Portsmouth Hospitals NHS
NHS Trust

Standard Operating Procedure (SOP) for Management of Amendments in PHT Sponsored Studies

For Completion by SOP Author	
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Document Author(s)	Laura Marshall, Research Trials Manager
Document Reviewer(s)	Alice Mortlock, Research & Quality Manager Elaine Baddeley, Research Coordinator Anna Cunnington, Research Coordinator Beth Giddins, Research Coordinator

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The definitive versions of all Portsmouth Hospitals Trust SOPs, Templates and Forms for Research are online at http://www.porthosp.nhs.uk/research-department

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

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

The Health Research Authority (HRA) defines a substantial amendment 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.'*

The Health Research Authority (HRA) defines a non-substantial amendment 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 to a study are required to be submitted to the following, before implementation;

- The Sponsor (Portsmouth Hospitals NHS Trust) for review and confirmation of continued Sponsorship
- 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.

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 Procedures for all amendments to studies Sponsored by Portsmouth Hospitals NHS Trust (PHT) 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 PHT, in which a change/addition to the original REC/MHRA application and approved study documentation is planned.

This SOP does not apply to externally Sponsored research studies.

This SOP should be followed by:

- All CI's / trial teams running single centre or multicentre studies Sponsored by PHT.
- All Research and Innovation Office personnel who are responsible for receiving and distributing planned amendments to the appropriate office members or reviewing the planned amendments for suitability and issuing continued Sponsorship on behalf of the Trust.

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 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 procedure then approval must be sought in writing from the Director of Research.

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

Term	Definition
PHT Sponsored Studies	Studies which Portsmouth Hospitals 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*
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	An Amendment to a research study that ALL participating NHS organisations are expected to consider.
HRA Category B amendment	An Amendment to a research study that only those participating NHS organisations affected by the amendment are expected to consider.

HRA Category C amendment	An amendment that has no implications that require management or oversight by the participating NHS organisations.
Trial Team	Includes any of the following: Chief Investigator (CI), Principal or co investigator (PI) Trial Coordinator, Trial Manager, Data Manager, Statistician, Co-Investigators and Research Nurses, laboratory team, pharmacy team
Devolved Nations/Administrations	England, Scotland, Wales & Northern Ireland.

Abbreviation	**Meaning**
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
HRA	Health Research Authority
ISF	Investigator Site File
IRAS	Integrated Research Application System
MHRA	Medicines and Health products Regulatory Agency
PHT	Portsmouth Hospitals NHS Trust
REC	Research Ethics Committee
R&I	Research & Innovation (Office)
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee

5. DUTIES AND RESPONSIBILITIES

The following parties are responsible as outlined below:

The Trial Team (of a PHT Sponsored study) should:

- Inform the PHT R&I Office of all planned amendments and associated updated documents prior to submission to the regulatory authorities unless related to urgent safety measures.
- Notify the Trial Steering Committee (TSC) and/or Data Monitoring Committee (DMC) should their terms of reference request notification and review of amendments.
- Consider whether an amendment will have any impact on the Case Report Form (CRF) and database and to contact the Data Management team accordingly.
- Prepare an amended protocol and any related documentation, as required, for submission and gain the necessary regulatory approvals and confirmation of capacity and capability from all participating sites, before implementation.
- Ensure that all participating sites, if applicable, are notified of an amendment and its categorisation (A, B or C) in a timely manner.
- Ensure any devolved administrations (Scotland, Northern Ireland & Wales) involved in the study are informed of an amendment in a timely manner, following categorisation by the HRA.

- Ensure that all relevant documentation and pertinent correspondence relating to amendments are filed in the Trial Master File (TMF).

- 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 and update/maintain the study version log following any amendments.

PHT Research & Innovation Office (Sponsor) should:

- Regularly check the research office mailbox for information on any planned amendments and track the progress of each amendment.

- Review each planned amendments 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.

- Authorise the submission of amendments to PHT Sponsored studies that are deemed appropriate and issue continued capacity & capability once regulatory approvals are received.

- To provide advice/assistance with the preparation of protocol amendments and related documents to the trial team, as required.

6. PROCESS

6.1. Preparation of the Amendment Documentation

- The CI/Trial team has identified the need for an amendment.

- This should be discussed with the TSC, DMC & Statistician, where required.

- The CI and/or trial team should ensure that all study documents affected by the proposed amendment are updated and saved as a new 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.

- *If the Trial team considers the amendment to be **substantial** they should prepare and provide to the R&I Office:*

  - All new or updated trial documents with tracked changes
  - A Notice of Substantial Amendment form (NoSA - created in IRAS)
  - A covering letter or email which includes a list of the updated documents, version numbers and dates. *NB: If there are extensive protocol changes it may be necessary to summarise in the letter/email what these changes are.*

- *If the Trial team considers the amendment to be **non-substantial** they should prepare and provide to the R&I Office:*;
  - A notice of non-substantial amendment form (available on the HRA website)
  - All updated trial documents with tracked changes.

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

- All planned amendments whether considered to be substantial or non-substantial should be sent to the R & I Office via research.office@porthosp.nhs.uk for review and approval prior to submission to any regulatory authorities and implementation.

6.3. Amendment Impact Review & Continued Sponsorship

- The R&I Office will check that all required documentation has been submitted for review and will request any outstanding documents as required.

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

- The R&I Office will review the amendment and associated documentation to:

  - Ensure that the participants safety and rights are still protected
  - Ensure that it meets the needs of the trial
  - 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
  - Check if the changes have any impact on support departments for the trial including; pharmacy, pathology, and / or radiology
  - Check if any changes to the study contract is needed (if applicable)
  - 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.

- As part of the review process the R&I Office will confirm whether the amendment is substantial or non-substantial.

- The R&I Office will complete the initial amendment review.

- Any suggested or required changes to the updated documentation will be provided to the CI or trial team using the tracked changes mode to allow quick review and agreement of the changes.

- Once the proposed amendment and all associated documentation has been reviewed and finalised, the R&I office will send an email to the CI and/or trial team confirming continued Sponsorship and authorisation for submission to the regulatory bodies (REC and/or MHRA) or notification to HRA and implementation of the amendment if it is non-substantial.

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

- All substantial amendments that were approved by a REC should be submitted to the REC that provided favourable opinion and to the MHRA (if CTIMP or medical devices study) by the trial team as soon as possible after continued Sponsorship and authorisation for submission has been given by PHT R&I Office. (Submissions are made to REC by email. Submissions to MHRA are made via the CESP system which the R&I Office can undertake on your behalf.) Amendments that do not require REC review should be submitted to the HRA.

- Where the study did not require REC approval, substantial amendments should be submitted to the HRA.

- 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.

- All non-substantial amendments should be notified to the HRA amendments team via email (hra.amendments@nhs.net)

- For multicentre studies, if 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 trial team, following authorisation.

- Specific guidance on the format and content of amendment submissions can be found on the HRA and MHRA websites. Alternatively the R&I Office can help facilitate the submission.

- Within 5 working days of submitting an amendment the HRA will provide confirmation of the amendment category as A, B or C.

- The REC and MHRA have 35 days from acknowledgement/valid receipt to review a substantial amendment.

    - The REC/HRA letter will confirm the documents received, including dates and version numbers. These should be checked as the approval will be based on the information contained in this letter.

    - The MHRA will confirm acknowledgement of the amendment and state the 35 day timeline for review.

- Written confirmation will be provided to approve or reject a substantial amendment by both regulatory bodies.

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

- If the amended study is multicentre, it is the duty of the CI / trial team to inform all participating sites of the amendment, following receipt of its catergorisation by the HRA.

- **For Category A or B Amendments:**
  - The CI / trial team should send each relevant participating site (along with their local Research departments), details of the amendment, including the category and any updated documents, in a timely manner.
  - 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 CI / trial team should send the documents related to the amendment to each participating site to file in the Investigator Site Files (ISF).

- Participating sites, including PHT, should then assess the amendment for local continued capacity and capability, and raise any objections to the Sponsor (PHT) within 35 working days.

- The Trial 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 & capability.

6.6. Receipt of Regulatory Approvals

- On receipt of regulatory approvals the CI or Trial Team should provide a copy of the approval letters to the PHT R&I Office and any other participating sites.

- 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 PHT R&I Office and participating sites.

- On receipt of these documents the R&I Office will check the document dates/version numbers listed in the approval letter are those of the submitted documents.

- The CI / trial 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 trial team to ensure that all amendment documentation including regulatory approvals is provided to any supporting departments, where appropriate.

7. TRAINING REQUIREMENTS

- CI's 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/

- The Research Dept. will endeavour to notify individuals of SOP developments that may be relevant to them. Updates on SOPs will feature in research newsletters and communications. It is the responsibility of all research active staff to ensure that they read the issued updates that may 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 and delivered to investigators on high risk PHT Sponsored studies when appropriate.

- 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 of the SOP.

- 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 and sponsors on request.

- A study specific SOP training plan will be developed for investigators on high risk PHT Sponsored studies.

8. REFERENCES AND ASSOCIATED DOCUMENTATION

- Notification of Substantial Amendment (Available on IRAS)
- Notification of non-substantial Amendment (Available on the HRA website)
- Planned Amendment Impact Form
- HRA Website http://www.hra.nhs.uk/
- MHRA Website https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

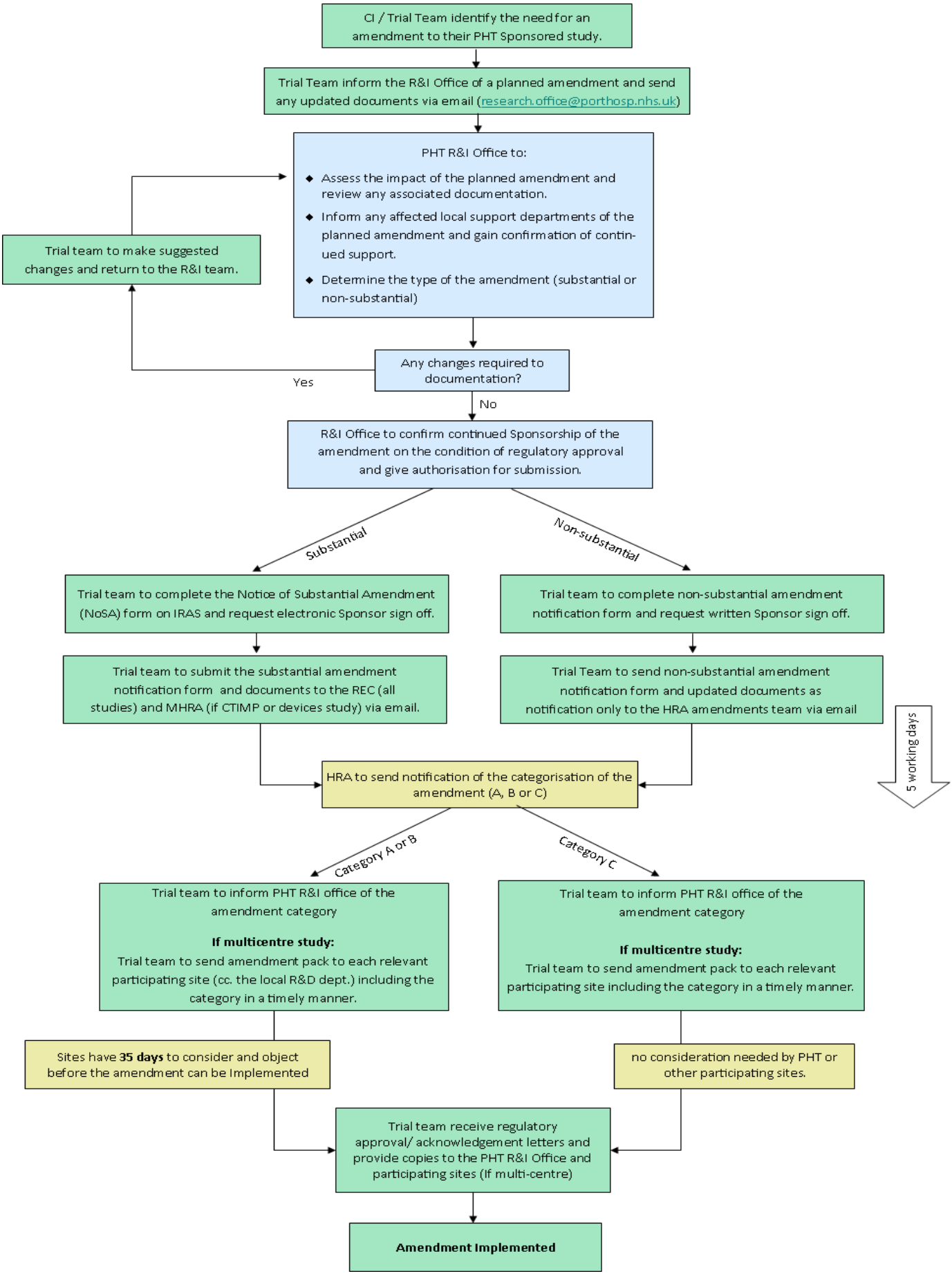
9. VERSION HISTORY LOG

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 Trial 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.

10. APPENDICES

10.1. Amendment Flow Chart for PHT Sponsored Studies



10.2. Training Record

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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 PHT Sponsored Studies
Reference Number	Insert SOP Reference Number. PHT/RDSOP/016
Version	V2.0 5th Oct 2017
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Implementation Date	5th Oct 2017

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 …….

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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 ……..