AMENDMENTS

Research & Development

Standard Operating Procedure for Preparation and Approval of Amendments to Clinical Trial Documentation for West Hertfordshire Hospitals NHS Trust Sponsored and Hosted Clinical Trials

SOP Number: SOP-09-08	**Effective Date:** October 2020
Version Number: v08	**Review Date:** 2-3 years

1.0 BACKGROUND

This document sets out the procedures to be followed by all West Hertfordshire Hospitals Trust (WHHT) staff who are responsible for submitting and implementing amendments for research studies run at WHHT.

It provides clear guidance on the procedure of classifying and seeking approval for amendments.

Notification of amendments

If WHHT is the Sponsor ensure that all amendments to clinical trial documentation are submitted to the R&D Office/Research & Development Steering Group (RDSG) for approval as well as the applicable Research Ethics Committee (REC) and/or the Medicines and Healthcare Products Regulatory Agency (MHRA) prior to implementation.

2.0 PURPOSE

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

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

Any Trust employee involved with clinical research sponsored by WHHT including, but not limited to,

Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Consultants, Co-investigators, Clinical Trial Pharmacists, Research Managers, Statisticians, Research nurses, Allied Health Professionals, Trial Coordinators, R&D Department, the Research & Development Steering Group (RDSG) & Data Managers.

4.0 PROCEDURE

4.1 Sponsor Assessment of Amendments

Completion of the amendment tool (available at: https://www.myresearchproject.org.uk/help/hlpamendments.aspx) will state whether the amendment is non-substantial or substantial, however this must be also be confirmed as correct by the Sponsor. 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 R&D Department when determining this classification for WHHT sponsored studies. R&D must also review the amendment and any implications it has for the management or delivery of the study.

4.2 Preparation and Submission of Amendments

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

4.2.1 **Notifying Amendments**

- Whether the amendment is deemed substantial or non-substantial the the amendment tool must be completed for all project-based research (defined as any of the IRAS Project Filter question 2 categories except for Research Tissue Banks (RTBs) and Research Databases (RDBs)). This replaces the Notice of Substantial Amendment and the non-substantial amendment form. Prior to submission the amendment tool must be locked.

- RTBs and RDBs continue to use the Notice of Substantial Amendment Form generated in IRAS.

- For all types of research, amendments and supporting documentation should be uploaded and submitted for review via online submission on IRAS.

- For CTIMP amendments that require submission to the MHRA, a copy of the amendment tool can be submitted which replaces the Annex 2 form previously used.

4.3 Categorisation of Amendments

4.3.1 Once the amendment tool is completed, based on the information entered into the tool, the amendment will automatically be categorised. This has replaced the categorisation emails that the HRA previously would issue, having initially reviewed the amendment..

- 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.

- New NHS/HSC site:
  Where the amendment is to add a new NHS/HSC site to the project, the set-up of this new site should proceed according to the process for local study set-up for the nation where the new site is located.

4.3.2 It is the applicant's responsibility to communicate the categorisation and the amendment to all participating sites sites (i.e. the local research team, the R&D office and the LCRN, where appropriate - contact details for R&D offices and LCRNs are available via http://www.rdforum.nhs.uk/content/contact-details/)

4.3.3 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.

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 raises 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, unless specified otherwise.

- 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 WHHT are a site, R&D 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 by relevant departments (or raise objections where necessary).

5.4.4 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 by R&D within 35 days of R&D 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 R&D office should be notified immediately, then in writing 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, in the form of an amendment, within 3 days - MHRA will provide guidance for this submission. In cases where NBT are sponsor, you must ensure you liaise with 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 - New online submission of amendments and amendments tool launches on 2 June
  www.hra.nhs.uk/about-us/news-updates/new-online-submission-amendments-and-amendments-tool-launches-2-june/

7.0 APPENDICES

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

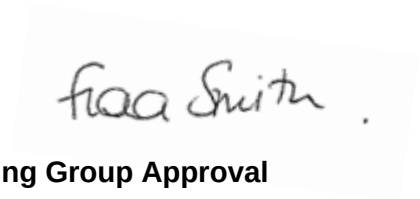
8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
SOP-09-08	**October 2021**	1. Change from general Standard Operating Procedures (gSOP) to SOP 2. Removal of the '10.0 Agreement' from the template - all agreement signatures will be collated on a new 'SOP Signature Sheet Document' 3. SOP modified in accordance with the new

		amendment tool and online submission process 4. Other minor amendments and clarification of terms following review
gSOP-09-07	**October 2017**	Minor amendments following review
gSOP-09-06	**01/10/2015**	Minor amendments following dissolution of consortium.
gSOP-09-05	**07/05/2014**	Minor amendments following review.
gSOP-09-04		SOP modified for implementation at ENHT/WHHT
gSOP-09-03 (MVCC)	**Oct 2011**	SOP modified for implementation at MVCC ● Amendment to flowcharts 2 and 4 in line with CSP amendment processing changes ● Amendment to Appendix 1 to include approval sections for supportive documents
gSOP-09-02	**06/12/2010**	● Addition of Flow chart 1 - Sponsored Study Amendment Application Flow Diagram Non-CSP studies ● Addition of Flow chart 2 - Sponsored Study Amendment Application Flow Diagram CSP Studies ● Addition of Flow chart 3 - Hosted Study Amendment Application Flow Diagram - Non-CSP Studies ● Addition of Flow chart 4 - Hosted Study Amendment Application Flow Diagram - CSP studies ● Addition of Appendix 2 - Urgent Measures cover sheet

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date** 28/10/2021

R&D Steering Group Approval

Signature  **Date** 28/10/2021

Appendix 1: Definitions

Chief Investigator
The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI. For Trust sponsored trials, the CI had been delegated the pharmacovigilance responsibility for identification, recording and reporting of safety events, including submission of Development Safety Update Reports (DSURs) to the MHRA and REC.

Clinical Trial
A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. A Study Type.

Clinical Trial of Investigational Medicinal Product (CTIMP)
A clinical trial that is within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. An investigation in human subjects, other than a non-interventional trial, intended: a) to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, b) to identify any adverse reactions, or c) to study absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products.

MHRA Clinical Trial Authorisation (CTA)
This is the authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) to conduct a Clinical trial of an investigational medicinal product (CTIMP). No CTIMP can commence in the UK without both a CTA and a favourable ethical opinion. Applications to the MHRA and the Research Ethics Committee (REC) may be made in parallel.

Investigational Medicinal Product (IMP)
A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a Clinical Trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial - a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation, b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or c) 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)

The investigator responsible for the research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person..

Substantial Amendment
A change to the terms of the approval given by either:

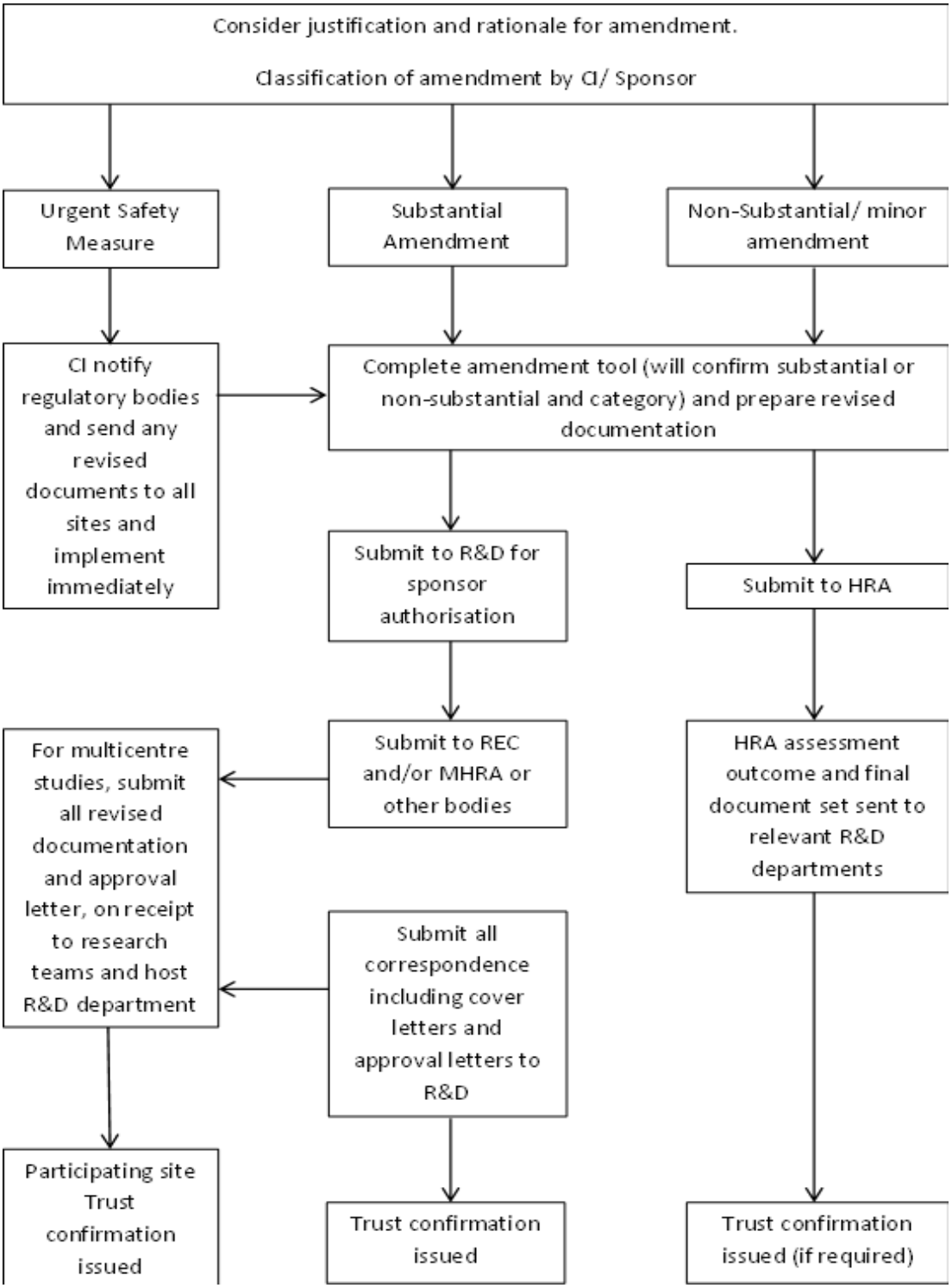
- the competent authority (MHRA in the UK) or the research ethics committee or;
- a change to the protocol or any other document submitted with the applications,

which significantly affects one of the following:

- the safety or physical or mental integrity of study participants
- the conduct or management of the study
- the scientific value of the study
- the quality or safety of any investigational medicinal product used in the study.

The Medicines & Healthcare products Regulatory Agency (MHRA)
The MHRA is the competent authority for the UK in relation to the Directive 2001/20/EC and the Clinical Trials Regulations, and for Medical Devices, the competent authority in relation to the Medical Devices Regulations 2002.

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 Changes likely to have a significant impact on the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study 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.