University of Hertfordshire

AMENDMENTS TO NHS RESEARCH STUDIES

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for Preparation and Approval of Amendments to Clinical Trial Documentation for University of Hertfordshire Sponsored/co-sponsored and Hosted Clinical Trials

SOP Number: gSOP-09-01	**Effective Date:** 26th April 2018
Version Number: 1.0	**Review Date:** 3 years (or as required)

1.0 BACKGROUND

This is a University of Hertfordshire standard operating procedure. University of Hertfordshire (UH) acknowledges West Hertfordshire Hospitals NHS Trust (WHHT) Research & Development (R&D) which has allowed UH to use the SOPs developed by WHHT where possible, modified for local implementation.

This document sets out the procedures to be followed by all UH staff who are responsible for submitting and implementing amendments for research studies run at UH. It provides clear guidance on the procedure of classifying and seeking approval for amendments.

Where there are potential conflicts between different collaborating organisations' SOPs, project level working instructions should be developed, to determine precedence.

Notification of amendments

For UH Sponsored clinical studies ensure that all amendments to clinical trial documentation are submitted to the CTSNMG for substantiality decision prior to Research Office submission for Sponsor approval as well as the applicable Research Ethics Committee (REC) and/or the Medicines and Healthcare Products Regulatory Agency (MHRA) documentation prior to implementation. For co-sponsored studies all documentation should also be submitted to the R&D office.

2.0 PURPOSE

This SOP describes the process for submitting and implementing both substantial and non-substantial amendments for UH sponsored/co-sponsored studies. Principles in this SOP also apply when amendments are made to studies hosted by UH.

Amendments are changes to research after a REC favourable opinion has been granted and/or in the case of a Clinical Trial of an Investigational Medicinal Product (CTIMP), MHRA Clinical Trial Authorisation has been granted. They can be 'substantial' or 'non-substantial'.

3.0 APPLICABLE TO

This applies to all staff involved in clinical research sponsored/co-sponsored by UH, including but not limited to: Chief Investigators, Principal Investigators, Research Fellows, Consultants, Statisticians, Clinical Trial Pharmacists, Research Managers, Research Nurses, Clinical Trial Practitioners, Allied Health Professionals, Trial Coordinators, Clinical Studies Officers, Data Managers, Research Assistants and Students.

4.0 RESPONSIBILITIES

The Sponsor is responsible for determining whether an amendment is substantial or non-substantial.

The chief investigator is responsible for ensuring all amendments to clinical trial documentation are submitted, processed and approved by the appropriate review bodies.

5.0 PROCEDURE

5.1 Sponsor Assessment of Amendments

It is necessary to identify if an amendment is substantial or non-substantial. It is the responsibility of the Sponsor to determine whether an amendment is substantial or non-substantial, therefore you must liaise with the CTSNMG/Research Office and/or the NHS R&D Department when determining this classification for UH sponsored studies. The CTSNMG/Research office and/or the NHS R&D department must also review the amendment and any implications it has for the management or delivery of the study. Sponsor approval to notify/submit an amendment is required.

5.2 Preparation and Submission of Amendments

The HRA must be notified of both substantial and non-substantial amendments

5.2.1 Substantial Amendments

- If the amendment is deemed substantial a 'Notice of Substantial Amendment' (NOSA) form will need to be completed through 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.

- For non-CTIMPs NOSA forms must be electronically authorised by both CI and Sponsor via IRAS

- For CTIMPs, the EU NOSA forms must be electronically authorised by the Sponsor, CI, or another person authorised by the Sponsor, via IRAS

- 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 in 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

- Substantial amendments for CTIMPs and/or Medical Devices with Clinical Trial Authorisation (CTA) 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 the CTSN/R&D to determine whether MHRA need to be notified).
- 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. Please liaise with the CTSN/R&D 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

5.2.2 Non-Substantial Amendments

- 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/

- The notification should be submitted, with any supporting documentation, by email to hra.amendments@nhs.net. Please include the IRAS ID for your project in the subject line of the email along with the text 'Notification of Amendment' and ensure that your email includes your contact details

5.3 Categorisation of Amendments

5.3.1 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.

5.3.2 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 other participating nations.

5.3.3 It is the applicant's responsibility to communicate the categorisation and the amendment to English

sites (i.e. the local research team, the R&D office and the CRN, where appropriate - contact details for R&D offices and CRNs are available via http://www.rdforum.nhs.uk/content/contact-details/

5.3.4 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.

5.4 Implementation of Amendments

5.4.1 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 raised an objection within this period or requests additional review time.

Details will be outlined in the HRA categorisation letter as to which sites need to be given 35 days before presumed implementation.

- 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)

5.4.2 In all cases, the CI must ensure that amendments and any supporting documentation are sent to the local PIs and their research teams, and the local R&D office at all affected sites. Contact details for all R&D offices are available at http://www.rdforum.nhs.uk/content/contact-details/

5.4.3 Where UH are a site, the Research Office/CTSN will review all Category A and B amendments once the categorisation email is received and aim to confirm continuing capacity and capability to host the study once it has been reviewed (or raise objection where necessary).

5.4.3 The confirmation of continuing capacity and capability email will confirm that the amendment is ready to be implemented at the site. The Sponsor or CI will then let the local site team know when they are ready for the amendment to be implemented (if not already made clear in the amendment submission). If no acknowledgment or request for additional review time is sent within 35 days of being notified of the amendment and its categorisation, presumed implementation can occur.

5.5 Urgent Safety Measures (USM)

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

- The REC, MHRA (in the case of the CTIMPs) and CTSN/NHS R&D office should be notified within 3 days of taking the measures, detailing the measures taken and the reasons why
- 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 - MHRA will provide guidance for this submission. In cases

where UH are sponsor/co-sponsor, you must ensure you liaise with the CTSN/Trust R&D throughout this process.

- Where USMs are taken and the participant suffers harm, safety reporting procedures should be followed
- Where a USM represents a substantial amendment to the protocol or other documentation, a substantial amendment will need to be prepared and submitted following procedures outlined in this SOP

6.0 RELATED DOCUMENTS

- Health Research Authority - Process for handling UK study amendments www.hra.nhs.uk/documents/2014/11/guide-researchers-uk-process-handling-uk-study-amendments
- IRAS guidance for substantial and non-substantial amendments https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx

7.0 APPENDICES

- Appendix 1 - Definitions
- Appendix 2 - Flowchart of Amendment Process
- Appendix 3 - Examples of Substantial and Non-Substantial Amendments

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**

9.0 AUTHORSHIP & APPROVAL

Author

Signature **Date**

Pro-Vice Chancellor (Research & Enterprise) Approval

Signature **Date**

10.0 AGREEMENT

Please detach and retain within your training files

I have read and understood the contents and requirements of this SOP (gSOP-09-01) and accept to follow UH policies in implementing it.

Recipient

Signature: ……...……Date: ……..

Name & Position: ……...……

Appendix 1: Definitions

Chief Investigator

A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or control) to evaluate the effects of those interventions on health outcomes.

Clinical Trial Authorisation (CTA)

Regulatory approval issued by a Competent Authority to conduct a clinical trial within a Member State.

Clinical Trial of Investigational Medicinal Product (CTIMP)

A study that looks at the safety or efficacy of a medicine/food stuff/placebo in humans as defined by the Medicines for Human Use Regulations (2004).

Investigational Medicinal Product (IMP)

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. This includes a medicinal product which has a marketing authorisation but is, for the purpose of the trial

- Used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,
- Used for an indication not included in the summary of product characteristics under the authorisation for that product,
- Used to gain further information about the form of that product as authorised under the authorisation

Non-Substantial Amendment

Minor changes to the original REC application, to the protocol, or any other supporting documentation that will NOT 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.
- The quality or safety of any investigational medicinal product used in the trial

Principal Investigator (PI)

A Registered Physician, Dentist, Pharmacist or Registered Nurse who has responsibility for the conduct of the trial at a host site.

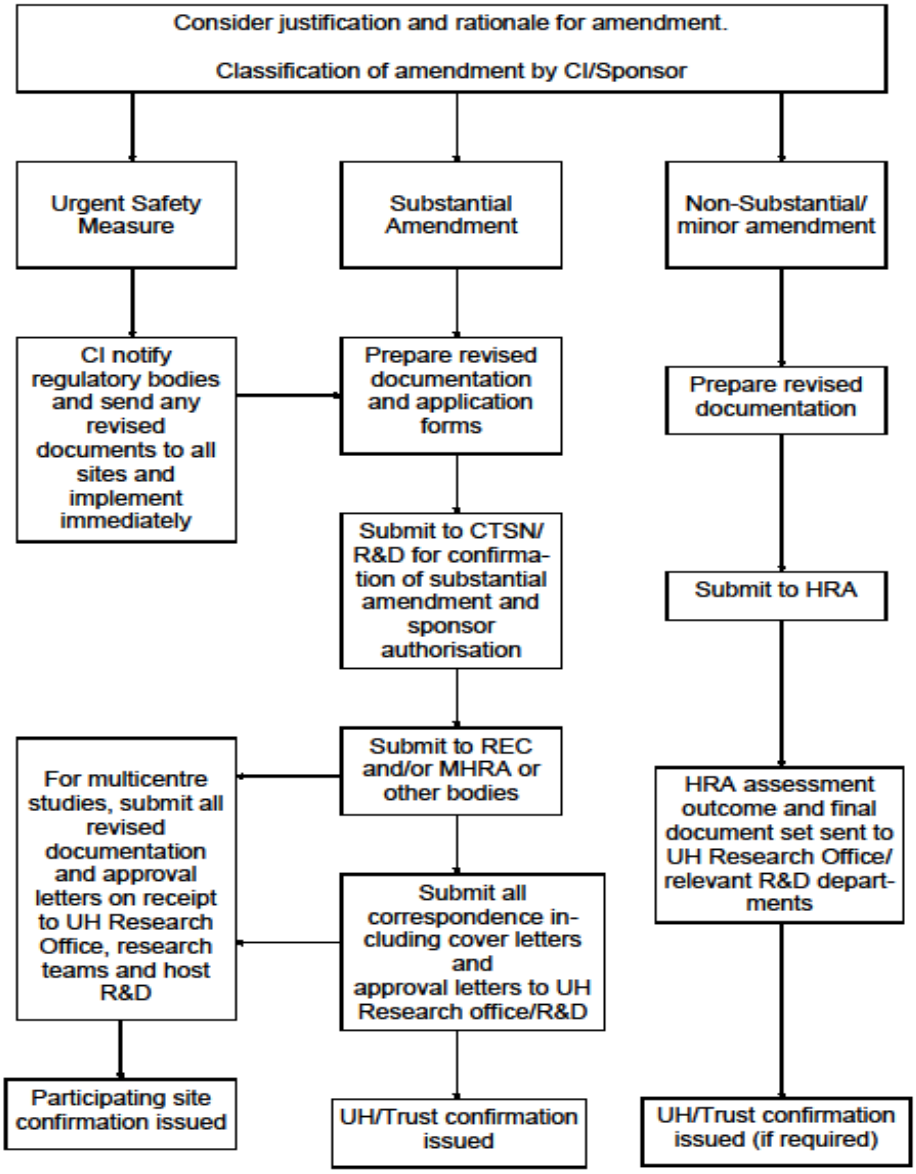
Substantial Amendment

Amendments to the original REC application, 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;
- The quality or safety of any investigational medicinal product used in the trial

The Medicines & Healthcare products Regulatory Agency (MHRA)
UK Competent Authority responsible for regulation of clinical trials.

Appendix 2: Flowchart of Amendment Process



Appendix 3: Examples of Substantial and Non-Substantial Amendments

Term	Examples (as defined by HRA)
Substantial Amendment	Changes to the design or methodology of the study, or to background information affecting its scientific value. Changes to the procedures undertaken by participants Any change relating to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers. A change of Sponsor(s) or Sponsor's legal representative. Appointment of a new CI or key collaborator. A change to the insurance or indemnity arrangements for the study. Inclusion of a new trial site (not listed in the original application) in a CTIMP. Appointment of a new PI at a trial site in a CTIMP. Temporary halt of a study to protect participants from harm, and the planned restart of the study following a temporary halt. A change to the definition of the end of study. Any other significant change to the protocol or the terms of the REC application.
Non-Substantial Amendment	Minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications, updates of

	the investigator's brochure (unless there is a change to the risk/benefit assessment for the trial). Changes to the CI's research team (other than appointment of key collaborators). Changes to the research team at particular trial sites (other than appointment of a new PI in a CTIMP). Changes in funding arrangements. Changes in the documentation used by the research team for recording study data. Changes in the logistical arrangements for storing or transporting samples. Inclusion of new sites and investigators in studies other than CTIMPs. Extension of the study beyond the period specified in the application form.