Imperial College London

Research Governance and Integrity Team

Imperial College Healthcare NHS Trust

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Amendments to Healthcare Research

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Version	Date	Reason for Change
Version 1.0	03 Jul 2006	Change in substantial amendment form
Version 2.0	10 May 2007	Annual review
Version 3.0	18 Jun 2008	Annual review
Version 4.0	08 Feb 2010	Formation of Joint Research Office
Version 5.0	14 Jul 2011	Annual Review
Version 6.0	30 Nov 2012	Annual Review
Version 7.0	18 Feb 2015	Scheduled Review
Version 8.0	25 Oct 2017	Scheduled Review
Version 9.0	19 Oct 2020	Scheduled Review Template removed and administrative changes to SOP. JRCO name change to RGIT.
Version 10.0	25 Mar 2021	Removal of annex 2 from Amendment Tool
Version 11.0	02 Nov 2021	Update to include submission via CWOW IRAS system

Table of Contents

1. PURPOSE

This SOP describes the procedure for making amendments, both substantial and minor, to the Health Research Authority (HRA), the National Research Ethics Service (NRES) and the Medicines and Healthcare products Regulatory Agency (MHRA). Other bodies that need to approve or be notified of which types of amendment include National Health Service (NHS)/Health and Social Care (HSC) Research and Development, Administration of Radioactive Substances Advising Committee (ARSAC), Confidentiality Advisory Group (CAG) and National Offender Management Service (NOMS).

2. INTRODUCTION

Please note that this amendment SOP gives generic amendment advice. For further specific advice on amendment related to CTIMP (drug studies) reference could be made to RGIT_SOP_008, which can be found on the SOP, Associated Documents & Templates page.

Amendments are changes made to a research study after a favourable ethical opinion or approval by a regulatory body has been given. They can be made to a protocol, other essential documentation or other aspects of a study's arrangements. All research protocols should have a clear version number and date in order to maintain accurate records and audit trails. Any amendment to a research protocol should have a concordant amendment to the date and version number.

An amendment to a research project can be either **substantial** *or* **minor (non-substantial)** in nature.

2.1. Substantial Amendment

A Substantial Amendment can be defined as an amendment to the terms of the REC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

1. The safety or physical or mental integrity of the subjects of the study;
2. The scientific value of the study;
3. The conduct or management of the study; or
4. The quality or safety of any investigational medicinal product used in the trial.

All substantial amendments should be notified to the Research Ethics Committee that gave a favourable opinion (the REC) using an amendment tool (see section 3.1).

Examples of substantial amendments include:

1. Amendments related to the protocol include:
   - Changes to the design or methodology of the study, or to background information affecting its scientific value;
   - Changes to the procedures undertaken by participants; any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study
   - Changes affecting measures of efficacy, schedule of samples, safety monitoring

- Significant changes to the inclusion and exclusion criteria likely to affect safety or scientific value
- Addition or deletion of tests or measures, changes to the number of study participants, age range of participants
- Duration of exposure to the investigational medicinal product(s)
- Changes of dose of the investigational medicinal product(s)
- Changes of comparator

2. Amendments to Other Study Documentation:

Significant changes to participant information sheets, consent forms, questionnaires, letter of invitation, letter to GP or other clinicians; information sheets for relatives and carers and IMP Dossier

3. Amendments related to the trial arrangements:

- appointment of a new chief investigator
- appointment of a new principle investigator at a non-NHS trials site in a CTIMPa change of the coordinating investigator
- inclusion of a new non-NHS trial site in a CTIMPChange of sponsor (s) or sponsor's legal representative
- a change to the insurance or indemnity arrangements for the study
- a change of the definition of the end of the trial
- temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt;
- a change in IMP supplier

2.2. Minor ('Non-Substantial') Amendments.

A minor amendment can be defined as a change to the details of a study which will have no significant implications for participants or for the conduct, management or scientific value of the study.

Examples of minor amendments include:

- Minor changes to the protocol or other study document; e.g. correction of typographical 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 sites (Including PI at an NHS site in a CTIMP study)
- Changes in funding arrangements;
- Changes in the documentation used by the research team for recording study data (i.e. Case Report Forms);
- Changes in the logistical arrangements for storing or transporting samples;
- Inclusion of new sites and investigators in non-CTIMP studies;
- Inclusion of new sites of the same type and investigators in NHS sites for CTIMP studies
- Extension of the study beyond the period specified in the application form;
- Changes in funding arrangements.

Classification of an amendment will also depend on the output of the amendment tool. To ensure the correct output is generated, the tool should be completed with reference to the **glossary of changes tab** on the tool.

3. PROCEDURES

For all studies, it is the responsibility of the sponsor to determine whether an amendment is substantial or non-substantial. If an amendment is required and the Chief or Principal Investigator or any member of the study team assigned by the investigator to initiate study amendment is not sure whether the proposed study amendment should be clarified as a substantial or minor amendment; for Imperial College AHSC sponsored studies the RGIT expects their team to be contacted via email: RGIT@imperial.ac.uk with a brief discussion of the proposed change(s). Alternatively call 020 7594 9480 for CTIMP studies and 020 7594 9832 or 020 7594 9459 for Non-CTIMP studies.

3.1. Preparing amendment (s)

Once the sponsor has categorised the amendment the following procedures should be followed, depending on whether the amendment is substantial or minor. Please note, the procedure will also differ according to whether the study is a Clinical Trial of an Investigational Medicinal Product (CTIMP) (including gene therapy) or other healthcare research.

On 2 June 2020 the process for preparing and submitting amendments to RECs and HRA and HCRW Approval / NHS/HSC R&D across the United Kingdom changed.

- For all project-based research, notice of substantial amendment and non-substantial amendment forms are no longer used and have been replaced by the Amendment Tool.
- Research Tissue Banks (RTBs) and Research Databases (RDBs) continue to use the Notice of Substantial Amendment Form generated in IRAS to notify substantial amendments to the REC.
- For all types of research, amendments and supporting documentation should be uploaded and submitted for review via the online submission functionality.

The Amendment Tool applies to all project-based research and replaces the Notice of Substantial Amendment (NOSA) Form and the non-substantial amendment form.

It is no longer possible to create a new NOSA in IRAS for project-based research, and the non-substantial amendment template form is no longer used. Any amendments must be prepared using the Amendment Tool as amendment forms will no longer be accepted.

The process for completing the Amendment Tool is as follows:

1. Download the Amendment Tool from the link below and fill in information about your amendment on the 'Amendment Tool' tab, referring to the on-screen guidance notes. When complete, the declaration section should be completed by the sponsor. This will be completed by the appropriate RGIT reviewer.

The amendment tool will allow you to enter up to 10 changes per tool. If more changes are required for one amendment, contact amendmamendments@hra.nhs.uk for assistance.

Please ensure that the list of documents to be submitted with the amendment are included in the main summary section of the amendment, so that it is clear what the latest dates and versions of the documents will be.

2. The RGIT reviewer will then 'Lock for submission'. This will generate a locked pdf copy of the completed tool. This will be returned to the study team member for submission as required.

3. If your project is a CTIMP and the amendment requires notification to MHRA (Medicines), you can now submit the Amendment tool only, and do not require the addition of Annex 2.

Prior to study amendment submission to ethics, if your study is sponsored by Imperial College AHSC, a draft copy of the Amendment Tool must be submitted to the RGIT for review and approval. The form must be submitted with the modified study documents (for examples the study protocol with associated applicable document) and any applicable cover letters. The documents must show the previous and new wording in tracked changes so that the changes can be readily identified.

Once the amendment is accepted and approved by the RGIT, an acceptance email is sent to the member of the study team who submitted the amendment, approving the amendment for submission along with the locked amendment tool.

For CTIMPs an amendment acknowledgment letter will be provided for filing in the TMF and the assigned RGIT monitor will also be copied in for their reference.

Non-Substantial amendments will be signed off by the RGIT reviewer and Substantial amendments will be signed off by the Research Governance Manager.

When the Amendment tool is Sponsor approved and finalised, you should proceed to submit your amendment via the online submission process and in line with the information contained in the tool's submission guidance tab.

The tool will have generated an amendment output and the overall amendment type and category will be shown in Section 4. of the amendment and the submission guidance tab will indicate how the amendment should be submitted. This guidance must be followed to ensure that the amendment is submitted correctly and can be validated.

The online amendment submission functionality requires a separate login to your main IRAS account. If you have not used it before you may need to set up a new account. If you have any difficulty creating an account, please contact the Technical Helpdesk for support on.

When you have logged in, refer to the on-screen step-by-step instructions which will guide you through the process. You will be asked to enter the IRAS ID, and answer some simple questions about your amendment.

You can then upload all documentation relating to your amendment, and proceed to submit. You will receive an automated email to confirm submission of your amendment.

Upon submission the amendment will be shared with REC and/or NHS/HSC as applicable.

Changes to contact details for the sponsor (or the sponsor's representative), chief investigator or other study staff are minor amendment but should be notified to the main REC for information.

3.2. Reporting of Substantial Amendments

Substantial amendments require an approval from the HRA, favourable opinion from the REC and/or the MHRA **before** they can be implemented. The only exception to this is where urgent safety measures need to be taken. Further information is detailed in section 3.6.

3.2.1 CTIMPS (Clinical Trials of Investigational Medicinal Products)

The chief investigator or appointed member of the study team may also include other supporting information, such as a summary of trial data, an updated safety analysis or a report from a trial monitoring committee. Where the amendment could significantly affect the scientific value of the research, further evidence of scientific and/or statistical review should be provided.

Further information can be found in the RGIT_SOP_008 Submitting a CTA application to the MHRA.

3.2.2 MHRA Device Studies

MHRA Devices must be notified of **all** proposed changes to the investigation (not just those classed as substantial amendments for the purposes of ethical review) and the researcher Chief Investigator must wait for a letter of no objection from MHRA Devices before any changes are implemented. This includes any changes requested by the REC. Failure to provide this notification could result in the manufacturer being liable to prosecution.

When notifying the MHRA of any changes, the following information should be provided in writing:
covering letter with:

- the MHRA reference number for the clinical investigation
- a table with a summary of each proposed change with the reason for each change
- red lined (showing changes being made) and clean copies of all amended study documentation
- a signed statement by, or on behalf of, the manufacturer that the proposed change(s) do not predictably increase the risk to the patient, user or third party
- details of who to invoice (full company name, address and registered tax/VAT number)

Notifications should be sent directly to MHRA devices. For further details, please see: Guidance Notify MHRA about a clinical investigation for a medical device

3.2.4 Notifying amendments to ARSAC

ARSAC should be notified of any changes concerning the administration of radioactive substances as this may affect the approval granted. Such changes include, but are not limited to:

- Changes to the study title
- Changes to the number of administrations of radioactive substances from Section A1 of the original Preliminary Research Assessment (PRA) form
- Addition or removal of a procedure involving the administration of a radioactive substance
- Addition of a new study population with a different clinical condition (including changing the age of the participants)
- Changes to the radiation risk information in the participant information sheet (PIS) following changes to the protocol

Such changes will normally meet the criteria for notifying substantial amendments to the Research Ethics Committee (or GTAC). Notification should be made to the ARSAC Support Unit by the sponsor, by email with the following information:

- Short summary of the changes
- Notice of Substantial Amendment when this is submitted to the REC
- Updated PRA form if there are changes to the number of administrations or procedures involving radioactive substances (note you will need to revise the integrated dataset Part A and/or Part B3 and then create an up to date PDF of the PRA form via the Submission tab)
- Any other relevant enclosures, for example Participant Information Sheet

All information should be emailed to the ARSAC Support Unit.

Once you have submitted your amendment request, ARSAC will send you a reference number and details on how and when to pay the £250 fee.

While ARSAC assesses the amendment, you remain authorised within the limits of the initial submission and administrations may continue in line with the original application.

Once approval has been granted to you, individual installations can proceed with the amended study for all procedures on their licence. It is not necessary for each installation to notify ARSAC of amendments.

Further guidance may be found on the ARSAC website or by contacting the ARSAC Support Unit.

3.3. REC procedures for reviewing substantial amendments

The co-ordinator of the REC will write confirming whether or not the notice of amendment is valid for review, normally within five working days of receipt.

Amendments may be reviewed either at a meeting of the REC subcommittee, or at a meeting of the full committee.

The REC will issue an ethical opinion on the amendment within a maximum of **35** days from the date of receipt of a valid notice of amendment. A copy will be sent to the sponsor and the MHRA.

Where an unfavourable opinion is given, the applicant may submit a modified amendment. The REC will give an opinion on a modified amendment within 14 days of receipt.

3.4. MHRA procedures for reviewing substantial amendments

Upon receipt of the Notification of Amendment form, the MHRA will review the amendment and should issue an opinion on the amendment within a maximum of **35** days from the receipt of a valid form. Healthy volunteer trials and sponsor-determined phase I trials in non-oncology patients may qualify for a shorter assessment time (average 14 days). State in the heading of your covering letter if you think your trial is eligible.

However, if the MHRA is over-burdened, the opinion may be delayed to beyond the 35-day deadline as set out in the Medicine for Human Use (Clinical Trials) Regulations 2004. The MHRA state in their acknowledgement letter that "It is the Authority's intention within 35 days of the date of receipt of the request, to notify you, where appropriate, by either setting out the grounds for not accepting the proposed amendment of accepting the application for amendment with or without conditions. If you are not sent either notice, then the amendment can be made." However, although the MHRA state this on their standard letter, it would be prudent to wait for their approval.

3.5. Urgent Safety Measures

There must be arrangements for taking appropriate urgent safety measures to protect participants against any immediate hazard where new events relating to the conduct of the trial or the development of the IMP are likely to affect the safety of the subjects. In many studies, the individual best able to take these measures will be the Chief Investigator or another identified person or organisation – rather than the Sponsor directly. The protocol should identify the specific individual(s) who accept(s) this responsibility. Otherwise, the Sponsor remains directly responsible.

These safety measures, such as temporarily halting the trial, may be taken without prior authorisation from the MHRA but must be reported to the MHRA, Ethics Committee and sponsor. For all other substantial amendments, MHRA authorisation must be sought before the amendment is implemented. For studies that have been processed via the Combined Ways Of Working (CWOW) IRAS system, notification of USMs can be done via IRAS rather than email to the MHRA. Selecting project information in as a substantial amendment will give the option to indicate if an amendment relates to a USM.

3.6 Amendments using CWOW

For studies that have received approval using the Combined Ways of Working IRAS system amendments should be submitted via the CWOW system rather than using the amendment tool. This can be done via 'My Projects' and the Project Details page by selecting 'New Amendment'. The sponsor amendment reference number and date should be entered, and non-substantial or substantial amendment should be selected. There are a number of options to select depending on amendment type.
Clicking on 'Create Amendment' will then take the user to the amendment dashboard, where details of the amendment can be given. Associated documents will also need to be uploaded via the Project Documents section.

When the amendment form is complete, and all documentation uploaded then the form can be submitted. This will send the amendment directly to the sponsor organisation for review and submission.

4. APPROVAL OF AMENDMENTS

If your study is taking place on Imperial College Healthcare NHS Trust premises, or involves Imperial College Healthcare NHS Trust participants, then you must follow the process set out in RGIT_SOP_032 to obtain Trust Confirmation of Capacity and Capability (CCC) for your study where necessary, **prior** to the amendment being implemented. The submission tab in the amendment tool will provide guidance on when REC/HRA/R&D approvals for the amendment are needed.

For ICHT the relevant Divisional Research Manager (DRM) will assess the amendment and any supporting documentation for any implications (e.g. regarding funding, contracts or imaging). For studies sponsored by Imperial College London or Imperial College Healthcare NHS Trust and taking place at ICHT, the RGIT will forward a copy of all amendment documents and approvals to the ICHT feasibility inbox to facilitate continued running of your study at the Trust. For all external sites, please follow the guidance in the submissions tab regarding provision of documents and approvals to sites.

If the amendment tool indicates that your amendment is a Category C non-notifiable amendment, which does not require REC/HRA or R&D approval, sites still need to be made aware of the amendment and should be provided with the amendment documents and approvals. For ICHT, RGIT will forward these to the ICHT feasibility inbox.

5. DATA PROTECTION IMPACT ASSESSMENT

All Imperial College London sponsored studies using personal data (which includes psuedonymised data) must be registered on the Faculty of Medicine Asset register and complete a Data Protection Impact Assessment. This must be completed by the study team, who are also responsible for updating the DPIA should an amendment have an impact on the GDPR aspects of the study. Please contact the FOM GDPR Team for further information (fom.gdpr@imperial.ac.uk)

6. REFERENCES

HRA NHS - Amending an approval
IRAS - Amendments for Projects conducted in the NHS/HSC
Submitting a CTA application to the MHRA SOP, ref: RGIT_SOP_008

IRAS - Maintaining your approvals - Amendments

ICHT Approval of Amendments RGIT_SOP_032

7. APPENDICES

The following Appendices list the following Templates associated to this SOP which can be found on the SOP, Associated Documents & Templates page.

Appendix 1: Amendment Tool – RGIT_TEMP_015