RD&I	NHS University Hospitals Plymouth NHS Trust **STANDARD OPERATING PROCEDURE**

DO NOT USE THIS SOP IN PRINTED FORM WITHOUT FIRST CHECKING IT IS THE LATEST VERSION

The definitive versions of all UHNPT RD&I Dept SOPs appear online, not in printed form, to ensure that up to date versions are used. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the Trust's website: https://www.plymouthhospitals.nhs.uk/research-sops

Research Study Amendments

SOP No: T8

Version No: 4.0

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Page: **1** of **10**

Last Review Date: Dec 2020 Next review date: Dec 2023

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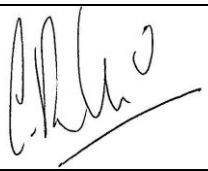
Signature:	
Date:	1st Dec 2020

1 Purpose and Scope

This Standard Operating Procedure (SOP) describes the process for submitting and implementing both substantial and non-substantial amendments for University Hospitals Plymouth NHS Trust (UHNPT) sponsored studies. Principles in this SOP also apply when amendments are made to studies hosted by UHNPT.

Amendments are changes to research after a Research Ethics Committee (REC) favourable opinion has been granted and/or in the case of a Clinical Trial of an Investigational Medicinal Product (CTIMP), the Medicines and Healthcare products Regulatory Agency (MHRA) Clinical Trial Authorisation has been granted. Amendments mat be 'substantial' or 'non-substantial'.

In scope: research sponsored by, and/or hosted by UHNPT.

Definitions

ARSAC	Administration of Radioactive Substances Advisory Committee
CESP	Common European Submission Portal - this system provides a simple and secure mechanism for exchange of information between applicants and the MHRA and other European competent authorities.
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
EDGE Database	The research database used by UHNPT for managing set up and delivery of studies
EudraCT	European Union Drug Regulating Authorities Clinical Trials is the European Clinical Trials Database of all clinical trials commencing in the European Union after 1st May 2004
GCP	Good Clinical Practice
HCA	Health Care Assistants
HRA	Health Research Authority
HSC	Health and Social Care
IRAS	Integrated Research Application System
LCRN	Local Clinical Research Network

MHRA	Medicines and Healthcare products Regulatory Agency
NIHR CRN Portfolio	National Institute for Health Research Clinical Research Network Portfolio
NOSA	Notice of Substantial Amendment
UHNPT	University Hospitals Plymouth NHS Trust
PI	Principal Investigators
RD&I	Research Development & Innovation
REC	Research Ethics Committee
RO	Research Office
SOP	Standard Operating Procedure
Sponsor	The individual, company, institution or organisation, which takes on ultimate responsibility for the initiation, management (or arranging the initiation and management) of and/or financing (or arranging the financing) for that research

2 Who should read this document?

This SOP should be used by Chief Investigators (CIs) and other members of the research team involved in preparing and submitting amendments to UHNPT sponsored studies.

In the case of UHNPT hosted studies, the UHNPT Principal Investigator (PI) can refer to section 3.4 of this SOP ('Implementation of Amendments') for guidance on how to implement amendments at UHNPT.

3 Procedure to Follow

3.1 Sponsor Assessment of Amendments

It is necessary to identify if an amendment is **substantial** or **non-substantial** (please see Appendix A for definitions of substantial and non-substantial amendments). **It is the responsibility of the Sponsor to determine whether an amendment is substantial or non-substantial**, therefore you must liaise with RD&I when determining this classification for UHNPT sponsored studies. RD&I must also review the amendment and any implications it has for the management or delivery of the study.

Please email plh-tr.RD-Office@nhs.net with details of the proposed amendment so that this assessment can be made.

5.2. Preparation and Submission of Amendments

Where a project has Health Research Authority (HRA) approval (this is virtually all NHS research projects), the HRA must be notified of both substantial and/or non-substantial amendments.

(a) Substantial Amendments

I. If the amendment is **substantial** you will have to generate and complete a 'Notice of Substantial Amendment' (NOSA) form though the Integrated Research Application System (IRAS). It will be necessary to have all modified documents including tracked versions for upload along with any further supporting documentation required. NOSA forms must be electronically authorised by both CI and Sponsor *via* IRAS. Sponsor electronic authorisation requests must be requested *via* plh-tr.RD-Office@nhs.net .

II. The method for submitting the amendment differs depending on the nature of the study:

- Where HRA approval for the study included NHS REC review, substantial amendments should then be submitted to REC *via* IRAS.
- Where the REC is in England, REC will notify HRA of the amendment, thus no separate submission to HRA is required. However, where the REC is in Scotland, Wales, or Northern Ireland you should also copy hra.amendments@nhs.net
- Where the project did not require NHS REC review, the substantial amendment should be submitted directly to hra.amendments@nhs.net

III. Substantial amendments for CTIMPs and/or Medical Devices with Clinical Trial Authorisation will require MHRA review in addition to HRA and REC (although not all substantial amendments that require REC review also require MHRA review; you must consult RD&I to determine whether MHRA need to be notified).

IV. Substantial amendments will need to be submitted to MHRA using the European Commission form. This document is available from the EudraCT website or can be downloaded from the Amendment tab in IRAS. The form must be accompanied by an amended EudraCT application. Submission to MHRA is done outside of IRAS using the Common European Submission Portal (CESP) which is administered by the RD&I Office. Please liaise with RD&I and refer to the MHRA website for the most up to date guidance: www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

V. Once a substantial amendment has been identified, it is important that the process of preparation and submission is done by the RD&I or CTU staff proactively and in a timely fashion. The RD&I Governance team will review the substantial amendment documents before authorisation.

VI. A substantial amendment covering the changes made as part of the Urgent Safety Measure must be submitted within 3 days of implementation. A substantial amendment covering the changes made as part of a response to a Serious Breach will be processed within 2 weeks of the notification to the MHRA.

(b) Non-substantial Amendments

I. If the amendment is **non-substantial** a 'Notification of Non-Substantial/Minor Amendment' form should be completed by the CI. The template form can be found in resources on the HRA website: http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/preparing-amendments/

II. The notification form should be submitted, with any supporting documentation, by e-mail to hra.amendments@nhs.net . Please include the IRAS ID for your project in the subject line of the e-mail along with the text “Notification of Amendment” and ensure that your email includes your contact details (e-mail and phone number).

3.3. Categorisation of Amendments

(a) When amendments (both substantial and non-substantial) are submitted to REC/HRA, the HRA will categorise the amendment as either category A, B, or C within **5 business days**.

- **Category A:** Amendment that impacts or affects all participating NHS organisations.
  All participating NHS organisations are expected to consider the amendment to determine whether they are able to continue to support the study.
- **Category B:** Amendment that impacts or affects specific participating NHS organisations.
  Only those participating NHS organisations affected by the amendment are expected to consider the amendment to determine whether they are able to continue to support the study.
- **Category C:** Amendment that has no impact on NHS organisations.
  Participating NHS organisations are NOT expected to consider the amendment.

(b) The applicant will be informed of this categorisation, and if there are participating NHS/Health and Social Care (HSC) sites in other nations, the HRA will share the amendment and categorisation with the other participating nations.

(c) It is the applicant’s responsibility to communicate the categorisation and the amendment to English sites (i.e. the local research team, the RD&I office and the LCRN, where appropriate – contact details for RD&I offices and Local Clinical Research Networks (LCRNs) are available *via* http://www.rdforum.nhs.uk/content/contact-details/).

(d) The CI must send the amendment and the categorisation information to participating NHS organisations so that, where necessary, arrangements can be put in place to

continue the site's capacity and capability to deliver the study. Instructions will be detailed further in the categorisation email from the HRA, thus this letter must be read carefully and the instructions followed.

3.4. Implementation of Amendments

(a) There can be 'presumed implementation' following regulatory approval, unless an objection to the amendment is raised by an NHS organisation within a reasonable time. Presumed implementation of an amendment can occur after **35 days** of notifying the site of that amendment (subject to other regulatory approvals being in place), unless the NHS organisation raises an objection within this period.

Details will be outlined in the HRA categorisation letter as to which sites need to be given 35 days before presumed implementation, thus this letter must be read carefully. As a rule of thumb, the case will usually be that:

- For **Category A and B amendments**, NHS organisations have a maximum of **35 days** to raise an objection; otherwise the amendment can be implemented after the 35 day period (Subject to regulatory approvals being in place).
- For **Category C amendments** can be implemented immediately (subject to regulatory approval being in place).

(b) In all cases, the CI must ensure that amendments and any supporting documentation are passed to the local PIs and their research teams at all sites.

(c) Where UHNPT are a site, RD&I will review all category A amendments once the categorisation letter is received, and aim to issue an acknowledgement of the amendment once it has been reviewed (or raise objection where necessary).

(d) Acknowledgement will outline when the amendment can be implemented (e.g. immediately, if HRA approval is already in place, or as soon as Sponsor confirms HRA approval is subsequently in place). If no acknowledgement is sent by RD&I within **35 days** of RD&I being notified of the amendment and its' categorisation, presumed implementation can occur.

(e) Category B amendments will also be reviewed, where UHNPT is deemed to be an organisation affected by amendment.

3.5 Urgent Safety Measures

The Sponsor, CI or PI may take appropriate Urgent Safety Measures in order to protect research participants against any immediate hazard to their health or safety. Approval is not required *before* taking these measures.

(a) The REC, MHRA (in the case of CTIMPs) and RD&I office should be notified within **3 days** of taking the measures, detailing the measures taken and the reasons why.

(b) In the case of CTIMPs, the MHRA's Clinical Trial Unit should be phoned on 020 3080 6456 to discuss the issue with a safety scientist, ideally **within 24 hours.** This should then be submitted to the MHRA in writing within **3 days** (as above) - MHRA will provide guidance for this submission when you phone. In cases where UHNPT are sponsor, you must ensure you liaise with RD&I throughout this process.

(c) Where Urgent Safety Measures are taken and the participant suffers harm, safety reporting procedures should be followed. Please refer to SOP T7_*Urgent Safety Measures* for further guidance.

(d) Where an Urgent Safety Measures represents a substantial amendment to the protocol or other documentation, a substantial amendment will need to be prepared and submitted following the procedures outlined in this SOP.

3.6 Notifying amendments to ARSAC

The Administration of Radioactive Substances Advisory Committee (ARSAC) should be notified for information of any changes to the administration of radioactive materials during a study, such as:

- Dose changes
- New modalities
- New classes of study participant

These changes will normally meet the criteria for substantial amendments. Please provide ARSAC with a copy of the Notice of Substantial Amendment when this is submitted to the REC, together with any supporting documentation (e.g. protocol, patient information sheets).

With a multi-site study, it is not necessary for the ARSAC certificate holder to notify ARSAC; the ARSAC certificate holder at the lead site or the trial co-ordinator can provide a single notification. ARSAC will contact certificate holders if further information is require and/or the changes could affect existing certification.

When applying for a study amendment if you are in doubt or unsure at any time in the process contact RD&I for help and advice.

4 Document Ratification Process

The review period for this document is set as ***default of three*** years from the date it was last ratified, or earlier if developments within or external to the Trust indicate the need for a significant revision to the procedures described.

This document will be approved by the ***RD&I Manager or their Deputy***.

Non-significant amendments to this document may be made, under delegated authority from ***a Senior RD&I manager***, by the nominated author. These must be ratified by ***a Senior RD&I manager***.

Significant reviews and revisions to this document will include a consultation with ***appropriately knowledgeable staff***. For non-significant amendments, informal consultation will be restricted to ***staff*** who are directly affected by the proposed changes.

Dissemination and implementation

4.1. Dissemination of this SOP

4.1.1. New SOPs and new versions of existing SOPs: The Research Governance Manager will be responsible for ensuring authorised SOPs are uploaded on the RD&I intranet site. Internal Trust Staff are expected to use the RD&I intranet site to access latest versions of SOPs and to check the website regularly for updates.

Notice of new or amended procedural documents that have undergone a major amendment will be given *via* the following routes:

- Inclusion in the Trust weekly e-bulletin Vital Signs
- Direct email to Trust Researchers and or teams

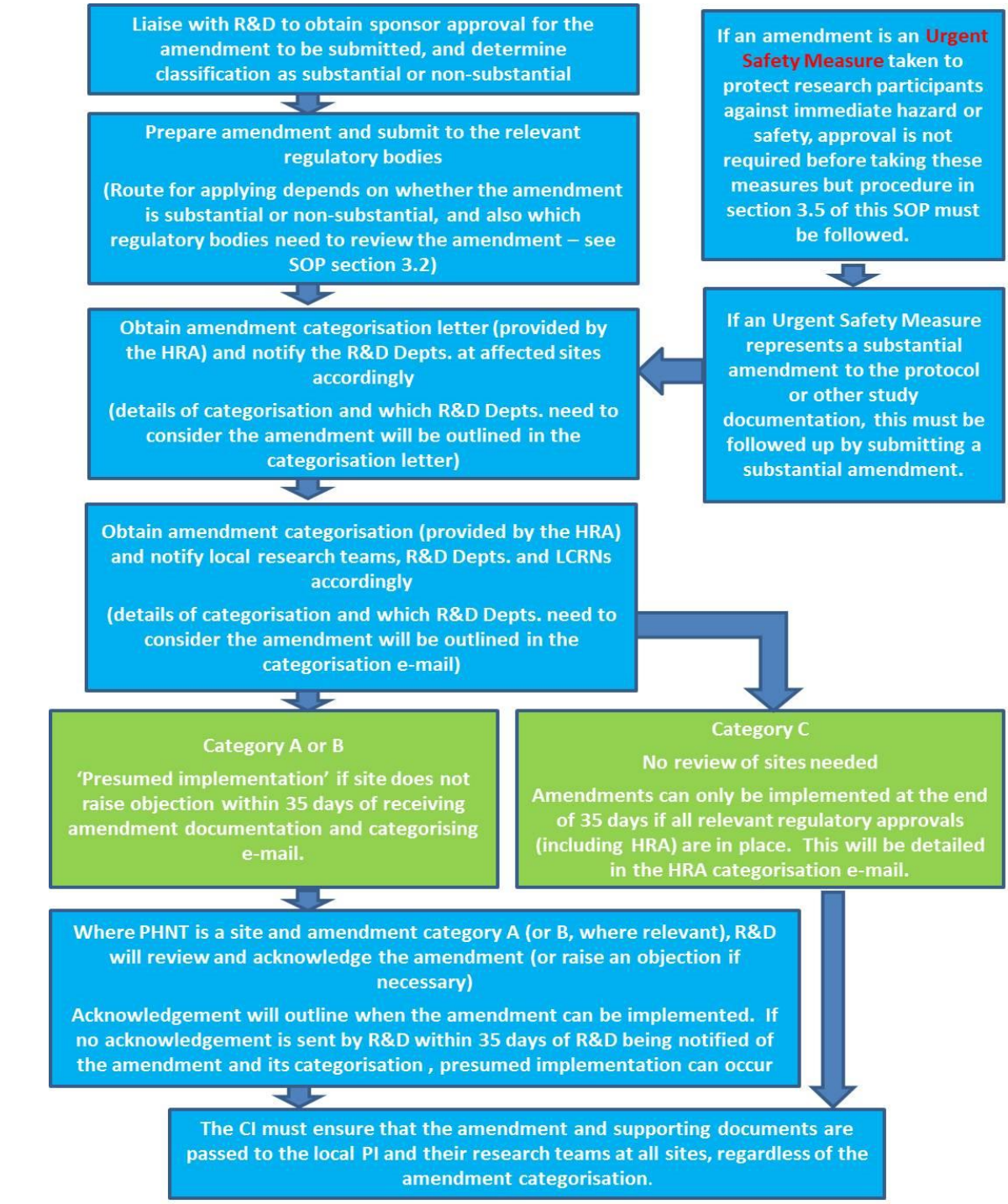
4.2. Training in this SOP

4.2.1. All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.

5 Reference material

Health Research Authority
Process for handling UK study amendments
www.hra.nhs.uk/documents/2014/11/guide-researchers-uk-process-handling-uk-study-amendments

Appendix: Amendment flowchart — Appendix 1



6 Amendment History

Version Number:	4.0
Date of Amendment:	Dec 2022
Details of Amendment:	Added: V. Once a substantial amendment has been identified, it is important that the process of preparation and submission is done by the RD&I or CTU staff proactively and in a timely fashion. The RD&I Governance team will review the substantial amendment documents before authorisation. VI. A substantial amendment covering the changes made as part of the Urgent Safety Measure must be submitted within 3 days of implementation. A substantial amendment covering the changes made as part of a response to a Serious Breach will be processed within 2 weeks of the notification to the MHRA.

Version Number:	3.1
Date Of Amendment:	Jan 2019
Details Of Amendment:	Updated Trust and Dept. name including Dept. e-mail address. Reduce signature requirement to single senior RD&I Manager.

Version Number:	3.0
Date Of Amendment:	Aug 2017
Details Of Amendment:	Updated SOP template and numbering system. Reviewed and updated SOP.

Version Number:	2.0
Date Of Amendment:	Jan 2015
Details Of Amendment:	Updated SOP and added new section on the implementation of a trial protocol amendment and HRA flow diagrams of the amendment process.

Version Number:	1.1 (minor amendment)
Date of Amendment:	Mar 2012
Details of Amendment:	Cover page - Change of SOP location address.