Standard Operating Procedure			52.003
R&I Review of Amendments			
Version	5.0		
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Approved by	Melissa Robert	Signature	Date
Released by	Julie Brittenden	Signature	Date

1. SOP Category

NHS GG&C Hosted R&I

2. Staff Category

- Research Co-ordinator
- Research Facilitator
- Senior Research Administrator
- Research Administrator

3. Scope

This SOP applies to R&I office staff during the receipt, processing, review and approval of amendments to all studies taking place in NHS Greater Glasgow & Clyde (GG&C). The process for Sponsor review of amendments is described in SOP 51.021.

4. Purpose

This SOP describes the procedures which the R&I office undertake when receiving, processing, reviewing and approving amendments to provide continued management approval of studies that GG&C hosts.

5. Procedures

Background

ICH E6 guidelines describe a protocol amendment as "a written description of a change(s) to or formal clarification of a protocol". The same description can also be applied to other changes/clarification to other study documents reviewed by R&I, the Research Ethics Committee (REC) and regulatory authorities. Changes to documents submitted during the assessment of a request for initial authorisation to the regulatory authority or during the assessment of a request for initial favourable opinion from the REC will not be considered amendments and will be reviewed during R&I approval process.

Amendments can be classified as substantial or non-substantial. Detailed guidance on what constitutes a substantial and non-substantial amendment can be found in Eudralex volume 10, chapter 1 2010/C82/01 (CT-1). Amendments for studies hosted by GG&C, require to be submitted to the R&I office for review in order to provide continuing management approval. An amendment cannot be implemented without receipt of local R&I continuing management approval (See 5.1 UK Process for study Amendments: Category C for any exception to this). This is part of the local site R&I management approval process.

5.1 UK Process for Study Amendments

The revised UK study amendment handling process, introduced across the UK in November 2014, reduces the number of study amendments that NHS organisations need to review for R&I continuing management approval. The scope of the revised UK process covers commercially and non-commercially sponsored multi-centre and single-site studies.

The process applies to both substantial and non-substantial amendments as defined by the Sponsor and runs in parallel to regulatory review and harmonises practice across all four UK nations. It follows the principle of a 35 day default implementation of amendments for NHS organisations and introduces the categorisation of amendments into Category A, B, or C. However, the 35 day timeline does not apply if the sponsor/submitting organization is notified of a query relating to the amendment, or a request to allow for additional time to review the amendment.

Category A: An amendment that impacts or affects ALL participating NHS organisations, therefore needs to be considered and may need change control actions.
Category B: An amendment that impact or affects SPECIFIC participating NHS organizations. Only at these organizations does it need to be considered and take any change control actions required.
Category C: An amendment that has no impact on NHS organizations hence does not require management or oversight. However the amendment should still be provided for information.

The sponsor, or authorised delegate, will complete the Amendment Tool in IRAS which will automatically recommend the category based on the responses to the questions. This is submitted, along with sponsor approved amended documents, through IRAS Identity Gateway and then shared with REC and/or for study-wide review as applicable. In Scotland the amendment is shared with NRSPCC (National Research Scotland Permissions Coordinating Centre), who then informs R&I for notification and review purposes.

For studies where GGC is the only UK site, the amendment will not be received through NRSPCC, but will only come directly from the sponsor. The RA should upload amendment documentation to SReDA and then process the amendment as normal.

For GG&C sponsored studies and trials (CTIMP and medical device) review of an amendment by R&I will only occur following Sponsor/co-sponsor approval and IRAS signoff.

5.2 Category A or B amendment review by R&I at GG&C

The following process applies to all GG&C research studies (sponsored and/or hosted), clinical trials and medical device trials. The applicable Portfolio team is responsible for the receipt, review and acknowledgment of all study amendments relating to projects taking place in NHSGG&C in their portfolio.

On receipt of an amendment, the Research Administrator registers the amendment on SReDA's Post Approval tab, under 'Record Licence Wide', within the associated Project by completing the required fields.

- The reference should be 'pending' or 'approved' depending on the state of the amendment
- The title should be in the format amendment number/date of amendment/category (e.g. SA04 10.11.2021 (Cat A)
- The Type and Date of the amendment can be found on the Amendment Tool, section 1 for the date and section 4 for the type.
- The Administrator can add notes to the 'Summary of Amendment' field in relation to activity taking place as part of the review (for example the amendment has been sent to Pharmacy for review on the following dates).

The Research Administrator creates a new amendment subfolder within the study email folder. The email subfolder name should be prefixed alphabetically or numerically in order of receipt to R&I. The Research Administrator also creates a sub-folder within the e-folder on the common drive and saves all available amendment documents. The Administrator will then send an email to the sponsor, if appropriate, requesting that the amendment is not implemented until confirmation of management approval is granted.

The Research Administrator must review the amended documentation along with the Amendment Tool to determine whether there will be any impact on NHS resources for GG&C.

If no impact then the Research Administrator will
- Await ethics and any other applicable approvals
- Aim to resolve any queries with the amendment
- When ethics approval received, check all documents are present according to the list in the ethics favorable opinion letter

Once any queries have been resolved and any missing documents collated, the Research Administrator will email the standard amendment email (Form 52.003A) of continuing management approval to the local PI. The Sponsor's representative and any other required individual should be copied into the email, eg. Pharmacy, research nurse, study coordinators, finance. The email will state that Management Approval is still valid and can contain a snapshot of the approved document list from the REC approval.

If however there are any unresolved issues, queries or questions then the Research Administrator will ask the Research Co-ordinator from the appropriate study portfolio team for guidance.

The entry for the amendment in SReDA should now be updated by completing the dates in the appropriate fields, updating any notes and changing the reference to 'Approved'. The approval email should be uploaded to SReDA.

5.3 Category A or B amendment review: Facilitator or Co-ordinator and Support department Review/ approval

For all substantial amendments that have financial implications, pharmacy or additional support department implications or contractual changes the Research Administrator will request the Research Co-ordinator's review by email. The Co-ordinator can delegate the review to the Research Facilitator working in their Portfolio team. The Research Administrator will also request Pharmacy review if applicable, in accordance with Guideline 52.003A Pharmacy clinical trials – Amendment Approvals.

The following should be considered when reviewing the amendment:
- financial implications
- pharmacy impact or
- support department implications
- contractual changes and impact on study budget

The following information requires Co-ordinator review and/ or subsequently support department approval.

- Implementation of amended Protocol
- Change of PI/Sponsor/legal representative/CRO
- Adding additional investigations/tests/scans
- Adding additional nurse/data management time
- Change of dosage
- Change in IMP:
    - Local Stock
    - Formulation
    - Pack Size
    - Dispensing Frequency
    - Fluid Volumes
    - Change in Storage
    - transportation/safety/IMP administration/
- Adding a new study arm/sub-study/new phase
- Early closure of a site/termination
- Study extension
- Change in treatment length
- Changes in supportive medication
- Increase to patient numbers
- Change of local PI

If the Research Co-ordinator (or their designee) has confirmed that extra resources from pharmacy/pathology/data monitoring/imaging/statistical services etc are required for implementation of the amendment for a **non-commercial** study, the Research Administrator will seek approval from pharmacy/Finance and any other Head(s) of department authorization approval as required. If the amendment provides new funding then the amended contract will be reviewed and negotiated by the Research Co-ordinator and signed by an authorized signatory of GG&C.

When the amendment has any impact on NHS resources for a **commercial** study, negotiation between the Research Co-ordinator and the Sponsor's representative occurs. An amended contract, or addendum to the contract, will be reviewed and negotiated by the Research Co-ordinator and signed by an authorized signatory of GG&C. The Research Co-ordinator will save the updated budget and contract in the appropriate folders and will make sure the internal redistribution sheet is updated with the new costs.

Details of any financial changes will be notified by the R&I department to R&I finance by including R&I finance in the amendment approval email.

Once the amendment has received favourable opinion from the REC (if applicable), authorisation from the MHRA (if applicable), and review from R&I, the Research Administrators will confirm continuing management approval for the amendment by email to the local PI (Form 52.003A). The Sponsor's representative and any other required individual should be copied into the email, eg. Pharmacy, research nurse, study coordinators, finance. The email will state that Management Approval is still valid and can contain a snapshot of the approved document list from the REC approval.

The entry for the amendment in SReDA should now be updated by completing the dates in the appropriate fields, updating any notes and changing the reference to 'Approved'. The approval email should be uploaded to SReDA.

5.4 Category C amendment review by GG&C R&I

Category C amendments will be received in R&I in the same way as Category A and B amendments, but are for information only and require minimal or no review.
The Research Administrators should log the amendment in SReDA, make folders and save the documents as normal.
If it involves any changes to the study end dates, then SReDA should be updated.
If there are changes to any of the IMP documentation then it should be sent to pharmacy for information.
No acknowledgment of the amendment to the sponsor is required.

6. Referenced documents

1. Form 52.003A – Amendment Approval Email Category A or B amendment
2. Form 52.003B – Amendment Acknowledgement Email
3. SOP 51.021 – Sponsor Review of Amendments
4. Guideline 52.003A Pharmacy clinical trials – Amendment Approvals
5. Guideline 52.003B Flow Chart for processing Amendments

7. Related documents

IRAS guidance: https://www.myresearchproject.org.uk/help/hlpamendments.aspx
MHRA guidance: http://www.mhra.gov.uk

8. Document History

Version	Date	Description
Draft 1.0	2008	Creation of SOP (Amendment Review)
Draft 2.0	2009	(Amendment Review)
Draft 3.0	29/01/2010	(Amendment Review)
Draft 4.0	21/05/2010	(Amendment Review)
1.0	06/09/2012	Release of version 1.0 (Process for Sponsor Approval of Amendments and Review by R&D)
2.0	10/12/2013	Removal of sponsor process and inclusion of recording of amendments on SReDA.
3.0	14/07/2016	Updated to template v1.4 Inclusion of information about categorization of Amendments and UK Process. Supporting documents: • Pharmacy Review Checklist (appendix 4) • Research & Development Q&A (appendix 5) • Pharmacy clinical Trials/ Amendment approval • Flow Chart for processing amendments (saved separately as Supporting Documents)
4.0	18/03/2020	Author temporarily changed. Temp. change to "Approved by" "Released by" changed. References to R&D Database staff removed from document. Role of Research Facilitator clarified. Minor typographical changes made to process. Version updated.
5.0	25/08/2022	Updated due to national changes imposed in March 2021. Changed from PR review to portfolio team review of all amendments. References to R&D changed to R&I throughout. Updated forms associated with this SOP

Appendix 1

Examples of Substantial Amendments:

- changes to the design, purpose or methodology of the study, or to background information affecting its scientific value;
- changes to the procedures undertaken by participants;
- changes to the recruitment procedure;
- any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study;
- significant changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers;
- a change of sponsor(s) or sponsor's legal representative;
- a change of the CRO assigned significant tasks;
- appointment of a new chief investigator or key collaborator;
- a change to the insurance or indemnity arrangements for the study;
- inclusion of a new trial site (not listed in the original application) in a CTIMP;
- appointment of a new PI at a trial site in a CTIMP;
- temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt;
- a change to the definition of the end of the study;
- any other significant change to the protocol or the terms of the REC application
- changes related to the IMP in a CTIMP;
- changes to non-clinical pharmacology and toxicology data in a CTIMP, where this is relevant to the ongoing trials (i.e. altered risk: benefit assessment);
- changes to clinical trial and human experience data in a CTIMP, where this is relevant to the ongoing trials (i.e. altered risk: benefit assessment.

Examples of Non-Substantial Amendments:

- minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications;
- updates of the investigator's brochure (unless there is a change to the risk/benefit assessment for the trial);
- changes to the CI's research team (other than appointment of key collaborators);
- changes to the research team at particular trial sites (other than appointment of a new PI in a CTIMP);
- changes in funding arrangements;
- changes in the documentation used by the research team for recording study data;
- changes in the logistical arrangements for storing or transporting samples;
- inclusion of new sites and investigators in studies other than CTIMPs (R&D permission is still required);
- extension of the study beyond the period specified in the application form.

Changes to contact details for the Sponsor (or the Sponsor's representative); CI or other study staff are minor amendments but should be notified to the REC and R&I Offices for information. The REC and the relevant local R&I should also be notified if the PI's contact details have changed.

Appendix 2

NHS Greater Glasgow & Clyde Required Documentation for Substantial Amendment Review:

Document	All Studies	Where Applicable
All REC reviewed documents	√	
All MHRA reviewed documents, if different from above		√
Amendment Tool	√	
REC favourable opinion	√	
MHRA approval		√
Signed amended agreement		√
ARSAC authorisation (for research involving administration of radioactive substances)		√

Appendix 3

Amendment filing

	File Type		
Study Type	*Electronic file*	*Paper file*	*Email file*
Hosted	Every submitted document, email, Amendment Appendix, etc, to be saved in the study's amendment folder, in the particular amendment subfolder. Commercial costing template & distribution amendments to be saved in the finance folder and CTA amendments in the CTA folder.	No amendment paperwork should be filed after the end of May 2013 when the R&I office went paper-lite.	All correspondence received and sent should be filed under the correct amendment subfolder of the associated Project folder.
Sponsored	Every submitted document, email, Amendment Appendix, etc, to be saved in the study's amendment folder, in the particular amendment subfolder. CTA amendments to be saved in the CTA folder.	Every submitted document, email, Amendment Appendix, etc, to be printed and filed in the study's amendment section with an amendment coversheet. The protocol and <u>all</u> supporting documents e.g. PIS, CF, GP letter, questionnaires etc, however should be filed in the protocol section, with the most recent version at the top. Old versions should be kept, not shredded. CTA amendments should be filed in the CTA section.	All correspondence received and sent should be filed under the correct amendment subfolder of the associated Project folder.