Portsmouth Hospitals University NHS Trust

Standard Operating Procedure (SOP)

Management of Amendments in PHU Sponsored Studies

For Completion by SOP Author	
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If you are reading this SOP in printed form then you are reading an uncontrolled document. You must therefore verify that the version number and date given below are the most recent, by cross-checking with the Trust research website before proceeding with implementation.

Portsmouth Hospitals University NHS Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their

individual needs and does not discriminate against individuals or groups on any grounds. This SOP has been assessed accordingly

Any change to the national processes related to this SOP will always override the information in this document.

CONTENTS

1. INTRODUCTION

During the course of a study, A Chief Investigator (CI), study team and/or the Sponsor may wish to change certain aspects of a study protocol and other study documentation following initial approval from the regulatory authorities (Research Ethics Committee (REC), Health Research Authority (HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA) etc.). This may be for various reasons; to ensure safety, to better inform participants, to allow the study to run more efficiently, to increase recruitment etc.

For all studies, it is the responsibility of the Sponsor to determine whether an amendment is substantial or not.

A substantial amendment is commonly defined as:

> An amendment to the terms of the application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:
>
> - the safety or physical or mental integrity of the subjects of the study;
> - the scientific value of the study;
> - the conduct or management of the study;
> - **or** the quality or safety of any investigational medicinal product used in the trial.

A non-substantial amendment is commonly defined as:

> An amendment made to any of the trial documentation including the application forms, protocol or supporting documentation which does not fall into the categories above.

Any amendments made to a Portsmouth Hospitals University NHS Trust (PHUT) sponsored study are required to be submitted to the following, before implementation;

- The Sponsor Portsmouth Hospitals University NHS Trust (Email: research.office@porthosp.nhs.uk) for review and confirmation of continued sponsorship, prior to submission to regulatory bodies.
- The required regulatory bodies (e.g. REC, MHRA, HRA) for review and approval (if substantial) or for notification only (if non-substantial).
- Any participating sites for review and confirmation of continued capacity and capability- following regulatory approval if required.

Amendments may affect the study and any participating research sites in a number of ways, including the resources/staff required to support the study amendment, the role of local support departments (e.g. pharmacy, pathology, radiology), subjects eligible for inclusion into the study, study end-points and more. The impact of amendments to a study should be considered by the CI and sponsor prior to gaining approval from the applicable regulatory authorities.

2. PURPOSE

The purpose of this document is to describe the Standard Operating Procedure (SOP) for all amendments to studies sponsored by PHU to ensure they are suitable, processed appropriately and undergo the necessary review to ensure they do not have any impact on the Trust's agreement to continue sponsorship of the trial.

3. SCOPE

This SOP applies to **all** studies sponsored by PHU, in which a change/addition to the original REC/HRA/MHRA application and approved study documentation is planned.

This SOP does not apply to externally sponsored research studies where PHU are a host site.

This SOP should be followed by:

- All CI's and study teams conducting a single centre or multicentre study sponsored by PHU.

All Research Office personnel who are responsible for receiving, distributing and processing amendments.

- All relevant support departments involved in delivering the study, internal to PHU and those supporting external delivery sites.

The Trust recognises that some external sponsors, networks, funders and employers may require the use of their own SOPs for the good governance of research. In such cases it is the responsibility of the Portsmouth Hospitals University Trust user (including those individuals contracted to work on behalf of the Trust), to ensure that the external SOP is compatible with the procedure outlined below. If the external SOP contradicts the Trust's SOP then approval must be sought from a senior manager within the Research & Innovation Department at PHU.

In the event of an infection outbreak, flu pandemic or major incident, the Trust recognises that it may not be possible to adhere to all aspects of this document. In such circumstances, staff should take advice from their manager and all possible action must be taken to maintain ongoing patient and staff safety.

4. ABBREVIATIONS & DEFINITIONS

Abbreviation	Meaning
ARSAC	Administration of Radioactive Substances Advisory Committee
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
EDGE	Local Portfolio Management System
HRA	Health Research Authority
ISF	Investigator Site File
IRAS	Integrated Research Application System
MHRA	Medicines and Health products Regulatory Agency
PHU	Portsmouth Hospitals University NHS Trust
RDM	Research Delivery Meeting
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee

Term	Definition
PHU Sponsored Studies	Studies which Portsmouth Hospitals University NHS Trust have ultimate responsibility for the initiation, management of and financing for. They take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting.
Substantial Amendment	A substantial amendment is defined as an amendment to the terms of the protocol or any other supporting documentation that is likely to affect to a significant degree: a. *the safety or physical or mental integrity of the subjects of the trial* b. *the scientific value of the trial* c. *the conduct or management of the trial* d. *the quality or safety of any investigational medicinal product used in the trial* *Examples can be found on the HRA website:* Examples of substantial and non-substantial amendments - Health Research Authority (hra.nhs.uk)
Non-substantial Amendment	An amendment made to any of the trial documentation including the application forms, protocol or supporting documentation which do not fall into the categories above.
HRA Category A amendment	Implications for or affects all participating organisations. This may involve changes to activity or cost implications
HRA Category B amendment	Implications for or affects specific participating organisations. This may involve changes to activity or cost implications for these organisations.
HRA Category C amendment	No implications that require management or oversight by the participating NHS organisations. The amendment will still be provided for information. There are no changes to site activity or cost implications. Participating organisations might need to take some action, such as updating contact details.
Study Team	The people involved in the conduct of a research project. There may be different research teams for the project at different sites.
Devolved Nations/Administrations	England, Scotland, Wales & Northern Ireland.

5. DUTIES AND RESPONSIBILITIES

The following parties are responsible as outlined below:

Role	Responsibilities
Delivery Team (of a PHU sponsored study)	▪ Inform the PHU research office of all planned amendments and associated updated documents prior to submission to the regulatory authorities unless related to urgent safety measures. ▪ Notify the TSC and/or DMC should their terms of reference request notification and review of amendments. ▪ Notify RDM (at one of their scheduled meetings) of a proposed amendment that will significantly impact capacity or costs, at the request of the research office ▪ Consider whether an amendment will have any impact on the Case Report Form (CRF), support departments such as research labs, clinical trials pharmacy, radiology and contracting and costing. Contact each team accordingly. ▪ Work with the research office to prepare an amended protocol and any related documentation, as required, for submission.. ▪ Ensure that an amendment is only implemented once all regulatory approvals and local confirmation of continued capacity and capability has been given. ▪ Ensure that all relevant documentation and pertinent correspondence relating to amendments are filed in the Trial Master File. ▪ Supersede any old versions of study documents in the TMF as soon as a new version is implemented. ▪ Ensure version control of all study documents using the study version log following any amendments. ▪ Ensure that any documents are only accessed from EDGE
PHU Research Office (as sponsor)	▪ Regularly check the research office and research amendments mailbox for information on any planned amendments. Review each planned amendment for compliance with regulatory standards and assess their impact on the study and participants. ▪ Determine whether an amendment is substantial or non-substantial. ▪ Inform the local support departments involved in a planned amendment and gain ongoing approval from each department, where necessary. ▪ Work with the delivery team to prepare protocol amendments and related documents to the study team, as required. ▪ Notify RDM of any amendments that impact capacity and capability and study costs. For particularly complex amendments with significant impacts the study CI or PI should be requested to attend RDM by a member of the research office.

	▪ Discuss amendments that do not impact capacity and costs at the sponsored studies meeting. ▪ Ensure that the amendment and related documents are entered on to EDGE. Ensure that the workflow on EDGE is only completed when each step of the EDGE workflow is signed off and dated by the responsible staff member(s). ▪ Submit all amendments and associated documents via the amendment tool on IRAS on behalf of the CI for approval ▪ Maintain and coordinate communication/correspondence between regulatory bodies and CI related to the amendment submission. ▪ Maintain and update the version control log ▪ Ensure that all participating sites, if applicable, are notified of an amendment and its categorisation (A, B or C) in a timely manner, unless this responsibility has been delegated to an external CRO, Research fellow or Research Nurse acting as Trial Managers. ▪ Ensure any devolved administrations (Scotland, Northern Ireland & Wales) involved in the study are notified of an amendment in a timely manner, unless this responsibility has been delegated to an external CRO, Research fellow or Research Nurse acting as Trial Managers. ▪ Ensure that the study costs are updated and are still within the study budget, or additional funding has been sought ▪ Ensure the study risk assessment is reviewed and updated in the case that the amendment changes the risk to a study. ▪ Ensure any regulatory approvals are gained and issue continued permission

6. PROCESS

6.1. Preparation of the Amendment Documentation

- The CI/study team identify the need for an amendment.
- This should be discussed with the TMG, TSC, DMC & Statistician, where required.

- All amendments should be presented at RDM/Sponsored Studies Meeting for sponsor oversight, where a study does not have its own TSC or DMC or where the amendment may fundamentally change the organisation's position on Sponsorship (speak to a member of the research office for more guidance)

- The CI and/or delivery team should ensure that all study documents affected by the proposed amendment are updated and saved as a new version. A tracked changes version should be

maintained alongside the updated version. *For example, an amendment to the protocol may also require an update to the patient information sheet and CRF's.*

- Depending on the nature of the planned amendment it may be necessary to obtain input from relevant support departments and/or study personnel (e.g. pharmacy, labs, study statistician, radiology, etc.)

- If the amendment has an impact on the CRF and database (e.g. changes to participant assessments, visits, samples taken or inclusion/exclusion criteria) the study's data management team, or person responsible for data management, should be contacted as early in the amendment process as possible to ensure that these systems will be updated and available for implementation following the amendment approval.

- *The study team should notify the PHU research office of a planned amendment, substantial or not, by sending*

  - All new or updated trial documents with tracked changes
  - A completed amendment tool (available from the HRA website)

6.2. Submission of Planned Amendments to the PHU R&I Office

All planned amendments whether considered to be substantial or non-substantial should be sent to the Research Office either directly or via the research office or research amendments group mailbox: research.office@porthosp.nhs.uk, research.amendments@porthosp.nhs.uk for review prior to submission to any regulatory authorities and implementation.

6.3. Amendment Impact Review & Continued Sponsorship

- The Research Office will check that all required documentation relating to the amendment has been received for review and will request any outstanding documents as required.

- The amendment review process will start when all required documents have been received.

- The Research Office will review the amendment and associated documentation to:

  - To work with the CI and delivery team to ensure study objectives are still likely to be met.

  - Ensure that the changes are made in accordance with the applicable guidelines and legislation.

  - Check whether the changes would affect the sponsor's agreement for continued sponsorship in conjunction with RDM quorum.

  - Check if the changes have any impact on support departments for the trial including pharmacy, pathology, and / or radiology.

  - Check if there is any financial impact involved with the amendment.

  - Check if any changes to the study contract are needed.

- Check whether the changes require patient re-consent and the urgency with which it is needed.
- Ensure updated participant documentation uses appropriate language and is easy to understand.
- Ensure all updated documentation is correctly version controlled and localised.
- Check whether the risk of the study has altered and update the risk assessment, if applicable.

- As part of the review process, the Research Office will confirm whether they agree the amendment is substantial or non-substantial.
- The Research Office will complete the initial amendment review.
- Any suggested or required changes to the updated documentation will be fed back to the CI and study team.

6.4. Submission of Amendments to the Regulatory Authorities (REC/HRA/MHRA)

- For all research, a completed, locked amendment tool along with the tracked changes and clean copies of updated study documents should be submitted for regulatory approval through IRAS as per the IRAS submission of amendments guidance. Upon submission, the amendment will be shared with REC and/or NHS/HSC as applicable.
- For multicentre studies where any participating sites are based outside of the UK, substantial amendments should also be submitted to the ethics committee and/or relevant competent authority according to the local country requirements, by the local study team, following authorisation. The research office should maintain oversight of this.
- The Research Office will submit amendments for Sponsored studies, on behalf of the CI and PHU as sponsor.
- Categorisation of the amendment is completed within the Amendment Online Tool
- Substantial amendments for review by the MHRA will incur an upfront amendment fee and evidence of payment must be included in the submission. Further information can be found on the MHRA website. Submissions of substantial amendment to the MHRA must also include:
    - A covering letter including the trial reference numbers along with the Purchase Order Number for the amendment charge.
    - PDF copy of the updated Clinical Trial Application Form with changes highlighted- if the amendment affects the information previously submitted.
    - Copy of the proposed changes to the protocol, and other documents, showing previous and new wording where applicable supporting data for the amendment.
    - PDF copy for he lock amendment tool.

- If you are amending a MHRA Device study there are different requirements to CTIMPs. All proposed changes to the investigation, not only those classified as substantial, must be notified and the Sponsor/investigator must await a letter of no objection from MHRA Devices prior to amendment implementation. Notifications of amendments should be sent directly to MHRA Devices (details of how to do so are available on the MHRA Devices website). This included changes made at the request of the REC. The following should be provided in writing:

    - MHRA reference number for the study.
    - Details of proposed changes to the study of design of the device.
    - Reason for the changes.
    - Signed statement by or on behalf of the manufacturer that the proposed change(s) do not predictably increase the risk to participants, user or third party.
    - PDF copy of completed and locked amendment tool.

- There are also separate amendment reporting requirements to CAG and ARSAC where these are applicable to a study. Please work with the research office team to support the facilitation of this, as with any sponsored amendment.

6.5. Notification of Amendments to Participating Sites (multi-centre studies)

- If the amended study is multicentre, it is the duty of the research office (or delegated persons) on behalf of the CI to inform all participating sites of the amendment in a timely manner.

- **For Category A or B Amendments:**
    - The CI / study team should send each relevant participating site (along with their local research departments), details of the amendment, including the locked amendment tool and any updated documents, in a timely manner. Refer to IRAS Help 'maintaining your approvals' for relevant email templates.
    - Amendments can be implemented 35 calendar days after the amendment is provided to relevant site unless concerns/objection raised (conditional on regulatory approval).

- **For Category C Amendments:**
    - The amendment can be implemented as soon as the relevant site is informed (conditional on regulatory approval), unless any concerns or objections are raised. The 35-day implementation period does not apply to category C amendments.
    - The CI / study team should send the documents related to the amendment to each participating site to file in the Investigator Site Files (ISF).

- Participating sites, including PHU, should then assess Category A & B amendments for local continued capacity and capability, and raise any objections to the Sponsor (PHU) within 35 working days. The 35 day implementation period in England and Wales starts when the sponsor emails the amendment to the research office and local research team.

- The study team should keep a record of any objections raised or confirmations of continued capacity and capability received from each participating site in the TMF. Please note however, it is not a requirement for sites to issue confirmation of continued capacity and capability.

6.6. Receipt of Regulatory Approvals

- On receipt of regulatory approvals, the CI or study team should ensure a copy of the approval letters is provided to the PHU research office and implemented at other participating sites as detailed above.

- If changes to any of the amendment documentation are made following the submission, as suggested by the authorities, a copy of the final amended documents, including clean versions should be provided to the PHU research office and then implemented at other participating sites as detailed above.

- On receipt of these documents the research office will check the document dates/version numbers listed in the approval letter are those of the submitted documents.

- The CI / study team should also provide a copy of the regulatory approvals to the trial data management team, where applicable, to ensure that any amendments to the CRF and database can be released for use.

6.7. Notification of Amendments to Support Departments

- It is the responsibility of the research office to ensure that all amendment documentation including regulatory approvals is provided to any supporting departments, where appropriate.

6.8. EDGE Workflow

- The Research Office is responsible for keeping track of each study amendment that is processed. This is done using an EDGE workflow.

- The workflow is constructed of several steps guiding the user through the amendment process. Each step on the workflow will be marked complete when finished.

- All steps have to be completed and dated for the amendment to be fully processed.

- The length of the workflow depends on the category of the amendment/impact on PHU resources, i.e. either Category A, B, or C.

- The workflow is visible to the members of the study team and the research office to enable tracking of the amendment from notification to approval.

- For a substantial amendment, the delivery team are responsible for completing the “research team approval” step on the EDGE workflow when they are happy with the amendment.

- Only staff who have manager access on EDGE for the study will be able to amend the workflow.

- Ensure that once the amendment is approved and implemented that the correct version of study documents are uploaded to EDGE for the research team to use. This is to support correct version control.

7. TRAINING REQUIREMENTS

- CIs are responsible for ensuring that all staff are appropriately trained to work on the study. They are also responsible for ensuring that all training records are kept up to date.

- All research staff should be trained in the use of EDGE. Additional training may be required in the use of new workflows as they are implemented; in such cases the user should contact their relevant EDGE super user or the R&I office.

  The Research Department, will endeavour to notify staff of SOP developments that may be relevant to them. SOPs are available on the research department website. Updates on SOPs will feature in research newsletters and communications and will be disseminated at local research meetings. It is the responsibility of all research active staff to ensure that they read the updates that are be relevant to them.

  When a new SOP is authorised, or when an existing SOP is revised, self directed training must be carried out by all staff to which the SOP is relevant, and this training documented in their training record. A template is provided to support this process. A study specific SOP training plan will be developed for investigators on high-risk PHU Sponsored studies.

  Staff should take time to read and fully understand the SOP and relevant documents, ensuring that they are able to implement the SOP when required. If clarification is needed, then the trainee should approach their line manager and the SOP controller who will arrange additional training. All staff should complete their training prior to the published implementation date which will normally be between 2-6 weeks after publication.

  All staff are responsible for maintaining their own SOP training records and copies must be made available to line managers, the SOP controller or study monitors on request.

8. REFERENCES AND ASSOCIATED DOCUMENTATION

Associated Documents

- Notification of Substantial Amendment (Available on IRAS)
- Notification of non-substantial Amendment (Available on the HRA website)

Reference

- HRA Website http://www.hra.nhs.uk/
- MHRA Website https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
- IRAS Website IRAS Help - Maintaining your approvals - Amendments for projects conducted in NHS/HSC (myresearchproject.org.uk)

9. VERSION HISTORY LOG

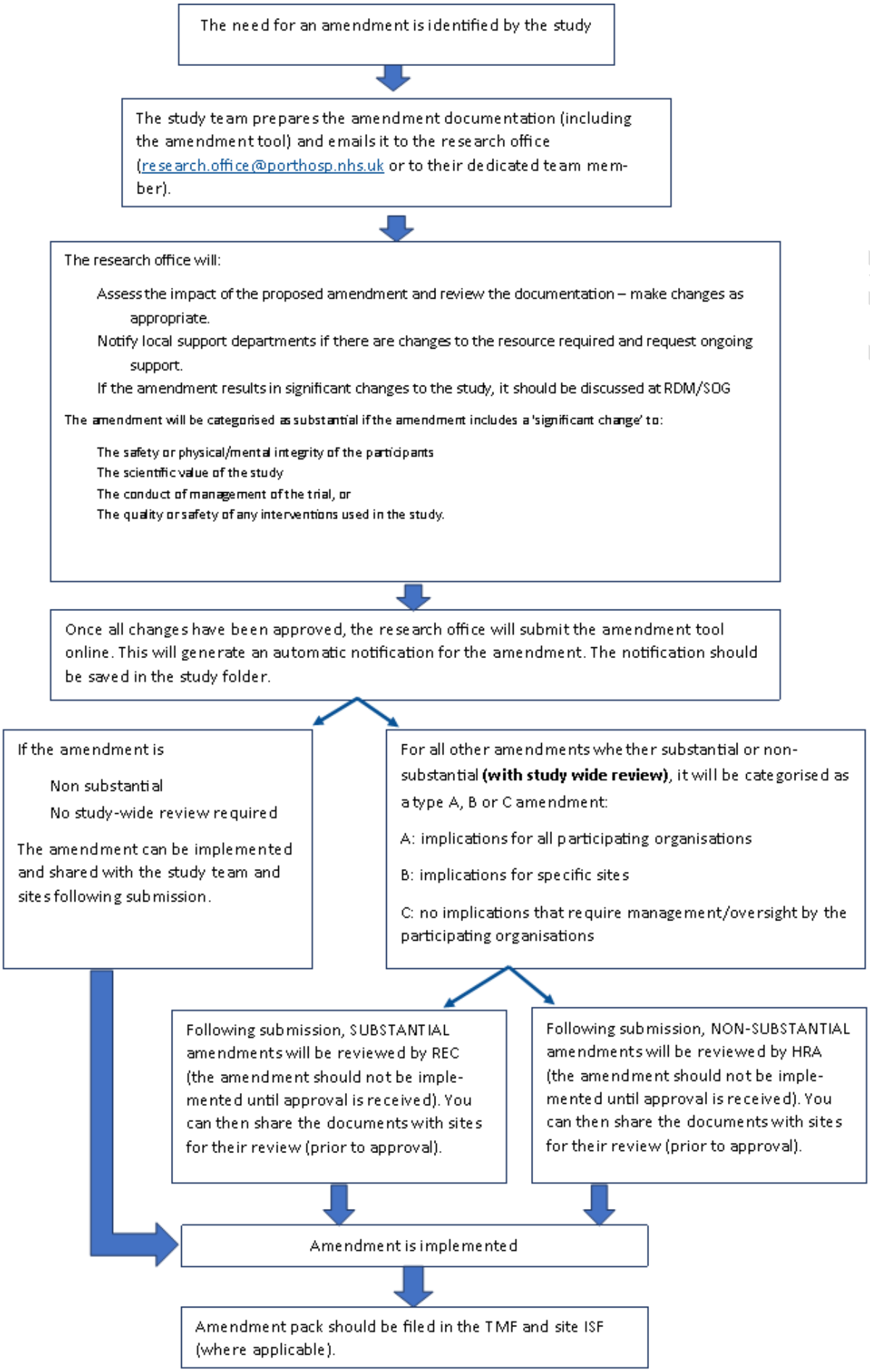
This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of Significant Changes
V1.0	23 May 2016	New document
V2.0	05 Oct 2017	Removal of the amendment categorisation 'minor', this these are now known as non-substantial. Redefined Category C amendment. Expanded the definition of the

		Study team to include PI, lab and pharmacy staff. Point 6.4 addition of the statement that amendments not requiring REC review should be submitted to the HRA.
V3.0	25 September 2023	Addition of the use of EDGE workflows to capture the steps in the amendment process. Renamed 'trial teams' to 'study teams'. Updates to reflect HRA/MHRA process updates (use of Amendment Tool, single submission etc.) Above updates reflected in flow chart also Some responsibilities remapped to the Research office to reflect what happens in practice Flow chart updated

10. APPENDICES

10.1 Amendment Flow Chart for PHU Sponsored Studies


The need for an amendment is identified by the study
The study team prepares the amendment documentation (including the amendment tool) and emails it to the research office (research.office@porthosp.nhs.uk or to their dedicated team member).
The research office will:
Assess the impact of the proposed amendment and review the documentation – make changes as appropriate.
Notify local support departments if there are changes to the resource required and request ongoing support.
If the amendment results in significant changes to the study, it should be discussed at RDM/SOG
The amendment will be categorised as substantial if the amendment includes a 'significant change' to:
The safety or physical/mental integrity of the participants
The scientific value of the study
The conduct of management of the trial, or
The quality or safety of any interventions used in the study.
Once all changes have been approved, the research office will submit the amendment tool online. This will generate an automatic notification for the amendment. The notification should be saved in the study folder.
If the amendment is
Non substantial
No study-wide review required
The amendment can be implemented and shared with the study team and sites following submission.
For all other amendments whether substantial or non-substantial (with study wide review), it will be categorised as a type A, B or C amendment:
A: implications for all participating organisations
B: implications for specific sites
C: no implications that require management/oversight by the participating organisations
Following submission, SUBSTANTIAL amendments will be reviewed by REC (the amendment should not be implemented until approval is received). You can then share the documents with sites for their review (prior to approval).
Following submission, NON-SUBSTANTIAL amendments will be reviewed by HRA (the amendment should not be implemented until approval is received). You can then share the documents with sites for their review (prior to approval).
Amendment is implemented
Amendment pack should be filed in the TMF and site ISF (where applicable).

CONFIRMATION OF SOP TRAINING RECORD

A copy of this record may be kept in your personal training file to confirm your training in a specific SOP. The research department or your line manager may request copies to verify your training. If required by a study Sponsor a record may also need to be kept in the Trial Master Files (TMF) or Investigator Site Files (ISF).

SOP Details: To be completed by the SOP Controller	
Title of SOP	Management of Amendments in PHU Sponsored Studies
Reference Number	PHU/RDSOP/016
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Implementation Date	09 October 2023

Personnel Details	
Name	
Job Title & Research Role	
Date of Training	
Nature of Training	Self Directed/Delivered by etc
Records of any meetings to clarify details in SOP	

Signatures
I confirm that I have read and consider myself to be sufficiently trained in the above Standard Operating Procedure with regards to my individual roles and responsibilities Signature of Trainee …… Date ……
I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date …… .

Additional Notes & Signatures
Signature of Trainer (where appropriate) I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date ……..