issue cCCC before HRA approval has been received the STH R&D Coordinator waits until this is received before issuing the cCCC email

2.4.13.2. The cCCC email will make it clear that this email does not constitute permission to implement the amendment at this site and the research team must liaise with the Study Manager to obtain confirmation of Sponsor Green Light to implement the amendment.

2.4.13.3. Where a 35 day review deadline has been set, if HRA approval is received after 35 day deadline has passed, the R&D Coordinator or delegate may continue to issue the cCCC email to close the loop even though this email is not required to allow the amendment to be implemented at this site. In the case where extra time has been previously requested this cCCC email is required before the amendment may be implemented at this site.

2.4.14. The R&D Coordinator or delegate uploads the cCCC email to Alfresco section 5.2 (or in the relevant study folder on the S drive for older studies without Alfresco folders).

2.4.15. The R&D Coordinator or delegate completes the amendment task in RMS (deleting the support service sub-task where no support services are affected by the amendment) and updates the RMS diary page accordingly.

2.4.16. The R&D Coordinator or delegate moves the amendment documents from the Amendments under Review section to the relevant sections in Alfresco, copying the newer version of the document over the top of the previous version to maintain a version control information record For older studies without Alfresco folders the documents should be filed in the relevant study folder on the S drive.

2.4.17. On receipt of the cCCC email the local PI team contacts the Study Manager (ie the person responsible for giving Sponsor Green Light) to enquire whether the Study Manager is ready to issue Sponsor Green Light for the amendment, making it clear that the amendment will not be implemented locally until Sponsor Green Light is received.

2.4.18. When HRA approval and cCCC are both available the Study Manager issues Sponsor Green Light for the amendment to the PI team by email, copying in the R&D Coordinator and copying in support services where the amendment involves an update to the study protocol.

2.4.19. When Sponsor Green Light for the amendment is received the local research team implements the amendment and updates the local investigator site file according to SOP A116.

2.5. STH Sponsored Studies: Further local review process for category B/C amendments for studies where STH R&D Department has delegated Sponsor Green Light to the CI team (or CTRU)

2.4.1 The R&D Coordinator or delegate confirms the amendment is category B/C and briefly reviews the amendment to confirm no impact for STH as a site.

2.5.2. The R&D Coordinator or delegate makes a diary page entry in RMS to note the receipt of the amendment

2.5.3. The R&D Coordinator or delegate saves documents associated with the amendment in the relevant sections in Alfresco, copying the newer version of the document over the top of the previous version to maintain a version control information record For older studies without Alfresco folders the documents should be filed in the relevant study folder on the S drive. (or in the relevant folder on the s drive for older studies not on alfresco).

2.5.4. When HRA approval is available the Study Manager issues Sponsor Green Light for the amendment to the PI team by email, copying in the R&D Coordinator and copying in support services where the amendment involves an update to the study protocol.

2.5.5. When Sponsor Green Light for the amendment is received the local research team implements the amendment and updates the local investigator site file according to SOP A116.

2.6. All amendments where STH is the study Sponsor for a multicentre study: process for the notification and implementation of amendments at other sites

2.6.2. Where there are multiple sites participating in an STH sponsored study, the CI or delegated CTRU or otherwise delegated Study Manager is responsible for ensuring that the amendment is disseminated to the PI teams, local R&D offices and LCRNs at other sites for review and local R&D approval as required, for tracking these notifications and the receipt of relevant local R&D cCCC and also for notifying those sites of the implementation of amendments (Sponsor Green Light) following receipt of regulatory approvals and either receipt of local R&D cCCC or expiry of the notification period with no objections raised by the local R&D office. STH R&D Department will have responsibility for these tasks only in exceptional circumstances and by prior arrangement with the STH Research Manager during grant award and study set up.

2.6.3. Preparation of the amendment for submission will follow the process as per section 2.1 above

2.6.4. Where the amendment is anticipated to have financial implications for sites the CI/ Study Manager or delegate liaises with the relevant Research Finance accountant or other relevant finance team to establish how to manage the necessary changes in financial arrangements for the sites, involving the R&D coordinator in the discussion where the necessary changes will involve new agreements or variations to agreements which will require formal Sponsor signature.

2.6.5. When automated confirmation of submission email is received the CI / Study Manager or delegate is responsible for notifying all relevant participating sites of the amendment according to HRA processes as set out in IRAS and on the HRA website using email templates provided by the HRA. Please note the process for notifying participating sites varies according to the location (devolved nation) of the participating site. For English and Welsh sites the CI/ Study Manager or delegate must copy in the local research team, local R&D office and LCRN (where locally required) to the notification emails. In the case of category A/B amendments for English and Welsh sites the CI or delegate must set the 35 calendar day deadline for local R&D review of the amendment for each participating site in the notification email (unless it is a non-notifiable amendment as these may be implemented immediately).

2.6.6. There is no need to notify STH of the amendment (unless this is required by local CTRU SOPs or similar) since STH R&D Department is already aware of the amendment. In this case there is no 35 day deadline set for STH to issue cCCC.

2.6.7. Local review and implementation of the amendment at STH as a site will be conducted as per section 2.3 or 2.4 above as appropriate.

2.6.8. The CI/Study Manager or delegate is responsible for fielding queries from participating sites and local R&D offices and LCRNs regarding the notified amendment.

2.6.9. The CI/Study Manager or delegate is responsible for keeping records of which sites have been notified of each amendment.

2.6.9.1. Where the amendment is categorised as Category A or Category B the CI/Study Manager is also responsible for keeping records of the 35 day review period set for each site, which sites have issued cCCC for the amendment, and which sites have requested additional time to review the amendment.

2.6.10. The CI/Study Manager or delegate is responsible for preparing each variation to site agreement or amendment to the statement of activities with each participating site with support from the R&D coordinator and/or relevant STH Research Finance accountant as necessary. The R&D coordinator will facilitate Sponsor signature as necessary and the CI/Study Manager or delegate is responsible for obtaining site signature as necessary, with support from the R&D coordinator when required.

2.6.11. The CI/Study Manager or delegate is responsible for issuing Sponsor Green Light to each site to implement the amendment when the CI/Study Manager or delegate is satisfied that:

2.6.11.1. HRA approval for the amendment is in place and is valid

2.6.11.2. For category A/B amendments either the local R&D Department or LCRN has issued cCCC or the 35 day notice period has elapsed without the receipt of any objection or request for extension

2.6.11.3. Any additional necessary processes (eg additional site training, update to case report forms etc) have been completed

2.6.12. In making the Sponsor Green Light notification the CI/Study Manager or delegate should use the recommended HRA template

2.6.13. The CI/Study Manager or delegate is responsible for following the necessary processes for submission of amendments to national coordinating centres for Scotland and Northern Ireland and any onward notification to sites in these countries as per the national processes set out in IRAS and on the HRA website.

Appendix 1 Documents Associated with the SOP

	Document	S-drive	Website	RMS	Who
1	CCCC email template – all studies with or without sponsor green light (except STH sponsored CTIMPs)		No	RMS 1, Alfresco section 5.2	EW
2	CRF Amendments Assessment Flowchart		No	RMS 1 section 8	CRF
3	Sponsor pre-submission Approval of Amendment email template		No	RMS 1, Alfresco section 5.2	AC

Appendix 2 SOP revisions and history

SOP number	Effective date	Reason for change	Author
THIS SOP			
C105 V5.0		To reflect update to amendment forms and submission process to REC/HRA. To bring procedures in-line with the non-notifiable processes. Addition of Sponsor pre-submission Approval of Amendment email	EW/AC
PREVIOUS SOPs			
C105 V4.0	02 Dec 19	Complete re-write to reflect HRA processes	EW
C105 V3.0	17 Nov 15	To incorporate use Support Service Forms for review, when an amendment impacts financially on a given Support Service. General reformatting.	RS
C105 V2.0		To bring procedures in-line with the notifiable and non-notifiable processes.	MH, GK, JDM
C105 V1.0			AP, TL