Papworth Hospital NHS
NHS Foundation Trust

Document Title: Amendments to Research Studies

Document Number: SOP037

Staff involved in development: *a. Job titles only*	R&D Governance Coordinator, Clinical Project Managers (CPMs), R&D Senior Managers
Document author/owner:	R&D Clinical Project Manager with responsibility for Governance
Directorate:	Research and Development
Department:	Research and Development
For use by:	NHS Staff Trust-Wide
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Summary of Significant Change(s) (for this version only)

Section(s):	Modification:
	To be read in conjunction with SOP071.
	Minor administrative changes throughout.

Key Points of this Document

- This document sets out the procedures to be followed by all Papworth Staff who are responsible for submitting and implementing amendments for research studies run at 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 changes 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 (GCP: 'a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected').

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 Papworth Trust-sponsored studies, the Sponsor duties are delegated to the Investigator for the study at 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 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, 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 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 and ensuring that all relevant regulatory approvals have been obtained prior to its implementation. 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 Papworth), or CRO.

f. The Sponsor (or their delegate; for Papworth Sponsored studies this is the local Investigator or their delegate) is responsible for alerting and sending the amendments and associated documents to the Principal Investigators and the R&D departments at the participating sites. This includes the sponsor site R&D and study teams.

g. It is the Principal Investigator and local study team's responsibility to file all documentation and correspondence in relation to an amendment in the study file. It is

the sponsor's responsibility to file these in the Sponsor file to then be amalgamated into the Trial Master 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 regulatory approval and Trust confirmation (TCCC). Any changes must be appropriately reviewed and approved by the relevant organisations and the change documented and filed in the study files 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.

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.

A substantial amendment is submitted following 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. These can be implemented immediately (see section 4.5.2 for further information and refer to SOP71).

b. **A non-substantial (minor) amendment.** Defined as minor changes that are not considered substantial as described above. Non-substantial amendments do not require submission to REC and /or MHRA but do require submission to the HRA.

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, proposed classification into substantial/non-substantial amendment and revision of any documentation.

b. For all clinical trials 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 and Approval for Amendments

a. Further specific guidance on the submission process and approvals requirements is available from the HRA website: www.hra.nhs.uk.

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

c. The submission package, a copy of which must be filed in the TMF, must contain:

1. An completed and signed amendment submission form:
- Minor submission form – available on HRA website

- Substantial amendment form – created from the project form in IRAS.

2. The new documents which have been given a new version number and date. It is likely that both the 'track changes' and clean form of the new version will be required.
3. Cover letter/email

d. The amendment submission package is to be submitted to the HRA at: hra.amendments@nhs.net.

e. The HRA will issue an email to verify that the submission is valid and to provide the amendment category. This email MAY specify that HRA assessment is not required; in this case HRA approval is considered complete. The amendment will be categorised as one of the following:

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.

f. Some amendments will not require a HRA approval letter to be issued. Whether this is required will be stipulated in an email from the HRA when the category of the amendment is confirmed.

g. The Sponsor or their delegate is responsible for submission to the necessary bodies in accordance with the requirements of those regulatory bodies. Non-substantial amendments do not require ethical or MHRA approval, although it is good practice to notify the relevant bodies of any non-substantial amendment in either annual reports, or when submitting substantial amendments.

4.3 Submission process for Papworth Sponsored studies

a. For 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 submitted to R&D for ratification of the classification **prior to submission to the HRA for authorisation** by the Sponsor delegate. This should be accompanied by an updated version control document.

c. R&D should be contacted for confirmation of what regulatory approvals, if any, the amendment requires.

4.4 Process for reviewing and permitting amendments

a. For Trust-sponsored or managed studies, **all** amendments regardless of categorisation, must be submitted to the Research Governance Team in R&D for review.

b. Sites, including Papworth, require the full amendment submission information to be sent to the R&D email addresses listed here: http://www.rdforum.nhs.uk/content/contact-details/.

c. Notification of amendments and submission of documents is via the generic R&D Enquiries email box.

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

1. Notice of substantial amendment or minor amendment
2. Electronic copies of all documents (include tracked changes versions) submitted for HRA review
3. The HRA assessment letter AND HRA categorisation email OR HRA approval
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 the Research Governance Team to ensure that all associated documentation has been received by the R&D department.

f. Trust R&Ds, including 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 days pass without objection or response the sponsor can assume no objection to the amendment.

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

h. 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 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 Research Governance Team on behalf of the Senior R&D Manager to the Sponsor's representative and Chief/Principal Investigator. 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 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 Governance Project Approval System Meeting (RGPAS) by the Research Governance Team.

4.5 Implementing Amendments

a. Once a notice of no objection has been granted by the Trust the amendment may be implemented at the Trust, but only once all relevant regulatory approvals have been received and the site 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 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 Papworth-sponsored and managed studies at Papworth.

4.5.2 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

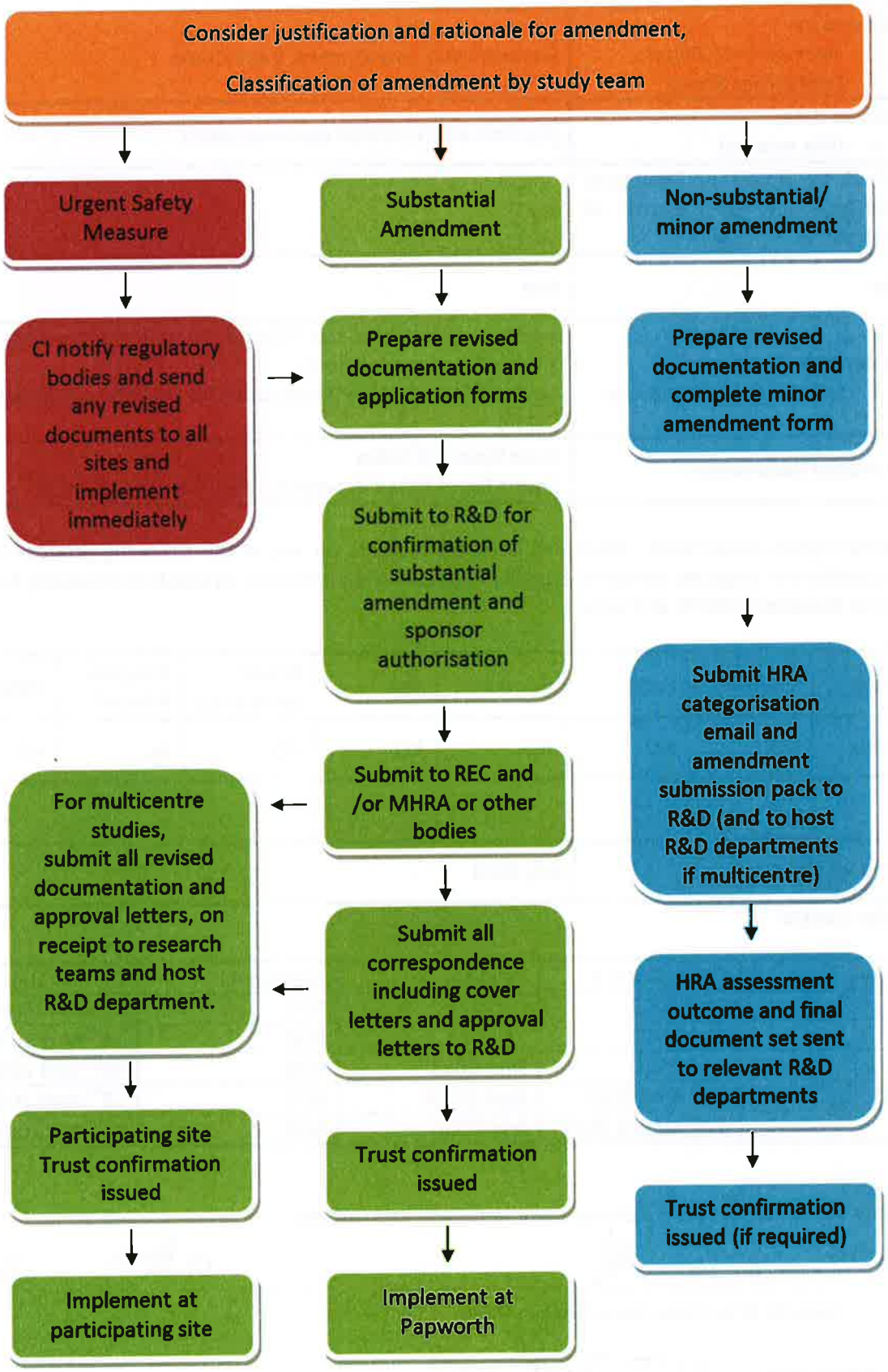
a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

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

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. Research Governance Framework for Health and Social Care (2005)
Key related documents:	Trust Research Policy [Insert list of linked or relevant documents to this SOP]

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:	July 2019

Version Control

Version	Date effective	Valid to	Approved by	Date of approval
1.0	Sept 2009		RDD	4th Sept 2009
2.0	May 2010		RDD	14th May 2010
3.0	Sept 2010	Sept 2012	RDD	10th Sept 2010
4.0	13th April 2012	April 2015	RDD	13th April 2012
5.1	22nd August 2013	July 2016	RDD	12th July 2013

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

..... 9th June 2017

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

SOP release date: 14th June 2017