DIVISION OF RESEARCH AND INNOVATION

Joint Research and Development Office / Clinical Research Facility

Document Number: GOSH/ICH/SOP/R/005	Version Number: 1
Title: Assessment and confirmation of implementation of amendments to hosted and GOCH/ICH sponsored CTIMPs and non-CTIMP studies	
Effective Date:	*Thursday 19th November 2020*

	Name	Position
Authored by:	Rebecca Norton	Quality Assurance and Research Governance Officer
Approved by:	Vanshree Patel	Head of Governance, Clinical Trials and Contracts

1. Scope

This standard Operating Procedure (SOP) details the Great Ormond Street Hospital NHS Trust (GOSH) and University College London's Great Ormond Street Institute of Child Health (UCL ICH) procedures for managing amendments to all trials, Hosted or Sponsored by GOSH/ICH including CTIMP and Non-CTIMP studies.

2. Purpose

The purpose of this SOP is to inform the Joint R&D Office staff, Investigators and trial staff on the process of assessing and approving amendments to hosted and sponsored, CTIMP and non-CTIMP studies at GOSH/ICH.

3. Definitions/Abbreviations

Amendments are alterations made to a study after a favourable opinion has been given.

Types of amendment:

- **Substantial** – a change that is likely to have a significant impact on: the safety, physical or mental integrity of the study subjects, the scientific value of the study, the conduct management of the study or the quality of safety of the Investigational Medicinal Product.
- **Non-Substantial** – have no significant implications on the trial, there is no legal requirement to inform the Research Ethics Committee (REC) or MHRA of these amendments, however, the HRA still needs to be notified and provide approval before implementation.

*Examples of different types of amendments can be found in Appendix 1.

These are then categorised by the Sponsor prior to processing and confirmed by the Health Research Authority (HRA). The categories are:

- **Category A** – Amendment made to a study where ALL participating NHS sites are expected to consider, sites have 35 days to raise any objections after which if no objections have been raised, the amendment can be implemented.
- **Category B** – Amendment made to a study that impacts/affects specific NHS sites. Only these sites will need to review the amendment prior to implementation, sites have 35 days to raise any objections after which if no objections have been raised, the amendment can be implemented.
- **Category C** – Amendment made to a study where NHS sites are NOT expected to consider the amendment or issue continued permission. These can be implemented immediately.

Types of study:

- **CTIMP** – Clinical Trial of an Investigational Medicinal Product
- **Non-CTIMP** – Any other clinical study which is not a Clinical Trial of an Investigational Medicinal Product
- **Sponsored** – any clinical study sponsored by GOSH or UCL ICH.
- **Hosted** – any clinical study not sponsored by GOSH or UCL ICH but GOSH or ICH are acting as a site where research is conducted

4. Responsibilities

Duties may be delegated but the responsibilities always remain with those listed, please refer to Appendix 2.

5. Procedure

This section will detail four different amendment processes:

- Substantial amendment process where GOSH or UCL ICH are the Sponsor
- Non-Substantial amendment process where GOSH or UCL ICH are the Sponsor
- Substantial amendment process where GOSH or UCL ICH are the Host site
- Non-Substantial amendment process where GOSH or UCL ICH are the Host site

Examples of minimum datasets for each amendment can be found in Appendix 3. Where GOSH or UCL ICH is the Sponsor the CI or delegate will create an amendment request. In some cases the CI/delegate may requests advice from the Clinical Trials Team (CTIMP/Device studies) or the Governance Team (non-CTIMPs) regarding whether the amendment is classified as substantial for the purpose of the REC and/or MHRA.

Where GOSH or UCL ICH is the Study Sponsor: Substantial Amendments

5.1.1 The CI or delegate informs the Research Governance Lead (non-CTIMPs) or the Clinical Trials Lead (CTIMPs) for the study of the amendment via email which will include the unlocked amendment tool (https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx) (which replaces the Notice of Substantial Amendment (NOSA) Form) and all the amended study documents. This email should be sent to Research.Govenance@gosh.nhs.uk.

5.1.2 For GOSH Sponsored CTIMPs, the study team (project manager, clinical trial manager, coordinator) are also required to complete the amendment log (template available on Q-pulse) and send it with all other amendment documents to GOSH R&D Clinical Trials Manager or Research.Governance@gosh.nhs.uk. The amendment log is a live document and each amendment need to be logged in chronological order.

5.1.3 The Research Governance /Clinical Trials Lead will review the Amendment Tool in conjunction with the revised/new study documents to ensure the amendment

meets the substantial amendment criteria and is submitted to the appropriate regulatory body, identify any risks or implications that implementing the amendment may have on running of the study, including but not limited to current risk assessments, e-crfs, monitoring plans, finances, to ensure that these can be accommodated. For GOSH sponsored CTIMPs a Change Control Form (available on Q-pulse) will need to be completed, by a member of the study team (Research Nurse, Coordinator, or data manager), the team can contact R&D for guidance if needed.

5.1.4 The Research Governance /Clinical Trials Lead as the sponsor representative would authorises/sign the Amendment tool on behalf of the Sponsor.

5.1.5 Once sponsor authorisation has been granted the CI or delegate then submits all the amended documentation listed in the Amendment tool including both clean and track change versions of the documentation along with the fully signed and locked amendment tool to the appropriate regulatory body (MHRA, REC or HRA, as applicable) via the Online Submission process on IRAS. All amendments requiring REC favourable opinion must be sent to the same REC committee that provided the initial REC approval for the study. All documentation for amendments that require MHRA approval must be submitted by the CI or delegate through CESP (Common European Submission Portal).

5.1.6 The REC and/or MHRA will acknowledge receipt of the amendment once received, and will aim to confirm approval within 30 days, the HRA will also issue a categorisation e-mail (categorising the amendment based on impact (A, B or C)).

5.1.7 The Clinical Trials team are responsible for carrying out a Risk Assessment on each Sponsored CTIMP amendment, they assess whether the amendment is likely to have any impact on the risk assessment for the study and takes forward any necessary reassessment.

5.1.8 Where the amendment impacts upon local Support Services and/or financial requirements for the study, the Research Governance /Clinical Trials Lead/delegate requests the appropriate Support Services/Financial approval via email.

5.1.9 At this point the Amendment workflow should be added to Edge and completed step-by-step as appropriate by the Research Governance /Clinical Trials Lead/delegate. To track the progress of the amendment and ensure the study teams have all the correct documentation, regulatory and local approvals in place in order to implement this amendment.

5.1.10 Once regulatory (REC/MHRA, as applicable), and Support Service/Finance approvals if required are in place, the Research Governance /Clinical Trials Lead issues an Approval email (arrange capacity and capability) to the CI and PI, copying to all appropriate contacts and Support Services using the current template email, with all approved documents attached (Appendix 4).

5.1.11 The Research Governance /Clinical Trials Lead or delegate then uploads the approved documents on to Edge/ReDA, including all local and regulatory approvals

5.2 Where GOSH or UCL ICH is the Study Sponsor: Non-substantial Amendments

5.2.1 The CI or delegate downloads and completes the Amendment tool from the HRA website (https://www.hra.nhs.uk/approvals-amendments/amending-approval/).

5.2.2 Once completed the CI or delegate sends the Amendment Tool and all amended documents to the Research Governance/Clinical Trials Lead/Clinical trials manager (for GOSH sponsored CTIMPs) for review to ensure no major change(s) have been made to the current practice and that the change(s) fulfil the minor amendment criteria before the CI submits to the HRA.

5.2.3 The CI/ delegate/R&D team should email the completed Amendment tools and all amendment documentation to hra.amendments@nhs.net and Research.Governance@gosh.nhs.uk and to GOSH Clinical Trials manager for GOSH sponsored CTIMPs as appropriate

5.2.4 The HRA acknowledges the minor amendment by email. A categorisation email will be sent to Research.Governance@gosh.nhs.uk, stating whether or not it also constitutes as approval, if not a separate email of approval will be sent. If a site know to be a part of the project has not been cc'd in to the categorisation/approval email, it is the CI/delegates responsibility to forward it on to them. Once the HRA approval is issued, the Research Governance /Clinical Trials Lead issues an Acknowledgement email to the CI, copying to all appropriate contacts and Support Services using the current template email, with all approved documents attached (Appendix 5).

5.2.5 Research Governance /Clinical Trials Lead or delegate then uploads the approved documents on to Edge/ReDA, including all local and regulatory approvals.

5.3 Where GOSH is the Host Site: Substantial Amendments

5.3.1 The Sponsor representative notifies the Research Governance team of the amendment by sending the Amendment Tool and all amendment documentation to Research.Governace@gosh.nhs.uk.

5.3.2 The Research Governance lead / Research Administrator will add the Amendment workflow to the study on Edge and update. For All studies the Research Governance lead / Research Administrator will also create a folder on the I Drive (Commercial studies - I:\R and D\Industry Amendments, Non-Commercial studies - I:\R and D\Non Commercial Amendments) where all the amendment documents will be saved as they are received. This should be suitably named (R&D number Amendment Number) within this folder there should be two separate folders one for all the approvals and one for the amendment documents. The approvals folder should then be split further into local and regulatory approvals.

5.3.3 The Research Governance lead / Research Administrator will check that all correct dated versions of the documents listed in the REC acknowledgement letter are included in the amendment package and that theses match the documents listed in the Notice of Substantial amendment form and cover letter sent from the Sponsor to the REC.

5.3.4 The Research Governance lead / Research Administrator using the email template in Appendix 6 will send a validation email to the Sponsor representative notifying them of receipt of the documentation as well as notifying them that it may take longer than 35 days for this amendment to be implemented.

5.3.5 An email (Appendix 7) with the amendment package attached should be sent by the Research Governance lead / Research Administrator to the PI/study team, pharmacy for review.

5.3.6 It is the PI/Study team responsibility to notify R&D if this amendment impacts upon other Support Services and/or the financial requirements for the study. If so the Research Governance lead /Research Administrator requests the appropriate Support Services/Financial approval via email.

5.3.7 Once all regulatory (HRA/REC/MHRA, as applicable), and Support Service/Finance approvals (if required) are in place, the Research Administrator would draft the email using the current template email, with all approved documents attached (Appendix 8) and sends it to the Research Governance Lead for approval.

5.3.8 Once approved the Research Governance lead/Research Administrator issues an Approval email (arrange capacity and capability) to the PI, copying to all appropriate contacts, Support Services and the sponsor.

5.3.9 Research Governance /Research Administrator then uploads the approved documents on to Edge/ReDA, including all local and regulatory approvals, updating the workflow on Edge.

5.4 Where GOSH is the Host Site: Non-Substantial Amendments

5.4.1 The Sponsor representative notifies the Research Governance team of the amendment by sending the Amendment Tool and all amendment documentation, including confirmation of categorisation email from the HRA to Research.Governace@gosh.nhs.uk.

5.4.2 The Research Governance lead / Research Administrator will add the Amendment workflow to the study on Edge and update.

5.4.3 There is no legal requirement to obtain REC approval prior to implementation for Non-substantial/ minor amendments however they do need to be submitted to the HRA.

5.4.4 The Research Governance lead / Research Administrator will check that all correct dated versions of the documents listed in the None Substantial amendment form sent from the Sponsor to the HRA/REC* are included in the amendment package, updating the Amendment workflow on Edge as they go.

5.4.5 Amendments categorised either A or B by the HRA will be sent out to the study team for review as an email, using the template in Appendix 5 with the documents attached. Category C amendments have no implications that require management oversight by NHS organisations and can be implemented once HRA/REC* approval has been received.

5.4.6 Once HRA approval and all local approvals have been received, the Research Governance lead / Research Administrator will send an email to acknowledge that they are aware of this amendment, update the workflow on Edge and upload the amendment documentation in a zip file, along with all approvals (regulatory, local and R&D) onto both Edge and ReDA.

*The regulatory approvals required before Amendment implementation at an NHS site differs depending on a number of factors, see Appendix 9 for more information.

6. Related Documents

GOSHICHSOPR005 Reporting and Escalation for Research V1.
GOSHICHTMPR057 Change Control Form

7. References

UK Policy Framework for Health and Social Care Research - https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/

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

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

GDPR Guidance - https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/what-you-need-do/

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

The Medicines for Human Use (Clinical Trials) Regulations 2004 https://www.legislation.gov.uk/uksi/2004/1031/contents/made

8. Appendices

Appendix 1: Examples of types of amendment

Substantial Amendments (SA)*	**Non-Substantial/Minor Amendments (NSA/MA)**
Appointment of new/change of Chief Investigator (CI)	Increases or decreases in subject size not affecting scientific value of trial
Change in insurance and indemnity arrangements	Correction of typographical errors in the protocol or other study documentation
Temporary halt and/or premature closure	Non substantial clarifications of the protocol
Significant modifications to the information provided on the original application and within an approved protocol	Changes in contact details (excluding changes to the Sponsor and CI)
Change in sponsor and/or legal representative	Change in site PI details
	Changes in funding arrangements
	Extension of study period

*These are sometimes referred to as Protocol Amendments (PA) by the Sponsor.

Note: The above examples are not exhaustive and where investigators are unsure as to the nature of their amendment they should consult relevant members of the Joint R&D Office and/or National Research Ethics Service (NRES), further examples can be found on the HRA website (*https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-substantial-amendments/*).

Appendix 2: Roles and Responsibilities

GOSH Sponsored Trials – Prior ethics committees

Step	Task	Person(s) Responsible	
		CTIMPs	Non-CTIMPs
1	Notifies R&D of Amendment	CI or Delegate	
2	Completes amendment log	Project Manager, Clinical Trial Manager or Trial Co-ordinator	Study team
3	Confirms that amendment is substantial	Clinical Trials Team	Research Governance Team
4	Completes change control form	Project Manager, Clinical Trial Manager or Trial Co-ordinator	N/A
5	Document Check (Check all documents listed on the Amendment tool have been received)	Clinical Trials Team	Research Governance Team
6	Authorises Amendment tool (on behalf of Sponsor)	Clinical Trials Team	Research Governance Officer
7	Assesses risk of Amendment	Clinical Trials Team	Research Governance Officer
8	Sends Amendment (Amendment tool / documents) to the Research Ethics Committee (that provided original favourable opinion)	Clinical Trials Team/Study team	CI or Delegate
9	Sends Amendment (Amendment tool / documents) to the MHRA	Clinical Trials Team/Study team	N/A
10	Categorisation of Amendment (A,B or C)	HRA	
11	Sends Amendment package and HRA letter of Categorisation to other sites (if multicentre trial)	CI or Delegate	
12	Sends Regulatory Approval letters to the CI	Clinical Trials Team	N/A
13	Sends to Support Service/Finance teams for Review (if required)	Clinical Trials Team	Research Governance Officer
14	Sends to CI, study teams, support services (once all approvals local and regulatory have been received)	Clinical Trials Team	Research Governance Officer

15	Updates Edge workflow adds amendment package/ all approvals (including R&D approval) to ReDA and Edge	Clinical Trials Team	Research Governance Officer

GOSH Sponsor and Hosted Trials – Prior to implementation

Step	Task	Person(s) Responsible		
		Commercial	**Non-Commercial/Sponsored Non-CTIMPs**	**Sponsored CTIMPs**
1	Add and update the Amendment workflow of Edge	Research Governance Administrator	Research Governance Office/ Research Governance Administrator	Clinical Trials Team
2	Document Check (Check all documents listed on the Sponsor cover letter/REC acknowledgement letter are there)	Research Governance Administrator	Research Governance Office/ Research Governance Administrator	Clinical Trials Team
3	Send to PI, Study Team and Pharmacy	Research Governance Administrator	Research Governance Office/ Research Governance Administrator	Clinical Trials Team
4	Review Amendment - confirm Capacity and Capability - Inform R&D whether amendment package should be sent to other supporting departments (if the PI has already contacted the supporting departments that would be affected confirmation of this is still needed) - Confirm whether or not amendment has any costing implications	PI (has final sign off) Study team (Lead nurse) Pharmacy (CTIMPs only) Contracts (if necessary) Finance (if necessary) Other Supporting Departments (e.g. radiology, if necessary)		

	- Confirm whether or not amendment will require contract change			
5	Ensure all local approvals have been received (PI, Study team, Pharmacy, Support Departments e.g Labs, Pathology, CRSM, Finance, Contracts)	Research Governance Administrator	Research Governance Office/ Research Governance Administrator	Clinical Trials Team
6	Ensure all the correct regulatory approvals have been received - HRA categorisation letter - MHRA approval (CTIMP only) - REC approval HRA approval Or any other regulatory approvals (CAG, ARSAC)	Research Governance Administrator	Research Governance Office/ Research Governance Administrator	Clinical Trials Team
7	E-mail template sent to authorised signature approval (only applicable to commercial studies)	Research Governance Administrator	Only required if carried out above process Research Governance Administrator	Clinical Trials Team
8	Authorised signature approval (only applicable to commercial studies)	Head of Governance and Clinical Trials	Research Governance Officer	Clinical Trials Team
9	Substantial Amendment Approved Non-substantial Amendment Acknowledged (confirmation email with attached amendment package zip file sent to PI, study team, pharmacy*, CRF registration*, Support teams*, Sponsor	Research Governance Administrator	Research Governance Office/ Research Governance Administrator	Clinical Trials Team
10	Upload all documents (amendment package and all approval (regulatory, local) and R&D approval/acknowledgement	Research Governance Administrator	Research Governance Office/ Research Governance Administrator	Clinical Trials Team

	confirmation email) to ReDA** and Edge			
11	Confirmation of when Amendment has been Implemented	Study Team		

*Only include these teams if they will be directly affected by this amendment.

Appendix 3: Minimum required documents for amendments

Substantial Amendments

- Cover Letter including description of the amendment and reason(s) for the proposed amendment
- The **signed** Amendment tool
- Copy of the proposed changes to the protocol or any other documents, showing previous and new wording, where applicable
- HRA Categorisation Letter
- REC Favourable Opinion
- MHRA related documentation (if applicable)
- HRA approval letter

Non-Substantial Amendments

- The **signed** Amendment tool
- Any documentation related to the amendment (if applicable)
- HRA Categorisation Letter
- REC Favourable Opinion (if applicable)
- HRA approval letter

Appendix 4: Sponsored CTIMP/non-CTIMP Amendment Approval Email Template (SAs)

REF: R&D number – Study Title – Substantial Amendment Number

Dear Dr,

PROJECT TITLE	
REC Reference	
R&D Reference	
Amendment Number	
Amendment Date	
Date of REC Approval	
Date of MHRA Approval	
HRA Approval	
Protocol version and date	
List of Approved Documents	
Approval comments/conditions	

Notification of host site amendment approval

Thank you for your correspondence with regards to the amendment(s) for the above named study. The Joint Research & Development Office can confirm that this/these amendment(s) do not affect current local approval for the study.

Thank you for keeping us informed.

Best wishes,

**The documents relating to this email should be attached to the email as a zipped file.

Appendix 5: Sponsored CTIMP/non-CTIMP Amendment Acknowledgment Email Template (NSAs/Mas)

REF: R&D number – Study Title – Non-Substantial Amendment Number

Dear,

Title:

REC Ref:

R&D Ref:

IRAS:

Non Substantial Amendment:

We have been informed of the following minor amendment to the above study.

As this is a Non substantial amendment, formal R&D acknowledgement is not required. Please therefore take this email as R&D acknowledgement of the amendment and confirmation that Trust NHS Permission continues to be valid.

Please note that the HRA has deemed this a **category C** amendment, an amendment to a research study that participating NHS organisations are not expected to consider.

Please ensure that a copy of this email is stored in your site file, along with the amendment documentation. This may be required for audit purposes

Kind regards,

**The documents relating to this email should be attached to the email as a zipped file.

Appendix 6: Hosted Amendment Validation e-mail template

REF: R&D number – Study Title – Substantial Amendment Number

Dear Sponsor,

PROJECT TITLE	
REC Reference	
R&D Reference	
IRAS Reference	
Amendment Number	
Amendment Date	
Date of Favourable Opinion	
Protocol version	
Protocol date	

Thank you for notifying Research Governance of the above amendment, which was received on (**Insert date received**). I can confirm that we have received the notice of substantial amendment and have sent it to the PI/research team and support departments so they can initiate their review. Once we have received all local and regulatory approvals we shall issue R&D confirmation.

Please note we may require **more than 35 days** to review and confirm implementation of substantial amendment (**Number**).

Documents Received

The documents sent to the PI/research team and support departments for review are as follows:

Document	Version	Date

Kind regards,

****The documents relating to this email should be attached to the email as a zipped file.**

Appendix 7: PI oversight Email Template

REF: R&D number – Study Title – Substantial Amendment Number

Dear Dr,

Study R&D Number:	
Study Title:	
CRF Supported:	Yes / No
Substantial Amendment Number:	
Date Amendment Received:	
Summary of Changes:	

Please could you review the supporting documentation attached and confirm that you and your team have the capacity to implement these changes by answering the following questions:

1. Would implementing this amendment result in any capacity issues? (e.g. Staff, facilities and impact on your time)

2. Would implementing this amendment result in any costing implications? (e.g. changes to procedures or investigations, duration of study or recruitment target)

3. Would implementing this amendment impact any supporting departments? If so please specify which department and confirm that they have been informed of this change.

Thank you for your correspondences with regards to the amendment for the above named study. The Joint Research & Development Office will now internally review this amendment, to track the approval process please refer to the Amendment workflow on Edge (www.edge.nhs.uk). If you do not have access to Edge please contact Research Information (Research.Information@gosh.nhs.uk).

**The documents relating to this email should be attached to the email as a zipped file.

Appendix 8: Hosted Amendment Confirmation of Amendment Implementation Email Template

REF: R&D number – Study Title – Substantial Amendment Number

Dear Dr,

PROJECT TITLE	
REC Reference	
R&D Reference	
IRAS Reference	
Amendment Number	
Amendment Date	
Date of Favourable Opinion	
Protocol version	
Protocol date	

Notification of host site amendment approval

Thank you for your correspondence with regards to the amendment for the above named study. The PI, research team and support departments reviewed the following documents and have confirmed that there are no capacity issues associated with this amendment, as a result the Joint Research & Development Office can confirm that this does not affect current local approval for the study.
This amendment can be implemented.

Please ensure that a copy of this email is stored in your site file, along with the amendment documentation. This may be required for audit purposes

Documents Approved

Document	Version	Date

Thank you for keeping us informed.

Kind Regards

**The documents relating to this email should be attached to the email as a zipped file.

Appendix 9: Regulatory/non-regulatory approvals required to implement an amendment at an NHS site

Lead Country	Location of REC	Regulatory/non regulatory Approvals Required
England	England or Wales	HRA and REC (Substantial/Non-substantial)
	Scotland or Northern Ireland	HRA and REC (Substantial) HRA only (Non-substantial)
	Non-REC study	HRA

For more information see:
https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx#Submitting-your-amendment