Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

Amendments

SOP Number	*C105*	**Version Number**	*V4.0*
Effective Date	*02 Dec 2019*	**Author**	*EW*
Related SOPs	*A109 Independent Scientific Review* *A116 Study Site File* *B122 R&D Master File* *C101 Document version control* *C117 Pharmacovigilance* *C118 Risk assessment of STH sponsored CTIMPs*		

Approved by (name & role)	Dipak Patel R&D Manager	**Date:**	04 Nov 2019
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.

Index

Acronyms

CCC	Confirmation of Capacity and Capability
cCCC	Continued Confirmation of Capacity and Capability
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
PIC	Patient Identification Centre
REC	Research Ethics Committee
RMS	Research Management System
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).

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.

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

- Addition of sites and change of PI at sites for CTIMPs are substantial amendments requiring approval by both REC and HRA.
- Addition of sites and change of PI at sites for all other studies (non-CTIMPs) are non-substantial amendments. These require submission to and approval by 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/or non-substantial amendments must be submitted to the HRA (via the allocated REC for both substantial and non-substantial amendments) and must be approved by the HRA. Amendments must be submitted using the appropriate form.

- Substantial amendment forms are generated in IRAS within the IRAS form (REC form for pre-HRA projects) for the specific project.
- The non substantial amendment form is a Word document template which is available to download from the help section of IRAS.

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

Following submission substantial and non-substantial amendments are categorised by the HRA (or lead country in the case of amendments led from Scotland or Northern Ireland) to ensure 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 - 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.
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 a categorisation email is received the Study Manager should share the notice of amendment and amended documents together with the categorisation 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 categorisation email 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.
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.

For category C amendments the HRA categorisation email will provide information on how to implement the amendment. Category C amendments do not require review by participating NHS

organisations and may be implemented (ie Sponsor Green Light (SGL) for the amendment may be issued) once HRA approval for the amendment has been issued

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 (eg 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 his/herself 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 him/herself 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.

Procedure

1. All amendments where STH is not the study Sponsor (ie 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 categorisation email 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 categorisation email. 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. 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 (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.

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 (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 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 (eg 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. However it is the Sponsor's decision to decide whether to ask the HRA to reclassify 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 which is not reclassified by the HRA.

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.

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.

1.2.6. Where HRA approval 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 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.

1.2.8.

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.

2.1.2. 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.**

2.1.3. The CI or delegate informs the R&D Coordinator of a planned amendment, forwarding a draft of all study documents containing the proposed changes as tracked changes. The CI or delegate re-versions draft updated study documents as per SOP C101.

2.1.4. The R&D Coordinator confirms by email whether the amendment is substantial or non-substantial for the REC and/or MHRA as appropriate.

2.1.4.1. 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

2.1.4.2. 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

2.1.5. The CI or delegate drafts the relevant Amendment Notification Form (see Definitions and National Context section) and forwards the draft to the R&D coordinator for review. The amendment form 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.

2.1.6. The R&D Coordinator reviews the amendment form for completeness and against the drafted amended study documents, requesting any revisions from the CI or delegate as necessary.

2.1.7. The R&D Coordinator electronically signs the relevant amendment form as Sponsor representative to confirm that the amendment form and associated documents are acceptable to STH Research Department as study Sponsor.

2.1.7.1. Where project management has been formally delegated (eg to a CTRU) this may include delegation of the signing of amendment forms as Sponsor representative to the CTRU/project management team.

2.1.8. The CI or delegate adds a CI signature to the relevant amendment form and finalises the form ready for submission as per the guidance in IRAS.

2.1.9. The CI or delegate submits the amendment to the REC and/or HRA as per the guidance in IRAS and on the HRA website.

2.1.10. 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.

2.1.11. The CI or delegate forwards the HRA classification email to the R&D coordinator on receipt.

2.2. STH Sponsored Studies: Further local review process for amendments (all categories) for studies where STH R&D Department retains responsibility for Sponsor green light

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. 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).

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

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

2.2.5. 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.

2.2.6. 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.

2.2.7. 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).

2.2.7.1. 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.

2.2.8. 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

2.2.8.1. 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

2.2.8.2. 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.

2.2.9. 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).

2.2.9.1. 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

2.2.9.2. 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.

2.2.10. 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.

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

2.2.12. 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.

2.2.12.1. 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

2.2.12.2. 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.

2.2.12.3. 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 REC letter in the case of substantial amendments and the non-substantial amendment form in the case of non-substantial amendments.

2.2.13. 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).

2.2.14. 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.

2.2.15. 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.

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

2.3. 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)

2.3.2. 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.

2.3.3. 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)

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

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

2.3.6. 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.

2.3.7. 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.

2.3.8. 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).

2.3.8.1. 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.

2.3.9. 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.

2.3.9.1. 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

2.3.9.2. 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.

2.3.10. 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.

2.3.10.1. 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

2.3.10.2. 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.

2.3.11. 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.

2.3.12. 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.

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

2.3.14. 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.

2.3.14.1. 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

2.3.14.2. 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.

2.3.14.3. 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.

2.3.15. 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).

2.3.16. 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.

2.3.17. 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.

2.3.18. 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.

2.3.19. 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.

2.3.20. 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.

2.4. 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)

2.4.2. 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.

2.4.2.1. Where the R&D coordinator or delegate determines that there is an impact to the site the R&D coordinator may discuss with the CI team / Study Manager whether to ask the HRA to reclassify the amendment.

2.4.2.2. 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 amendments for assessing local capacity and capability at the site.

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

2.4.4. 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).

2.4.5. When HRA approval is available, providing there has been no decision to treat the amendment as category A (see item 2.4.2.2 above) 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.

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

2.5.2. 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.

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

2.5.4. 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.

2.5.5. When HRA categorisation 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.

2.5.6. 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.

2.5.7. 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.

2.5.8. 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.

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

2.5.9.1. 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.

2.5.10. 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.

2.5.11. 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:

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

2.5.11.2. 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

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

2.5.12. In making the Sponsor green light notification the CI/Study Manager or delegate should use the recommended HRA template

2.5.13. 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

Appendix 2 SOP revisions and history

SOP number	Effective date	Reason for change	Author
THIS SOP			
C105 V4.0	02 Dec 19	Complete re-write to reflect HRA processes	EW
PREVIOUS SOPs			
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