STU-SOP-TM-015 – Standard Operating Procedure on Managing Substantial and Non-Substantial Amendments

1. Purpose and Definitions

The purpose of this SOP is to describe the procedures and responsibilities for seeking approvals for and implementing amendments for research projects involving Swansea Trials Unit (STU).

Definitions	
Substantial amendment	A change to the protocol or any other supporting documentation (e.g. participant information sheet, participant consent form), that is likely to affect to a significant degree any of the following: • The safety, physical or mental integrity of the participants; • The scientific value of the research project; • The conduct or management of the research project; • The quality or safety of any medicinal product (MP) under investigation; • For CTIMPS - Addition of new research sites or changes to local Principal Investigators.
Non-substantial amendment (minor)	A minor change to the details of the research project, which will have no significant implications for participants, the scientific value, conduct, funding or management of the project, or quality and safety of any MP or other intervention.
Amendment category	The completed Amendment Tool will output the recommended amendment category automatically based on your responses to the questions. The IRAS (Integrated Research Application System) website will have the current version of the Amendment Tool for use. Sponsor is responsible for ensuring that the amendment tool is completed correctly and for comparing the outcomes against their own expectations of how the amendment should be processed. Further details can be found on the HRA website. Amendments are categorised as per Table 1 below: Further information is available on the HRA website or IRAS help section.

Table 1:

Category:	This category includes any amendment to a research project that has:
A	Implications for, or affects, <u>all</u> participating NHS/HSC organisations hosting the research project.
B	Implications for, or affects, <u>specific</u> participating NHS/HSC organisations hosting the research project.
C	No implications that require management or oversight by the participating NHS/HSC organisations hosting the research project. However, the amendment should still be submitted for information.

	***Note** - Updated Investigator Brochure (IB; CTIMPs only): Where the IB update, annual or otherwise, constitutes a non-substantial amendment for REC and MHRA and this is the only amendment (e.g. the update to IB does not give rise to updated pharmacy manual or protocol) the updated IB should NOT be submitted for categorisation. These amendments will always be category C and they will not be assessed by NHS/HSC if submitted. The IB should be provided to each participating NHS/HSC organisation*
New NHS/HSC site	Guidance on adding additional NHS/HSC sites is provided in the IRAS form. 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 (on IRAS) for the nation where the new site is located.
Implementation: ***Category A and B:** NHS organisations have a maximum of 35 days to raise an objection; otherwise, the amendment can be implemented (subject to regulatory approvals being in place). These may be implemented sooner than 35 days in cases where all regulatory approvals have been issued and where the NHS organisation has confirmed that the amendment may be implemented prior to this date* ***Category C:** can be implemented immediately (subject to regulatory approvals being in place).*	

2. Background

For any research project there is a requirement for permissions and approvals to be gained before recruitment can proceed. When the project does not involve the NHS or HSC organisations local approval procedures should be followed, and will likely include sponsor agreement and a local REC opinion to proceed. When the NHS are involved there are requirements for an NHS REC favourable opinion, permission by the nation(s) involved and, local R&D confirmation of Capacity and Capability (C&C).

Following the initial project permission, amendments are changes made to any aspect of a research project and are also subject to review. When the NHS are involved, all research project amendments are categorised by the HRA/HCRW for England and Wales and their equivalent in Scotland and Northern Ireland, via the IRAS Amendment Tool. This SOP assumes that STU-adopted trials will be led from either Wales or England and refers to the HRA/HCRW as the national approval body. Substantial amendments also require a favourable ethical opinion before implementation.

For projects which involve the NHS, IRAS has a help section for further information on amendments and provides access to the forms required for submitting amendments.

For CTIMPs and medical devices, there are legal requirements for certain types of substantial amendments to be reviewed by the country's competent authority (MHRA in the UK). Further information and guidance can be found on the HRA and MHRA websites (see references).

3. Roles and Responsibilities

The **Sponsor** is responsible for deciding whether an amendment is substantial or non-substantial and which approvals are required if substantial. They are also responsible for reviewing and agreeing the amendment prior to its submission to the relevant review bodies, for ensuring that the amendment tool is completed correctly and for comparing the outcomes against their own expectations of how the amendment should be processed

The **Chief Investigator (CI)** is responsible for submitting all amendment documentation for Sponsor oversight and agreement prior to submission for REC review. The CI must also

coordinate amendment submission, signing amendment documentation, dissemination of approved amendments to relevant parties and not implement an amendment until all permissions are given. Responsibilities may be delegated to the Trial Manager or other authorised member of the project team.

The **Trial Manager** (TM) may be delegated responsibility for compiling documentation for amendments, entering information into an online system (e.g. IRAS), sourcing applicable notification forms and coordinating signatures with the Sponsor and CI to enable submission for REC review. The TM will also file all amendment and approval documentation in the Trial Master File (TMF) and disseminate information to research sites.

External use of SOP: this SOP and Associated Documents (AD) may be used for research projects not adopted by STU where Swansea University (SU) staff and associated NHS organisations require guidance. In such instances, oversight responsibility for any associated tasks will not be the responsibility of STU.

For non-NHS projects with University REC approval, local committee procedures for amendments should be followed.

4. Procedure

4.1 Creation and management of Amendment Documentation

Each amendment should be allocated an amendment reference number which should increase incrementally with every amendment. A record of all amendments, where they have been submitted, outcome and implementation date should be kept in a trial specific Amendment Log (STU-AD-TMP-045).

It is usually the CI's delegated responsibility to complete, authorise and submit the appropriate amendment forms, together with all relevant documents (in the appropriate format) to the required parties. Completion of the Amendment Tool, preparation of any supporting documents and submission of the amendment should be reviewed by the Sponsor prior to submission

The Amendment Tool applies to all project-based research (defined as any of the IRAS Project Filter question 2 categories) and replaces the Notice of Substantial Amendment Form and the non-substantial amendment form.

For projects which involve the NHS, HRA, MHRA (CTIMP and device projects only) and IRAS, websites provide information and access to the appropriate amendment forms and guidance on the different requirements for each review body (see references).

4.2 Grouping of Amendments

If there are several amendments to make to a research project, it is sometimes acceptable to submit them as a group amendment. However, if one of those amendments is time critical, consideration should be made to submitting this separately.

The IRAS website (see references) provides further information and examples of when group amendments are considered appropriate.

Amendments which should not be grouped with other amendments are:

- Addition of new NHS/HSC participating organisations

- Change of the CI or a local Principal Investigator

4.3 Sponsor Review and Agreement

For all research projects, the CI must notify the Sponsor of their intention to amend the research project by following the processes outlined by the Sponsor. The CI may provide their opinion on whether the amendment is substantial or non-substantial but it is the Sponsor's responsibility to decide although categorisation via the Amendment Tool helps the decision making.

The CI or delegate will forward the amended documentation and part-completed Amendment Tool to the Sponsor for review. If approved, Sponsor will lock the Amendment Tool and return it ready for submission. The Trial Master File (TMF) will have copies of this correspondence.

The Sponsor will review the documentation and confirm:

i) their agreement (or rejection) of the proposed change(s),
ii) whether the amendment categories selected from the dropdown lists within the Amendment Tool are appropriate
iii) whether it requires review by other organisations e.g. the MHRA.

Although it is the Sponsor's responsibility to ensure that no amendment involving the NHS is implemented without the required approvals, this is usually delegated to the CI.

4.4 Submission of Amendments

The locked Amendment Tool and supporting documentation should be submitted for review via online submission via the standard IRAS website for standard review or via the "My Projects" section of the new IRAS system.

The detailed process for submitting an amendment to the standard and the combined review system can be found on the IRAS help pages, including the most up to date Amendment Tool.

Upon submission of all documentation, an automated email will be received which will confirm submission. The amendment will be shared with REC and/or for study-wide review as applicable. For substantial amendments notified to the REC, you should await email communication from the REC with the outcome of their review before implementing the amendment.

4.5 Submission of Amendments to the MHRA (CTIMPs or devices only)

Substantial Amendments

Some substantial amendments will require approval from the relevant regulatory body (e.g. MHRA) before proceeding. The MHRA website provides guidance on notifying and submitting amendments for both CTIMPs and Medical Devices.

For clinical trials authorised via the combined review process you should register to use, prepare and submit the application form using the new part of Integrated Research Application System.

For clinical trials not approved or yet transitioned over to the combined review process, you should use MHRA submissions. This process should also be used for Medical Devices.

On receipt of the documentation, the MHRA will acknowledge and validate the submission. If the application is invalid, the person making the submission will be informed of the issue and will need to resubmit. Following receipt of a valid amendment, the MHRA will usually review the amendment within 35 working days.

After the amendment has been assessed, the applicant will be informed of the outcome via email.

For projects involving Northern Ireland the MHRA website will provide up to date information.

Non-substantial Amendments
Non-substantial amendments do not need approval by the regulatory body as they arise.

4.5 Following Amendment Approval

All correspondence and documents sent (including signed copies of cover letters) to and from the REC, HRA/HCRW, R&D and MHRA must be filed in the TMF.

For multicentre research projects, it is the responsibility of the CI to ensure that all sites involved agree to support the amendment. The CI must also distribute the amendment documents and approvals to the PI, local departments or other organisations involved (e.g. drug supply company, labs, pharmacy etc.) as required.

The implementation date should be coordinated across all sites and include any database version changes, which requires sites to move to a new version.

The CI should discuss with the Sponsor any problems that sites might have in supporting an amendment. Such sites may be unable to continue their involvement with the research project.

5. References

- HRA amendment web pages - (http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/definitions-of-substantial-and-non-substantial-amendments/
- MHRA amendment web pages - https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues
- UK policy framework for health and social care research (2017) - https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/
- UK Medicine for Human Use (Clinical Trials) Regulations 2004 - http://www.legislation.gov.uk/uksi/2004/1031/contents/made

It is assumed that by referencing the principal regulations that all subsequent amendments are included in this citation.

6. Associated Documents

Number	Title	Location
STU-AD-TMP-045	Amendment Log	Q-Pulse

7. Abbreviations

List of Abbreviations	
C&C	Capacity and Capability
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
HRA	Health Research Authority
HSC	Health and Social Care
IRAS	Integrated Research Application System
MP	Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PCU	Permissions Coordinating Unit
PI	Principal Investigator
R&D	Research and Development
REC	Research Ethics Committee
REIS	Research, Engagement and Innovation Services
RGO	Research Governance Office
SSA	Site Specific Assessment
SOP	Standard Operating Procedure
STU	Swansea Trials Unit
SU	Swansea University
TMF	Trial/Project Master File

8. Appendices

Appendix 1: Document History

Version No:	3	**Effective Date:**	22-Apr-2024
Description of changes:	Procedure clarification Updated to SOP Template v5		