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-09-02	**Effective Date:** 16th March 2022
Version Number: 2.0	**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 and approved by Health Research Authority (HRA). 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.

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 an applicant has received the initial approvals and 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 or authorised delegate is responsible for ensuring that the amendment tool is completed correctly, comparing the outcomes against their own expectations of how the amendment should be processed and to approve the Amendment Tool for the CI/PI to proceed.

5.0 PROCEDURE

5.1 Preparation and Submission of Amendments

The Amendment Tool applies to all project-based research (defined as any of the IRAS Project Filter question 2 categories except for RTBs and RDBs).

The Amendment Tool is used to prepare both substantial and non-substantial amendments and automatically categorises the amendment. Further ethical review is required for any substantial amendment and a favourable opinion must be obtained prior to implementing the amendment.

5.1.1. Urgent Safety Measures (USM)

If the amendment requires immediate implementation due to safety concerns this must be discussed with the MHRA, in the case of a CTIMP, as soon as possible and a formal amendment submitted within three days.

For non-CTIMP research, the Chief Investigator must notify the main REC immediately of any USMs and in any event within three days. NHS R&D offices will also require notification in accordance with local policies/procedures.

5.1.2 Preparation of Amendments

- Both substantial and non-substantial amendments must be prepared using the Amendment Tool and submitted online for review. The Amendment Tool can be used for all amendments to all project-based research. The completed Amendment Tool and amended documents should be submitted online as directed on the “Submission Guidance” tab of the tool.

- For CTIMP and/or Medical Devices with Clinical Trial Authorisation (CTA) amendments that require submission to the MHRA, the Amendment Tool must be completed and submitted alongside any other appropriate documentation. Alternatively, for ‘bulk’ amendments to MHRA only, where the same change affects a large number of trials (e.g. change to the reference safety information in an investigator’s brochure), the Annex 2 form which is available from the MHRS website, can still be completed and submitted to the MHRA.

- For both substantial and non-substantial amendments, when complete, the amendment tool should be sent to the sponsor to complete the declaration section (section 3). For substantial amendments, the locked Amendment Tool should then be uploaded for review online via online amendment submission. Amendments must not be submitted without prior authorisation from or on behalf of the sponsor.

5.1.3 Submission of Amendments

- The method for submitting the amendment is as follows:
    - All types of project submit amendments to the REC and/or HRA and HCRW Approval/ NHS/HSC R&D coordinating functions via online amendment submission (http://www.myresearchproject.org.uk/amendment).
    - Once the Amendment Tool (or Notice of Substantial Amendment form in the case of RTB and RDB projects) has been completed and all supporting documentation has been finalised and gathered, the amendment should be submitted via online amendment submission. The online amendment submission functionality requires a separate login to your main IRAS account, you may need to set up a new account if you have not used it before.
    - Upon submission, the amendment will be shared with REC and/or NHS/HSC as Applicable.
    - For substantial amendments notified to the REC, you should await communication from the REC with the outcome of the review.
    - For projects involving NHS/HSC the completed Amendment Tool with confirmation of amendment category and, if applicable, amended documents together should be shared with relevant participating NHS/HSC organisations. In England and Wales, the NHS R&D Office, LCRN (where applicable) and the local research team should also be included. Templates for notification can be found on the HRA website
    - For multicentre studies in Northern Ireland and/or Scotland, there is no need to send the amendment to R&D offices of participating organisations as the National Coordinating Function will pass this on to them along with any amendment documents on your behalf.
    - Single centre study amendments in Northern Ireland and/or Scotland should be sent directly to the R& D team at the participating organisation.

- Research Tissue Banks (RTBs) and Research Databases (RDBs) continue to use the Notice of Substantial Amendment Form (NOSAF) generated in IRAS. This is created from the Amendment tab associated with the RTB/RDB form. The completed NOSAF should be electronically authorised by all parties listed on the form's authorisations tab in IRAS and submitted to the REC.

5.2 Categorisation of Amendments

5.2.1 The completed Amendment Tool will output the recommended amendment category automatically based on the question responses.

- 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.

5.2.2 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/

5.2.3 The CI must send the amendment and the categorisation information (Amendment Tool) 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. Templates for notification can be found on the HRA website

5.3 Implementation of Amendments

For non-substantial amendments requiring a study-wide review email confirmation of HRA and HCRW Approval via email if the amendment affects NHS sites in England and/or Wales.
For non-substantial no study-wide review required amendments there will be no email confirmation. The automated acknowledgement email received on submission of the amendment is the approval. The amendment can be implemented according to the categorisation information contained in the Amendment Tool.

5.3.1 After submitting the amendment, the completed Amendment Tool with confirmation of amendment category and any supporting documentation should be shared with 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/

5.3.2 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).

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).

5.3.3 If all relevant regulatory approvals are in place and there has been no objection from site, the amendment can be implemented. Sponsors should not expect to receive a letter or email confirmation from NHS/HSC organisations before implementing the amendment.

- Category A and B amendments can be implemented sooner than 35 days providing:
  a. HRA and HCRW Approval has been issued for the amendment where this is required.
  b. A participating NHS organisation does not request additional time to assess.
  c. A participating NHS organisation does not decline to implement the amendment.

- Category C amendments can be implemented immediately (subject to regulatory approval being in place).

5.4 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, without prior approval authorisation from a regulatory body.

- 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
  - Guidance for amending an approval https://www.hra.nhs.uk/approvals-amendments/amending-approval/
- Gov.uk
  - Guidance for CTIMPs and medical devices amendment process https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues
- IRAS:
  - Guidance for all amendments https://www.myresearchproject.org.uk/help/hlpamendments.aspx
  - Amendment Tool https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool
  - Online Submission https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Online-Submission

- Implementing amendment at NHS organisations in England email templates:
  - Category A or B site notification email template where HRA Approval is pending at categorisation https://www.hra.nhs.uk/documents/1320/Template_email_to_share_category_A_or_B_amendment_-_approvals_are_outstanding.docx
  - Category A or B site notification email, where HRA Approval is issued at

categorisation
https://www.hra.nhs.uk/documents/1322/Template_email_to_share_category_A_or_B_amendment_-_approvals_in_place.docx
- Category C site notification email
https://www.hra.nhs.uk/documents/1326/Template_email_to_share_category_C_amendment_docs_with_sites.docx
- Amendment implementation email
https://www.hra.nhs.uk/documents/1319/Template_email_to_confirm_implementation_of_an_amendment.docx

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**
1.0	**26th April 2018**	**HRA updated submission of amendments on the 2nd June 2020. Amendments are now submitted online, and the amendment tool has replaced the previous Notice of Substantial Amendment (NOSA) Form and the non-substantial amendment form.**

9.0 AUTHORSHIP & APPROVAL

Author Megan Smith

Signature  **Date** 08/03/2022

Pro-Vice Chancellor (Research & Enterprise) Approval

Signature  **Date 01/03/2022**

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

An individual who is responsible for the conduct of the whole project in the UK.

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.

Integrated Research Application System (IRAS)

A single system for applying for the permissions and approvals for health, social and community care research in the UK.

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

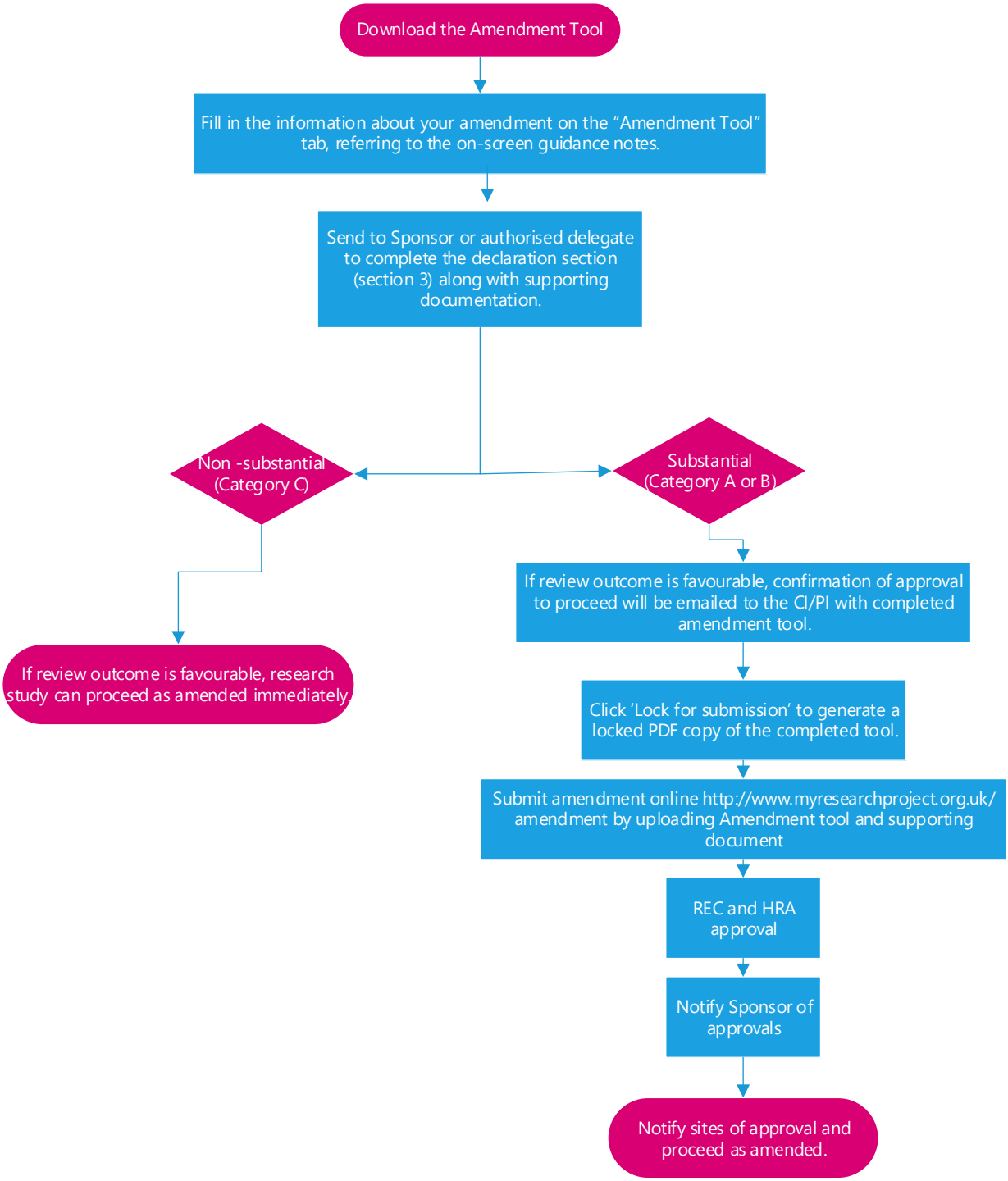
Amendments to the original REC application, to the protocol, or any other supporting documentation that is likely to affect to a significant degree:

- 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.