Document Title: Amendments to Research Studies

Document Number: SOP037

Staff involved in development: *a. Job titles only*	R&D Senior Manager, R&D Operational Manager, Clinical Project Managers
Document author/owner:	Senior R&D Manager
Directorate:	Research and Development
Department:	Research and Development
For use by:	NHS Staff Trust-Wide
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Summary of Amendments

Section(s):	Modification:
	To be read in conjunction with SOP071.
Version 7	Clarification of process of submitting amendments to the MHRA Updated process for submitting amendments to REC, HRA, and R&D Offices to reflect changes introduced June 2020 across the United Kingdom
Version 8	Updated to bring the process in line with the new HRA amendment approval process, starting June 2020.

Key Points of this Document

- This document sets out the procedures to be followed by all Royal Papworth Staff who are responsible for submitting and/or implementing amendments for research studies sponsored, managed, or run at Royal Papworth.

- It provides clear guidance on the procedure of classifying and seeking approval for amendments.
- This SOP should be read in conjunction with SOP071: Urgent Safety Measures.

1 Purpose and Content

a. This document defines the Trust's procedure for amendments to research studies following regulatory and Trust approval.

b. The document defines amendments and the approval and implementation process so as to meet the standards described in Good Clinical Practice

2 Roles & Responsibilities

a. This Policy applies to all research studies being conducted at the Trust.

b. Staff involved in amendment applications, both submission and review, must comply with the requirements set out in this document.

c. For Royal Papworth Trust-sponsored studies, the Sponsor duties are delegated to the Investigator for the study at Royal Papworth. The Investigator may in turn delegate the duties to a member of the study team including appropriate members of the R&D department or CTU e.g. the study Clinical Project Manager (CPM). Regardless, the process described herein must be completed for Royal Papworth as they are for external sites i.e. sending documents to R&D for review and confirmation prior to implementation.

d. The Sponsor is responsible for initiating any amendments to a study including the classification and authorisation of the amendment prior to submission to regulatory bodies. For Trust-sponsored studies, the classification may be delegated to a member of the R&D department/CTU e.g. CPM. The classification will be reviewed and confirmed by the HRA subsequent to submission for approval.

e. The Sponsor of a research study is responsible for ensuring that all relevant regulatory approvals have been obtained prior to the implementation of an amendment. The actual procedure of applying for and implementing amendments may be delegated to the Chief Investigator (or a member of their research team including the CTU/R&D team at Royal Papworth), or CRO.

f. The Sponsor (or their delegate; for Royal Papworth Sponsored studies this is the local Investigator or their delegate) is responsible for notifying the participating NHS organisations of the amendment and sending the amendment and associated documents

to the participating organisation's R&D Office and the Principal Investigator (PI) / local study team. This includes the sponsor site R&D and study teams.

g. It is the PI and local study team's responsibility to file all documentation and correspondence in relation to an amendment in the Site File. It is the Sponsor's responsibility to file these in the Sponsor File.

3 Policy

a. This SOP is mandatory and, as per the Trust's Information Governance and Records Management framework, non-compliance with may result in disciplinary procedures.

4 Procedure

4.1 Definition and Classification of amendment

a. An amendment is any change that is made to the design, conduct and management, and associated changes to the documentation, of a study following initial ethical and/or regulatory approval. Any changes must be appropriately reviewed and approved by the relevant organisations to ensure compliance with Good Clinical Practice and national legislation and guidelines.

b. All amendments must be documented in the Trial Master File (TMF), including the rationale for its classification if it is a Royal Papworth Sponsored study.

c. Further details on the classification and examples of amendments is available from the HRA website:

http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/definitions-of-substantial-and-non-substantial-amendments/

d. Additional information concerning amendments to CTIMPs and non-CE marked devices can be found at:

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

4.1.2 Amendments are classified as either:

a. **A substantial amendment.** Defined as likely to affect to a significant degree any of the following:

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

The substantial amendment will require approval from the relevant bodies before it can be implemented, unless it is an **Urgent Safety Measure,** which is taken by the Sponsor or Investigator in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety (see section 4.6.1 for further information and refer to SOP71).

b. **A non-substantial (minor) amendment.** Defined as a minor change that is not considered substantial as described above.

4.1.3 Process for classification of an amendment for Trust-sponsored studies

a. The Sponsor is responsible for the decision to make a change, the classification of an amendment as either substantial or non-substantial and the revision of any documentation.

b. For all clinical trials, the rationale and justification for the proposed amendment (and whether this is substantial or non-substantial) must be documented (e.g. meeting minutes, emails or file notes) in the Trial Master File.

c. Any implications of an amendment must be considered, actions identified and delegated, and documented in the TMF. This should include, but is non-exhaustive: trial documentation, data collection and management systems, study processes, staff training requirements, contracts, indemnity, finances, imaging including IRMER/ARSAC, regulatory limitations/expectations, reporting requirements including stakeholders e.g. funding bodies, sites including PIC sites, etc.

d. If the substantial protocol amendment is as a result of an unexpected incidence of ARs / SARs then the sponsor should consider reporting this as an Urgent Safety Measure / SUSAR. This discussion must be documented (e.g. meeting minutes, emails or file notes).

e. Flow chart A summarises the process for review, classification and implementation of an amendment.

4.2 Regulatory Submission

a. The Sponsor or their delegate is responsible for submission to the necessary bodies in accordance with the requirements of those regulatory bodies.

b. With the exception of urgent safety measures, the Sponsor of a clinical trial is required to obtain authorisation (as applicable) from the HRA, REC and/or MHRA and the relevant Trusts before implementing the amendment.

c. Further specific guidance on the submission process and approvals requirements is available from the IRAS website help pages, the MHRA website and HRA website: www.hra.nhs.uk.

4.2.1 Notifying Amendments for research requiring REC and/or HRA review

a. Since June 2020, for all project-based research (i.e., defined as any of the IRAS Project Filter question 2 categories except for Research Tissue Banks (RTBs) and Research Databases (RDBs)): Notice of Substantial Amendment (NOSA) and non-substantial amendment forms are **no** longer used and have been replaced by the Amendment Tool in IRAS.

b. For RTBs and RDBs: continue to use the Notice of Substantial Amendment Form generated in IRAS to notify substantial amendments to the REC.

c. When you have completed the Amendment Tool (or Notice of Substantial Amendment form in the case of RTB and RDB projects) and finalised all supporting documentation for your amendment, you should proceed to submit your amendment online, using the online submission functionality in IRAS.

d. For information and access to the Amendment Tool and online submission functionality, see https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool. For queries, contact: amendments@hra.nhs.uk

4.2.2 Notifying Amendments to MHRA Medicines

a. For all CTIMPs, substantial amendments must be notified to the main REC and the MHRA using the European Commission form, which is available under the 'Annex 2' tab of the Amendment Tool, or on the EudraCT website at: https://ec.europa.eu/health/documents/eudralex/vol-10_en.

b. For guidance on submission of CTIMP substantial amendments to the MHRA, please see https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues.

c. All substantial amendments should be approved in principle by the sponsor(s) before submission.

d. A copy of the submission package must be filed in the TMF.

e. There is a fee associated with MHRA review of amendments, please refer to the website.

f. Notification to the MHRA is not required for non-substantial amendments.

4.2.3 Notifying amendments to MHRA Devices

a. MHRA Devices must be notified of **all** proposed changes to the investigation (not only those classified as substantial amendments for the purposes of ethical review).

b. A letter of no objection from MHRA Devices must be received before the changes may be implemented.

c. Notifications should be sent directly to MHRA Devices. For details, see https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device.

4.3 HRA Categorisation of Amendments

a. Following completion of the Amendment Tool, a recommended amendment category will be automatically calculated based on responses to the questions. The sponsor or authorised delegate is responsible for ensuring that the amendment tool is completed correctly, and for comparing the outcomes against their own expectations of how the amendment should be processed.

b. Categories are as follows:

Category	Participating centre submission and review requirements
A	Any amendment to a research study that has implications for, or affects, ALL participating NHS organisations hosting the research study. All participating NHS organisations, including the sponsor site, must be informed of, and be sent the full submission for review. All participating NHS organisations are expected to consider the amendment to determine whether they are able to continue NHS research permission (or TCCC).
B	Any amendment to a research study that has implications for, or affects, SPECIFIC participating NHS organisations hosting the research study. Only those participating NHS organisations affected by the amendment must be informed of the amendment. However, all participating NHS organisations will have access to the amendment through the relevant national coordinating function. Only those participating NHS organisations affected by the amendment are expected to consider the amendment to determine whether they are able to continue NHS research permission (or TCCC).
C	Any amendment to a research study that has no implications that require management or oversight by the participating NHS organisations hosting the research study. Participating NHS organisations are NOT expected to consider the amendment or give continued permission for these amendments. There may be amendments of a confidential nature that the Sponsor is required to submit to the MHRA. Such amendments will have no

	implications for, or affect, the participating NHS organisations hosting the research study. Therefore these amendments will not be notified to the NHS organisations.

4.4 Submission process for Royal Papworth Sponsored studies

a. For Royal Papworth Trust-sponsored studies a delegated member of the research team will coordinate the amendment application process.

b. All proposed amendments and revised documentation should be reviewed by the Royal Papworth Trials Unit, who maintain Sponsor oversight of the study and, along with the CI/PI, decide on the classification of the amendment **prior to submission to the HRA and relevant regulatory bodies**. The submission should be accompanied by revised study documentation and an updated version control document.

c. The HRA will confirm what regulatory approvals, if any, the amendment requires upon submission of the new amendment tool through the online process outlined in 4.2.1

4.5 Process for reviewing and permitting amendments

a. For Trust-sponsored or managed studies, **all** amendments regardless of classification and categorisation must be submitted to participating organisation R&D Offices (i.e., Research Governance) for review.

b. Participating Organisations, including Royal Papworth, require the full amendment submission information to be sent to the relevant R&D email addresses listed here: http://www.rdforum.nhs.uk/content/contact-details/. A template email to notify participating NHS organisations in England and/or Wales is provided on the HRA website (https://www.hra.nhs.uk/approvals-amendments/amending-approval/).

c. For Royal Papworth, notification of amendments and submission of documents is via the generic R&D Enquiries email box (papworth.randdenquiries@nhs.net).

d. Once the HRA have issued the categorisation email, the following must be submitted for amendments to be reviewed:

1. The completed Amendment Tool (or Notice of Substantial Amendment form in the case of RTB and RDB projects)
2. Electronic copies of all documents (include tracked changes versions) submitted for HRA and regulatory review)
3. HRA categorisation email and HRA approval (if received by the time of local submission to site)
4. Any other applicable regulatory body approval

5. Updated version control document
6. Any associated paperwork e.g. contract amendments, which will need localised review and completion in response to implementing the amendment.

e. The amendment will be reviewed by participating organisation R&D Office (i.e., Research Governance) to ensure that all associated documentation has been received by the R&D department.

f. Participating organisation R&D Offices, including Royal Papworth, have 35 days to raise an objection to the amendment from the date the notification email is received. In line with the HRA process, if 35 calendar days pass without objection or response the Sponsor can assume no objection to the amendment, and provided HRA Approval been issued where this is required.

g. The impact of the amendment to risks, finance, contracts and resources will be reviewed by the participating organisation R&D Office to ensure the amendment is feasible and does not affect the Trust's confirmation status for capacity and capability (or NHS permission).

h. For studies being conducted at Royal Papworth any impact on departments and services must be discussed and agreed with the directorates implicated – the process for directorate authorisation (SOP034) may be repeated specifically for amendments. Their agreement to support, or otherwise, must be documented in the study file.

i. If an amendment is submitted that cannot be implemented for any reason, or more time is required to assess the suitability of the amendment, an objection may be raised by the participating organisation R&D Office with the sponsor. This removes the 35 day deadline for amendment implementation and allows more time for the amendment to be considered.

j. If an amendment has no implications or the implications have been fully addressed, including completion of any contract amendments, then an email confirming no objection to the amendment will be issued by the participating organisation R&D Office (i.e., Research Governance) to the Sponsor's representative. Where Royal Papworth is the Sponsor, a copy of the email must be stored in the TMF. Where applicable a copy will also be sent to the Pharmacy department.

k. If regulatory bodies request for changes to be made to the amendment prior to issuing their approval, the amendment must be resubmitted to R&D Offices with the changes highlighted and any modified documentation, including version control document, attached.

l. Amendments received and their Trust review outcomes are tabled for information at the next Research & Development Directorate meeting.

4.6 Implementing Amendments

a. Once a notice of no objection has been granted, the amendment may be implemented at the Trust/Participating Organisation, but only once all relevant regulatory approvals have been received and the Trust/Participating Organisation is deemed ready to implement the amendment i.e. the relevant actions identified for implementing the amendment according to section 4.1.3c have been completed.

b. It is the Sponsor's responsibility to ensure the necessary approvals have been sought and received, and confirm site readiness, before implementation of the amendment.

c. The Trust/Participating Organisation notices of no objection and relevant regulatory approvals, together with evidence of completing site readiness, must be stored in the TMF.

d. It is the Sponsor's responsibility to provide an updated version control document to all site study teams and R&Ds. This includes Royal Papworth-sponsored and managed studies at Royal Papworth. If the sponsor does not provide an updated version control document, then the study team should ensure a record of version control documentation is kept in the site file.

4.6.1 Exceptions: Urgent Safety Measures

a. Amendments due to urgent safety measures can be implemented immediately with all subsequent documentation forwarded to R&D.

b. It is the sponsor's responsibility to determine if an urgent safety measure is required, this may include as a response to an increase in adverse reactions, or SUSAR.

c. All decisions and rationale for the urgent safety measure must be documented in the Trial Master File (TMF).

d. Urgent safety measures must follow MHRA and ethical process for follow-up of amendment.

e. The Sponsor will be responsible for determining whether amendments to the study documentation, including the participant information, may be required.

f. This SOP should be read in conjunction with SOP071, Urgent Safety Measures.

5 Risk Management / Liability / Monitoring & Audit

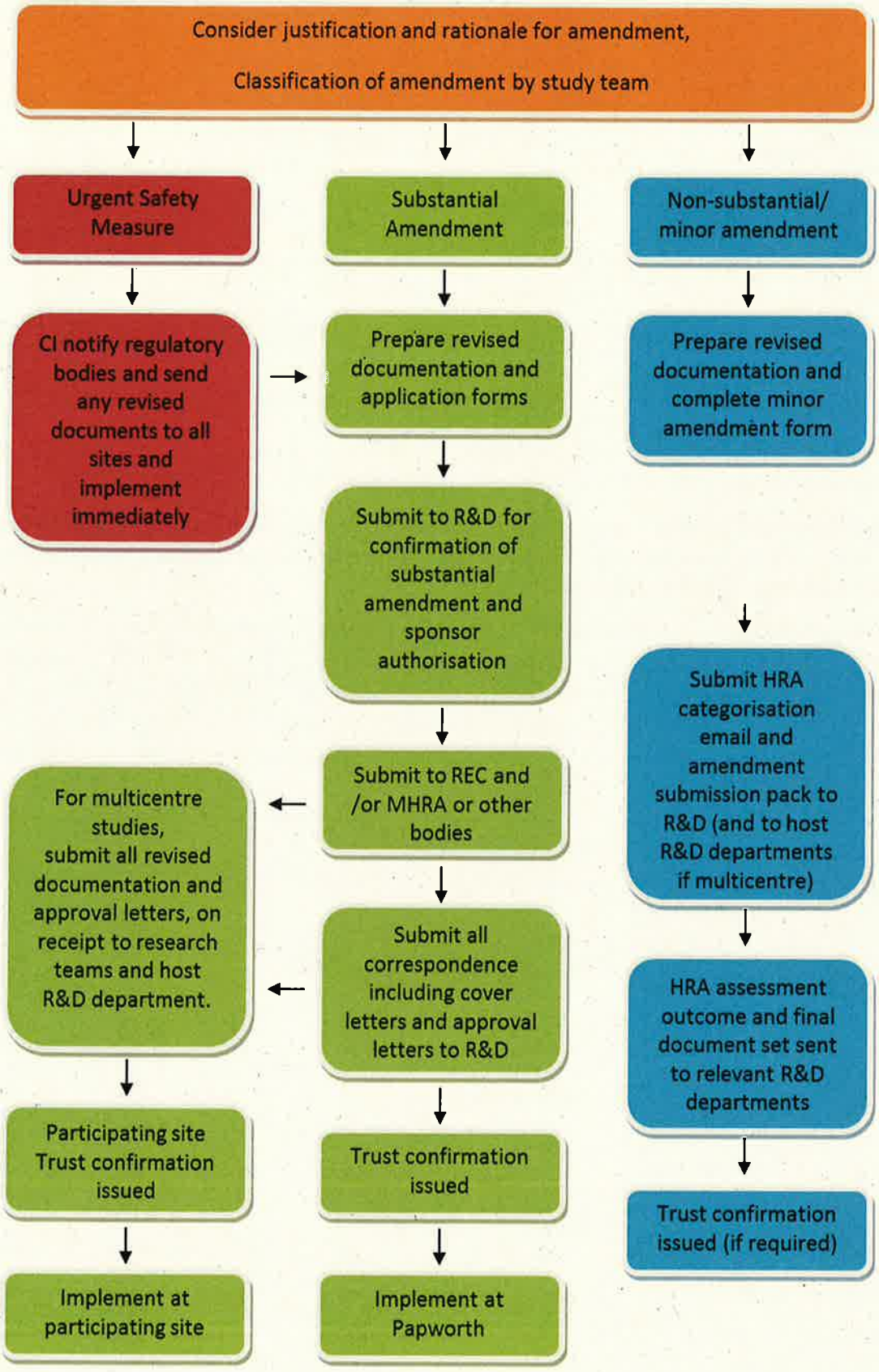
a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Investigator and Sponsor Master File.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Flow Chart A


Consider justification and rationale for amendment,
Classification of amendment by study team
Urgent Safety Measure
Substantial Amendment
Non-substantial/ minor amendment
CI notify regulatory bodies and send any revised documents to all sites and implement immediately
Prepare revised documentation and application forms
Prepare revised documentation and complete minor amendment form
Submit to R&D for confirmation of substantial amendment and sponsor authorisation
Submit HRA categorisation email and amendment submission pack to R&D (and to host R&D departments if multicentre)
Submit to REC and /or MHRA or other bodies
For multicentre studies, submit all revised documentation and approval letters, on receipt to research teams and host R&D department.
Submit all correspondence including cover letters and approval letters to R&D
HRA assessment outcome and final document set sent to relevant R&D departments
Participating site Trust confirmation issued
Trust confirmation issued
Trust confirmation issued (if required)
Implement at participating site
Implement at Papworth

SOP037: Amendments to Research Studies
Further Document Information

Approved by: *b. Managment/Clinical Directorate Group*	Research and Development Directorate
Approval date: *c. (this version)*	[Current active version approved date]
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *d. Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Framework for Health and Social Care Research (2018)
Key related documents:	Trust Research Policy

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	NO	NO	NO	NO	NO	NO	NO

Review date:	November 2023

I certify the contents of this SOP has been reviewed and ratified

..... 30th November 2020.

Signed by Dr Ian Smith, Clinical Director of R&D — Date

SOP release date: 9th December 2020