

SOP number	<b>51.021</b>	Version	<b>5.0</b>
Title	<b>Review and Approval of Amendments for Research Sponsored by NHSGGC or Co-Sponsored by NHSGGC and the University of Glasgow</b>		

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SOP category	NHS GG&C Sponsor R&I			
Staff category				
<b>Staff Category</b>	<b>R</b>	<b>A</b>	<b>C</b>	<b>I</b>
Research Governance Manager		X		
Research & Innovation Systems Manager			X	
Chief Investigators	X			
Sponsor Research Co-ordinators	X			
Research Facilitator	X			
Senior Research Administrators	X			
Innovation Contracts Manager	X			
R&I Sponsor Pharmacy	X			
Project Management	X			
Research Governance	X			
University of Glasgow Research Regulation and Compliance team			X	
Principal Investigator				X

## 1. Scope

This procedure applies to NHS Greater Glasgow and Clyde (NHSGGC) Research staff involved in the assessment, review and distribution of amendments sponsored by NHSGGC or Co-sponsored with University of Glasgow (UoG).

## 2. Purpose

To describe the process for Sponsor review, approval and notification of amendments to appropriate organisations, departments and individuals when NHSGGC are the Sponsor or Co-Sponsor with UoG. This applies to research studies, CTIMPs (Clinical Trial of an Investigational Medicinal Product) and CIMDs (Clinical Investigation of a Medical Device).

### 3. Procedures

#### 3.1. Abbreviations/Definitions

CI	Chief Investigator
CIMD	Clinical Investigation of a Medical Device
CRF	Clinical Research Facility
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trial Unit
GCP	Good Clinical Practice
HoD	Head of Department
HRA	Health Research Authority
ICM	Innovation Contracts Manager
IRAS	The Integrated Research Application System
ISF	Investigator Site File
MA	Management Approval
MHRA	Medicines and Healthcare products Regulatory Agency
NRS PCC	NHS Research Scotland Permission Coordinating Centre
PI	Principal Investigator
PM	Project Manager
PR	Proportionate Review
PV	Pharmacovigilance
REC	Research Ethics Committee
R&D	Research and Development
R&I	Research & Innovation department
RC	Sponsor Research Co-ordinator
RF	Research Facilitator
SRA	Senior Research Administrator
SReDA	Scottish Research Database Application
RCB	Robertson Centre for Biostatistics
TMF	Trial Master File
UoG	University of Glasgow

#### 3.2. Background

The Health Research Authority (HRA) defines amendments as changes made to a research project or trial after approval from a review body has been given. Changes to documents submitted during the assessment of a request for authorisation to the Medicines and Healthcare products Regulatory Agency (MHRA) or during the assessment of a request for favourable opinion from the Research Ethics Committee (REC) will not be considered amendments and will be reviewed during the Sponsor/Co-sponsor R&I approval process.

The Sponsor Research Co-ordinator (RC) (for the Systems team), the Innovation Contracts Manager (ICM) for the Innovation team and the Research facilitator (RF) (for proportionate review (PR) team) are responsible for classification of the amendment, provision of authorisation for an amendment to be submitted to REC and/or MHRA and provision of approval for the amendment to be implemented. Furthermore the Sponsor Research Co-ordinator and the Innovation Contracts Manager submit amendments to the regulatory authorities, unless the trial was submitted through the combined review process and this responsibility falls with the CI or delegate such as Project Manager (PM).

Designated members of staff working across Glasgow Oncology Clinical Trials Unit (GO CTU) will process and approve amendments as per this SOP and relevant GO CTU SOPs. An amendment cannot be implemented without confirmation from Sponsor/Co-Sponsor and local R&I continuing management approval with the exception of Category C amendments as explained in section 3.3.2.

### 3.3. Definitions

#### 3.3.1. Amendment Classification (As Substantial and Non-Substantial)

Amendments can be classified as substantial or non-substantial. Detailed guidance on what constitutes a substantial and non-substantial amendment can be found on the HRA website and listed in Appendix 1. In short, a substantial amendment is deemed likely to have an impact on: the safety or physical or mental integrity of the study participants or to the scientific value of the study.

#### 3.3.2. Amendment Categorization (As Category A, B or C)

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 process applies to both substantial and non-substantial amendments as defined by the Sponsor/Co-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/Co-Sponsor submitting organization is notified of a query relating to the amendment, or a request to allow for additional time to review the amendment. Implementation of the amendments at sites and oversight of the timelines is managed by the CI or delegate such as relevant Project Managers.

Category A\*: An amendment that impacts or affects all participating NHS organisations. All participating NHS organisations are expected to consider the amendment to determine whether they are able to continue to support the study.

Category B\*: An amendment that impact or affects specific participating NHS organizations. Only those participating NHS organisations affected by the amendment are expected to consider the amendment to determine whether they are able to continue to support the study.

Category C\*\*: An amendment that has no impact on NHS organizations hence does not require management approval or oversight. However the amendment should still be provided for information.

**\* For Category A and B amendments, NHS organisations have a maximum of 35 days to raise an objection; otherwise the amendment can be implemented after the 35 day period (Subject to regulatory approvals being in place)**

**\* For Category B Change/New PI for Non-NHSGGC sites do not require Management Approval and no Management Approval email should be sent.**

**\* For Category B New site amendments also do not require Management Approval and no Management Approval email should be sent.**

**\*\* For Category C amendments, can be implemented immediately (Subject to regulatory approval being in place)**

### **3.4. Filing Requirements**

All documentation relevant to the process for reviewing and implanting amendments must be filed within the relevant section of the TMF. This will be predominantly in Section 6 but may also be found in other sections of the TMF as several departments may be required to interact with an individual amendment and follow relevant processes. Form 51.016A outlines where document must be filed. Working copies of documentation will also be filed in the relevant e-Folders for trials as detailed within this SOP.

### **3.5. Submission of Amendment and Receipt by Sponsor**

The Chief Investigator (CI) or delegate, will complete the Amendment Tool template from the Integrated Research Application System (IRAS) which will automatically recommend the amendment classification (3.3.1) and categorisation (3.3.2) based on the responses to the questions.

According to the type of study, the Amendment Tool will be sent to the Senior Research Administrator (SRA), Research Administrator (RA), Sponsor Research Co-ordinator, Innovation Contracts Manager or Research Facilitator for sponsor review alongside all amended documentation.

On receipt of an amendment, the Senior Research Administrator or Research Administrator will:

- Inform the Sponsor Research Co-ordinator, the Innovation Contracts Manager or Research Facilitator and create a new study amendment subfolder in the email repository and a study amendment subfolder in the study/trial eFolder with the amendment reference, date and category (e.g. 01. SA01 12.05.2024 Cat A). The email subfolder name will be prefixed numerically in sequential order of receipt to R&I regardless of whether it is substantial or non-substantial.
- Save all documents in amendment subfolder and move all emails to the email subfolder.
- Save one blank copy of Form 51.021B in the general amendment subfolder for the study (if not already present).
- Save a blank copy of Form 51.021C in the specific amendment subfolder.
- Registers the amendment on the Post Approval tab on SReDA with all details and status 'Pending' (for Cat C amendments status should be Cat C).
- If single centre, create a new amendment folder on the Documents tab on SReDA.

### **3.6. Review of Amendment prior to submission to REC and/or MHRA through IRAS**

The Sponsor Research Co-ordinator, the Innovation Contracts Manager or Research Facilitator will review the Amendment Tool, ensuring that the information reflects the amended documents and that the classification (3.3.1) and categorisation (3.3.2) of amendment automatically generated by the Amendment Tool is accurate, in the event there is dubiety over this see 3.6.1.

Before signature and lock of the Amendment Tool, the Sponsor Research Co-ordinator, Innovation Contracts Manager or Research Facilitator will complete Form 51.021C and:

- Provide feedback on all amended documents taking into account input from the relevant stakeholders involved.
- Confirm any costs implications with R&I Finance and the funder.
- For Co-Sponsored studies/trials liaise with the University of Glasgow Research Regulation and Compliance team and confirm implications on insurance cover as well as amend any contractual arrangements as required.
- Confirm any implications on support from all NHS departments involved and confirms feasibility and Head of Departments (HoD) approvals.
- Amend any contractual arrangements (if applicable).
- Assess if the amendment could potentially have a negative impact on an upcoming research study established milestone.
- Assess if the proposed amendment contains information that participants already recruited in the study will need to re-consent.
- For CTIMPs will liaise with pharmacy, pharmacovigilance (PV), Project Management, monitor, CRF, imaging and data management teams when reviewing amended documents and save any relevant decision making correspondence in the trial eFolder. Each department will have their own relevant processes to be followed and will document their actions accordingly.
- Assess the potential risks with the wider sponsor team (as explained at section 3.6.2).
- Once sponsor review of amendment is concluded, the Sponsor Research Co-ordinator, Innovation Contracts Manager or Research Facilitator will complete the “Date of Sponsor permission for REC and/or MHRA submissions” field on Form 51.021.C.
- Sponsor Research Co-ordinator, Research Facilitator, Innovation Contracts Manager or their delegates, email the standard amendment email (Form 51.021A) to the CI with confirmation of the Sponsor decision of amendment type along with the locked Amendment tool and a list with the reviewed documents. For substantial amendments the email will indicate that it is now acceptable for the amendment to be submitted to REC and/or MHRA. For non-substantial amendment the email will indicate that the REC should be notified and that details regarding this amendment will be included in the next substantial amendment to the REC.
- Save evidence of the communication in the sponsor amendment email subfolder (of the study/trial eFolder) and Trial Master File (TMF) for CTIMPs/CIMDs.

#### **3.6.1. Dubiety with Classification or Categorization**

In general, the assessment relating to classification and categorisation is straight forward. However, if an amendment is submitted where there is dubiety this must be escalated through governance structures, R&I Senior Management and where appropriate discussed directly with the Regulatory Authority.

### **3.6.2. Assessment of Risk**

The Sponsor Research Co-ordinator, Innovation Contracts Manager or Research Facilitator will review the effect of the amendment on the risk to the research participants and the Sponsor – i.e. the potential for harm to participants and impact upon the integrity of data. Any pharmacy changes will already have been assessed by an appropriate person in the Sponsor Pharmacy team and financial/resource implications will have been discussed with the R&I Finance and grant holder(s).

For CTIMPs, the risk assessment (SOP 51.004) completed by the Sponsor Research Co-ordinator or Innovation Contracts Manager prior to the original Sponsor approval of the trial will be reviewed. If the amendment has implications on the risk level - resulting in increased risk, potentially affecting participant safety and/or the validity of outcome measures - the Sponsor Research Co-ordinator or Innovation Contracts Manager will discuss the change in risk and agree on mediating strategies with the research team and the wider Sponsor/Co-Sponsor team. If additional risks are identified, the Sponsor Research Co-ordinator and Innovation Contracts Manager will amend the Risk assessment to reflect these changes.

In the event the amendment is determined to have no impact on the Risk Assessment, the decision to not revisit the risk assessment will be captured in Form 51.025B and Form 51.025C.

### **3.7. Submission through IRAS to REC and/or MHRA**

After R&I Sponsor review of the proposed amendment is complete, the CI (or delegate) will submit the locked Amendment Tool along with the Sponsor approved amended documents, through IRAS Identity Gateway (via IRAS Help - Maintaining your approvals - Amendments ([myresearchproject.org.uk](http://myresearchproject.org.uk)) and then share with REC and/or MHRA (if submitted through IRAS CWOW gateway). In Scotland the amendment is shared with NRSPCC (National Research Scotland Permissions Coordinating Centre) by IRAS, who then informs all additional Scottish R&D/I offices for notification and review purposes. For CTIMPs and/or CIMDs not submitted through the IRAS CWOW gateway, the Sponsor Research Co-ordinator or Innovation Contracts Manager will submit the amendment through the MHRA portal.

#### **3.7.1. NHSGGC as Sole UK Site**

For studies where NHSGGC is the only UK site, the amendment will not be communicated through NRSPCC. The REC and/or MHRA decision letter is received directly by the Sponsor Research Co-ordinator, Innovation Contracts Manager or Research Facilitator. The Project Manager will ensure that the right amended documentation is sent to all participating sites.

#### **3.7.2. Non-Substantial Amendment Notifications to REC and/or MHRA**

Non-substantial amendments do not need to be submitted to the REC or regulatory authorities. However NHSGGC advocates notifying these organisations (with the exception of CIMDs). Notification need not be prospective therefore, it may be provided at the same time as the next substantial amendment.

For CIMDs, the MHRA will need to be notified for any non-substantial amendments to ensure MHRA records are up-to-date. If upon review of the proposed non-substantial modification for a CIMD, the MHRA consider it to fall within the substantial category, the MHRA will inform the sponsor, and the proposed modification should not be implemented until an MHRA authorisation is received.

The notification may be communicated in any written form acceptable to the REC and/or regulatory authority. The notification will be sent to the following (and stored in accordance with SOP 50.011):

- CI
- All R&D/I departments where the site is identified as undertaking the trial (will include sites that may not have given R&D/I approval to start the trial)
- Stakeholders within the Glasgow Clinical Trials Unit (CTU), specifically the PV Office, PMs, Data Managing Centre (such as Robertson Centre for Biostatistics (RCB)), etc.
- Glasgow Oncology-CTU (when appropriate)
- Clinical trial monitors
- Clinical Units (CTUs) involved in the study such as the centre involved in data handling and management
- Clinical Research Facilities (CRFs) involved in the study
- NHSGGC R&I Pharmacy
- PIs on all sites (ensuring that the site is aware that the non-substantial amendment cannot be implemented until local R&D/I approval is given)
- Other individuals or organisations identified by the CI or Sponsor/Co-sponsor to be informed

For multicentre studies/trials the NRS PCC will notify all the Scottish participating sites R&D/I offices.

### **3.8. REC and/or MHRA Approvals**

Depending on the classification of the Amendment and if there was a requirement for REC and/or MHRA approvals, they must be in place before proceeding with the subsequent steps laid out within this SOP. When the approvals are in place, they will be documented within Form 51.021B and Form 51.021C.

### **3.9. Sponsor Process for NHSGGC Local Management Approval of Amendments**

As with all amendments to be implemented at an NHSGGC site, whether NHSGGC are acting as the Sponsor/Co-Sponsor or not, Local Management Approval is required before they are to be implemented. This will act as the notification of the amendment to NHSGGC Sites.

#### **3.9.1. Non-Substantial Amendments:**

Once sponsor review of amendment and Form 51.021C is completed by the Sponsor Research Co-ordinator, Innovation Contracts Manager or Research Facilitator, the Systems Team Senior Research Administrator or Research Administrator:

- Ensures all requirements stated by the Sponsor Research Co-ordinator, Innovation Contracts Manager or Research Facilitator in section B of Form 51.021C are met before issuing local management approval (MA) email confirmation.
- Seeks approval from the corresponding departments and any other HoDs authorisation approval as required, if extra resources from pharmacy, pathology, data monitoring, imaging, statistical services, etc are required for implementation of the amendment.
- Updates SReDA to reflect any changes to the study end dates including NHSGGC site specific updates.
- If it involves changes to the study team, then check CVs and GCP certificates as applicable.
- Liaises with local pharmacy and HoD for approvals for CTIMPs (if applicable).
- Sends 'Management Approval remains valid email' (Form 51.021D) to study team and sponsor team including the appropriate representatives from the local pharmacy team, for CTIMPs that require no other documents.
- Saves both the Sponsor Decision and Management Approval emails in the study amendment email subfolder.
- Updates the status of amendment on Post Approval tab on SReDA to 'Approved'.
- Uploads amendment approval email and all amended documentation to SReDA under documents tab. For multicentre studies the approved amended documents will be updated by the NRS PCC.
- Updates Sponsor review of amendment checklist (Form 51.021C) and the Amendment Log (Form 51.021B).

#### **3.9.2. Substantial Amendments:**

Once REC and/or MHRA approvals are in place the Senior Research Administrator:

- Ensures all documents on file and SReDA match all documents approved by REC and/or MHRA
- Updates SReDA to reflect any changes to the study end dates including NHSGGC site specific updates.
- Communicate continuing management approval for the amendment by email to the local PI (Form 51.021D) including the study team, the appropriate members of the sponsor team as well as appropriate members of the local pharmacy team (once all documents on SReDA Checklist (Form 51.021C Part C) are received and after ensuring all requirements stated by the Sponsor Research Co-ordinator, Innovation Contracts Manager or Research Facilitator in section B of Form 51.021C are met). Included in this email are the relevant approvals.
- Saves all email correspondence in the corresponding folders (study eFolder and email subfolder).
- Updates SReDA Post Approval tab status to 'Approved'.
- Uploads amendment approval email under documents tab and for single centre studies also upload all amended documents.
- Updates Sponsor review of amendment checklist (Form 51.021C) and the Amendment Log (Form 51.021B).



### **3.10. Notification of Substantial Amendment to Non- NHSGGC Trial Sites, Principal Investigators (PI) and Organisations Involved In the Study**

As NHSGGC are notified through the Management approval process covered in 3.9, this only applies to Non-NHSGGC sites. When the amendment has been given REC approval/favourable opinion and MHRA approval (dependent on the classification of research) a communication will be sent by the Sponsor Research Co-ordinator, Innovation Contracts Manager, Research Facilitator (or their designee e.g. Project Manager or Senior Research Administrator/Research Administrator) to the CI/designee to indicate that it is now acceptable for the amendment to be circulated to sites, (if relevant, via national co-ordinated approvals agencies) relevant support departments and implemented when all local approvals have been received. Evidence of the communication will be saved in the sponsor study E-file. As per SOP 56.003, for CTIMPs/CIMDs the PM will ensure that all participating site teams are provided with amendment details, supporting documentation and approvals. The PM will contact the site on the amendment implementation date asking for site PI and local R&I confirmation that the amendment has been implemented (or otherwise if local R&I amendment approval is refused).

The Sponsor Research Co-ordinator, Innovation Contracts Manager or delegated individual will send the amendment covering letter, amended documents, MHRA approval and favourable REC opinion to the following (and where appropriate stored in accordance with SOP 50.011):

- CI
- All R&D departments where the site is identified as undertaking the trial (will include sites that may not have given R&D approval to start the trial)
- Stakeholders within the Glasgow Clinical Trials Unit (CTU), i.e. Pharmacovigilance Office, Lead Monitor, Project manager, Data Management Centre (such as RCB) , Glasgow Oncology CTU
- CTUs involved in the study such as the centre involved in data handling and management
- Clinical Research Facilities (CRFs) involved in the study
- NHSGGC R&I Pharmacy PIs on all sites
- Other individuals or organisations identified by the CI or Sponsor to be informed
- NRS PCC (NHS Research Scotland Permission Coordinating Centre) for categorisation

**n.b The covering letter to sites should state that the amendment cannot be implemented without local R&D/I approval as applicable.**

### **3.11. Urgent Safety Measures**

Following an Urgent Safety Measure (USM) as detailed in SOP 53.001, changes required to study documents will be subsequently submitted to the relevant organisation, as a substantial amendment according to usual substantial amendment notification procedures, as quickly as possible and including reference to urgent safety measure and justification as to why the USM has to be implemented immediately.

#### 4. Referenced Documents/Links

- SOP 50.011 - Setting up and Maintaining Research and Innovation project files (for R&I office approvals)
- SOP 51.004 – Risk Assessment
- SOP 53.001 – Handling urgent safety measures for clinical trials for investigational medicinal products
- SOP 56.003 - Project Management: Managing an Active Trial
- Form 51.021A – Amendment Type Confirmation
- Form 51.021B - Amendment log
- Form 51.021C - Sponsor review of amendment checklist
- Form 51.021D - Management Approval is still valid - email template
- Form 51.016A – Sponsor TMF Index
- <https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-substantial-amendments/>
- <https://www.gov.uk/guidance/guidance-on-substantial-amendments-to-a-clinical-trial>
- IRAS Help - Maintaining your approvals - Amendments (myresearchproject.org.uk)

#### 5. Related Documents

- NRES guidance: <http://www.nres.nhs.uk>
- MHRA guidance: <http://www.mhra.gov.uk>

#### 6. Document History

Version	Date	Description
1.0	06/09/13	Release of First Version
2.0	08/01/16	Minor changes to section 5.2.1
3.0	14/07/2016	Renumbered with minor changes on process for informing stake holders
4.0	02/03/2020	Temp. author change. Staff category updated to include relevant staff groups. “Research Co-ordinator replaced with “Sponsor Research Co-ordinator” to clarify responsibility of this staff group. 5.3.1 updated to reflect revised process in response to audit finding. Version updated.
5.0	04/10/2024	Version no and author change with additional information to clarify the amendment review process. The title was updated to include co-sponsorship scenario. Included Appendix 1 with Examples of substantial and non-substantial amendments, as per HRA guidelines. Three new forms were introduced: <ul style="list-style-type: none"> <li>- Form 51.021B - Amendment Log – to capture an overview of all amendments of a study/trial</li> <li>- Form 51.021C - Sponsor Review of Amendment Checklist – to capture sponsor review, processing and local approval of amendments</li> <li>- Form 51.021D - Management Approval is still valid - email template</li> </ul> Additional information on sponsor process for review and local approval of amendment with clarity on SRA/RA and RC/ICM/RF associated tasks. Cancer Research UK-CTU updated to Glasgow Oncology-CTU

## Appendix 1

Examples of substantial and non-substantial amendments, as per HRA guidelines

### Examples of substantial amendments:

- Changes to the design or methodology of the study, or to background information likely to have a significant impact on its scientific value;
- Changes to the procedures undertaken by participants;
- Changes likely to have a significant impact on 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;
- Change of sponsor(s) or sponsor's legal representative;
- Appointment of a new chief investigator
- Change to the insurance or indemnity arrangements for the study;
- CTIMP or regulated investigation of a medical device wishing to add a new Non-NHS/HSC site
- Appointment of a new principal investigator at a non-NHS/HSC trial site in a CTIMP or regulated investigation of a medical device
- Temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt;
- Change to the definition of the end of the study;
- Any other significant change to the protocol or the terms of the REC application.

### Examples of non-substantial amendments:

- Minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications;
- updates of the investigator's brochure (unless there is a change to the risk/benefit assessment for the trial);
- Changes to the chief investigator's research team
- Changes to the research team at particular trial sites (other than appointment of a new principal investigator at a Non-NHS/HSC site in a CTIMP or a regulated investigation of a medical device);
- 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 (other than a CTIMP or a regulated investigation of a medical device wishing to add a new Non-NHS/HSC site)
- Change to the study end date.
- Changes to contact details for the sponsor (or the sponsor's representative), chief investigator or other study staff are minor amendments but should be notified to the REC that approved your original application.