

Reference Number: UHB 302 Version Number: 3.0	Date of Next Review: 21/10/2023 Previous Trust/LHB Reference Number: UHB 027/028
<p style="text-align: center;">MANAGING AMENDMENTS FOR UHB SPONSORED RESEARCH</p> <p style="text-align: center;">Standard Operating Procedure</p>	
<p>Introduction and Aims</p> <p>Changes to the study after initial approval by the review bodies are called amendments. Some changes may have impact on the study resources or timescales or may have impact on the participants. Some are more minor.</p> <p>This standard operating procedure (SOP) complies with The UK Policy Framework for Health and Social Care Research (2017) and the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments.</p> <p>It aims to describe, for Cardiff and Vale University Health Board (C&V UHB) sponsored studies, the process for Sponsor authorisation, submission to reviewing bodies (Health Research Authority (HRA) and Health and Care Research Wales (HCRW), Research Ethics Committee (REC) and Medicines and Healthcare Products Regulatory Agency (MHRA) and approval and the implementation of amendments.</p>	
<p>Objectives</p> <p>To describe the process for obtaining Sponsor authorisation for amendments prior to submission to reviewing bodies and their classification as substantial or non-substantial.</p> <p>Provide guidance on submission to the reviewing bodies, the external review process and authorisations required before implementation of amendments. For multicentre studies, guidance on notifying participating site Research and Development (R&D) Offices and Principal Investigators (PIs).</p> <p>Provide timelines and guidance on the implementation of amendments and Urgent Safety Measures: their implementation and notifications required.</p>	
<p>Scope</p> <p>This SOP should be used by Chief Investigators (CIs) and other members of the research team involved in preparing and submitting amendments for C&V UHB sponsored studies. For Clinical Trial of an Investigational Medicinal Product (CTIMPS), this may include external Clinical Trials Unit (CTU) staff as it is expected for sponsored CTIMPs to be managed by C&V UHB approved CTUs.</p>	

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Equality Impact Assessment	An Equality Impact Assessment has not been completed. This is because this procedure has been written to support the implementation of the Research Governance Policy. The Health Equality Impact Assessment completed for the policy found there to be no impact.
Health Impact Assessment	A Health Impact Assessment (HEIA) has not been completed as this was considered unnecessary.
Documents to read alongside this Procedure	<ol style="list-style-type: none"> 1. Research Governance Policy (UHB 099) 2. The UK Policy Framework for Health and Social Care Research (2017).
Approved by	Research Governance Group

Accountable Executive or Clinical Board Director	Executive Medical Director
Author(s)	Governance Team, R&D Office
<p><u>Disclaimer</u> If the review date of this document has passed please ensure that the version you are using is the most up to date either by contacting the document author the Governance Directorate.</p>	

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Summary of reviews/amendments			
Version Number	Date of Review Approved	Date Published	Summary of Amendments
1	26/04/2016	19/05/2016	New SOP that replaces UHB027 v 2.1 (SR-RP-001) and UHB 028 v 1 (SR-RP-002)
2	30/08/2019	02/09/2019	SOP updated to reflect revised submission process as per IRAS and HCRW/HRA guidance. Information added on requirements for device studies.
3	21/10/2020	15/12/2020	SOP updated to reflect revised submission process as per IRAS and HCRW/HRA guidance using amendment tool which was mandated 2 nd June 2020.

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1. GLOSSARY/ABBREVIATIONS

ARSAC	Administration of Radioactive Substances Advisory Committee
CAG	Confidentiality Advisory Group
C&C	Capacity and Capability
C&V UHB	Cardiff and Vale University Health Board
CI	Chief or Co-ordinating Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit.
HCRW	Health and Care Research Wales (equivalent to the HRA in England for Wales)
HMPPS	Her Majesty's Prison and Probation Service
HRA	Health Research Authority
HSC	Health and Social Care
IB	Investigator Brochure
IRAS	Integrated Research Application System
LCRN	Local Clinical Research Network
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
PI	Principal Investigator
R&D	Research and Development
REC	Research Ethics Committee
RGT	Research Governance Team, R&D Office
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
USM	Urgent Safety Measure

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2. PROCEDURE

2.1 SPONSOR ASSESSMENTS OF AMENDMENTS

It is a REC requirement that all amendments be classified as either **substantial** or **non-substantial**. Refer to Appendix 1 for definitions of substantial and non-substantial amendments.

The CI (or delegate), should liaise with the R&D Office (acting as sponsor representative) in a timely manner to discuss potential amendments and to determine their classification. The MHRA may review the classification and rationale during a GCP inspection.

The CI (or delegate), should email the Research Governance Team (RGT) on research.governance@wales.nhs.uk with details of the proposed amendment, together with any new documentation and tracked changes copies of amended documents and explanation for the requested changes.

As appropriate, the CI (or delegate), should liaise beforehand with support departments/third parties if additional activities or changes to original activities are required as a result of the proposed amendment. Evidence of continued support by the support departments/third parties and adequate funding arrangements will be a pre-requisite for Sponsor authorisation.

The RGT within the R&D Office will lead on the review of the amendment and any implications it has for C&V UHB's continued Capacity and Capability (C&C). They will also liaise with the R&D Office contract managers to ensure any required changes to the original contractual arrangements will be in place. RGT will document this review and will also update the sponsorship risk assessment for the study, where necessary (a Risk Assessment Form is required for CTIMP trials).

The CI (or delegate) should ensure version control and maintain a log of all amendments. This log and amendment correspondence, with all parties, should be retained in the Trial Master File (TMF).

2.2 PREPARATION AND SUBMISSION OF AMENDMENTS

Please refer to the advice on the HRA website which is updated on a regular basis: <https://www.hra.nhs.uk/approvals-amendments/amending-approval/>

Also please use the IRAS help pages on amendments for up to date information on submission:

<https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx>

(a) **Substantial Amendments- REC and HRA/HCRW submission**

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- i. If the amendment is substantial for a non-CTIMP or CTIMP study, the CI (or delegate) will need to generate and complete an Amendment Tool excel document. Full guidance and the most up to date amendment tool can be downloaded from this site:
<https://www.myresearchproject.org.uk/help/hlpamendments.aspx>
- ii. It will be necessary to have all modified documents including tracked versions for upload along with any further supporting documentation.
- iii. The amendment tool will generate the categorisation of the amendment automatically with the information submitted within it. More information on this can be found in section 2.3 of this SOP and how you submit to other NHS sites depending on the type of categorisation.
- iv. For non-CTIMPs and CTIMPs, the declaration section within the amendment tool must be signed off by the **Sponsor** in order to lock the form ready for submission.
- v. Please note that although the amendment tool provides an option for either the CI or Sponsor to sign off and lock the amendment tool, for C&V UHB sponsored studies, this authority has **NOT** been delegated to the CI, and therefore the Sponsor representative **MUST** sign the amendment tool.

Sponsor electronic sign off of the amendment tool must be requested by the CI (or delegate) via email to research.governance@wales.nhs.uk
- vi. The method for submitting the amendment to the review body(ies) from whom you have received approvals (e.g. HRA and HCRW Approval or REC favourable opinion) is the same for both non-CTIMPs and CTIMPs.
- vii. Once the amendment tool has been locked by the sponsor representative, the CI (or delegate) can submit the amendment through IRAS. This will automatically submit the amendment to both REC and HRA/HCRW.

Details of this can be found here:

<https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Online-Submission>

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(b) Substantial Amendments- CTIMPs MHRA submission

- i. Substantial amendments for CTIMPs and/or Medical Devices with Clinical Trial Authorisation may require MHRA review in addition to HCRW and REC review. The CI (or delegate) must consult with the RGT to determine whether the MHRA need to be notified or not and **the R&D Director should review and approve the amendment prior to MHRA submission.**
- ii. In addition to the Amendment Tool, for CTIMPs you must also complete the European Commission 'Annex 2' form for submission to MHRA. This is available under the 'Annex 2' tab of the Amendment Tool, which is only enabled when the information entered into the amendment tool tab indicates that an Annex 2 notification is required.

(c) Substantial Amendments- Devices MHRA submission

- i. The following guidance applies to amendments to clinical investigations of medical devices subject to regulation by the Competent Authority.

MHRA Devices must be notified of all proposed changes to the investigation (not only those classified as substantial amendments for the purposes of ethical review). A letter of no objection from MHRA Devices must be received before implementation. This includes changes made at the request of the REC. Failure to notify proposed changes could result in the manufacturer being liable to prosecution.

When notifying MHRA of changes, please provide the following information in writing:

- the MHRA reference number for the trial;
- details of the proposed change(s) to the clinical investigation plan or the design of the device;
- the reason for the change(s); and
- a signed statement by or on behalf of the manufacturer that the proposed change(s) do not predictably increase the risk to the patient, user or third party.
- A copy of the completed [Amendment Tool](#)

Notifications should be sent directly to MHRA Devices. Details of where to send notifications can be found on the MHRA website

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at: <https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device>

(d) Substantial Amendments- Research Tissue Banks and Research Databases submission

- i. Research Tissue Banks (RTBs) and Research Databases (RDBs) do not need to complete the amendment tool for substantial amendments, but instead continue to use the Notice of Substantial Amendment Form generated in IRAS. More information can be found here: <https://www.myresearchproject.org.uk/help/hlpamendments.aspx#1>

Please also note that for studies which required approval from other regulatory bodies for example: Confidentiality Advisory Group (CAG), Her Majesty's Prison and Probation Service (HMPPS) and Administration of Radioactive Substances Advisory Committee (ARSAC) or if you are including involvement of adults lacking capacity for the first time, or extending involvement of adults lacking capacity to a new nation, please refer to IRAS for submissions requirements:
<https://www.myresearchproject.org.uk/help/hlpamendments.aspx>

(e) Non-Substantial Amendments

- i. Non-substantial amendments for CTIMPs and non-CTIMPs follow the same amendment tool process as written above in section 2.2a, but may have differing regulatory approvals.
- ii. For CTIMPs, notification to the MHRA of non-substantial amendments is not required.
- iii. For both non-CTIMPs and CTIMPS, non-substantial amendments do not require REC approval.
- iv. Non substantial amendments to clinical investigations of medical devices subject to regulation by the Competent Authority must be submitted to MHRA Devices for review, as detailed above in section 2.2a.

For queries on how to complete the Amendment Tool or questions on the results from it, once complete, support can be accessed as follows. Please flag in the email subject that your query relates to the Amendment Tool so that it can be identified and handled efficiently:

For England and Wales led studies: amendments@hra.nhs.uk

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2.3 CATEGORISATION OF AMENDMENTS AND NOTIFYING SITES (IF APPLICABLE)

After completing the amendment tool, the amendment will automatically be categorised and shown in section 4 of the tool. After following the submission guidance tab within the amendment tool, the amendment is sent for REC review (if required), MHRA review and or other review (if required) and assessed for continued HRA and HCRW approval automatically.

Category:	This category includes any amendment to a research project that has:
A	Implications for, or affects, <u>all</u> participating National Health Service /Health and Social Care (NHS/HSC) organisations hosting the research project.
B	Implications for, or affects, <u>specific</u> participating NHS/HSC organisations hosting the research project.
C	<p>No implications that require management or oversight by the participating NHS/HSC organisations hosting the research project. However the amendment should still be provided for information.</p> <p><i>Note - Updated Investigator Brochure (IB; Clinical Trials of Investigational Medicinal Products (CTIMPs) only):</i> Where the IB update, annual or otherwise, constitutes a non-substantial amendment for REC and MHRA <u>and</u> 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.</p>
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.

- i. The CI will receive an e-mail containing confirmation that the amendment has HRA or HCRW Approval or that HRA and HCRW

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Approval for the amendment is pending. The REC validation e-mail is also attached to this e-mail, where applicable.

ii. Notifying NHS Site R&D offices

For multi-centre studies involving research sites in England and/or Wales, the CI (or delegate) should share the completed Amendment Tool with confirmation of amendment category and, if applicable, amended documents together with relevant participating NHS organisations.

In doing so, you should include the NHS R&D Office, Local Clinical Research Network (LCRN) (where applicable) as well as the local research team.

A template email to notify participating NHS organisations in England and/or Wales is provided on the HRA website:

<https://www.hra.nhs.uk/approvals-amendments/amending-approval/>

For multi-centre studies involving research sites in Scotland and/or Northern Ireland, the coordinating function of the lead nation will, upon categorisation, share the amendment with the coordinating function of any other participating nation(s). (HRA, HCRW, NHS Research Scotland Permissions Co-ordinating Centre and Northern Ireland CRN Co-ordination Centre, respectively). There is no need to separately submit to each of these nations.

However the CI or delegate should share these documents upon receipt of the categorisation email with the research teams at relevant participating NHS/HSC organisations in Northern Ireland and/or Scotland who should prepare to implement the amendment.

- iii. Each participating site should review the amendment (except category C where R&D Office review is not necessary) in parallel to HRA/HCRW, REC and MHRA review (as appropriate) and put in place the necessary arrangements, as required, for continued local C&C to deliver the study.
- iv. The CI (or delegate) should promptly relay the REC, HRA/HCRW, and MHRA (as required) amendment review outcomes to the participating site PIs /R&D Office (and LCRNs as appropriate) as they become available.
- v. It is the CI's (or delegate) responsibility to retain all amendment correspondence with REC, HRA/HCRW, MHRA and participating sites within the TMF.

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2.4 MODIFYING AN AMENDMENT IF REC GIVE AN UNFAVOURABLE OPINION

- i. Where the REC gives an unfavourable opinion of a substantial amendment, the CI must inform the R&D office and then may submit a modified amendment taking into account the Committee's concerns. In this case a new amendment tool should be completed, indicating that it relates to a modified amendment at the relevant question. It should then be submitted to the REC alongside all supporting documentation by email. Where applicable, the REC will share the amendment and Amendment Tool with the relevant national coordinating function for the lead nation.

Modified amendments must not be submitted using online submission. REC email addresses can be looked up on the [HRA website](#)

2.5 IMPLEMENTATION OF AMENDMENTS

- i. There can be presumed implementation following regulatory approval, unless an objection to the amendment is raised by an NHS organisation within a reasonable time. For Category A and B amendments, 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). Category C amendments can be implemented immediately (subject to regulatory approval being in place).
- ii. In all cases, the CI (or delegate), must ensure that amendments and any finalised approved supporting documentation are passed to the local PIs and their research teams at all sites.
- iii. Where C&V UHB is a research site, the R&D office will review Category A (and Category B amendments where C&V UHB is deemed to be an organisation affected by the amendment) once the categorisation email is received, and issue an acknowledgement of the amendment once it has been reviewed, or raise an objection where necessary.
- iv. Acknowledgement will outline when the amendment can be implemented (e.g. immediately if all necessary approvals are in place or subject to approvals (HRA and HCRW Approval, REC and MHRA, as required) being in place. If no acknowledgement is sent by R&D

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within 35 days of R&D being informed of the amendment and its categorisation, presumed implementation can occur. **However, all researchers are strongly advised to contact the R&D office before implementing category A or B amendments.**

- v. An amendment concerning the addition of a new research site for C&V UHB sponsored studies can be implemented once favourable REC and HRA and HCRW approvals are in place and the research site has confirmed C&C. For studies requiring MHRA approval C&V UHB will also need to have issued 'Green Light'.

2.6 URGENT SAFETY MEASURES (USMs)

- i. The Sponsor, CI or PI may take appropriate USMs in order to protect research participants against any immediate hazard to their health or safety. For example, there is a significantly higher incidence of death at one UK site, and as a result suspends recruitment at that site as an urgent safety measure, or incidence of Serious Adverse Events (SAEs) or Suspected Unexpected Serious Adverse Reactions (SUSARs) require additional immediate safety measurements at all sites. **Approval is not required before taking USMs.**
- ii. REC, HCRW/HRA, the MHRA (in the case of CTIMPS) and the R&D office should be notified immediately and in any event within **3 days** of taking the USM and details of the measure and the rationale should be provided.
- iii. 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 be submitted to the MHRA in writing within 3 days (as above). The CI **MUST** liaise with the R&D office throughout the process.
- iv. The C&V UHB safety reporting procedures should be followed (refer to SR-RG-015 UHB 253).
- v. Where a USM 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. TRAINING

Education and support should be available from the C&V UHB R&D Office and HCRW Support & Delivery Centre for Researchers who are involved in

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conducting clinical research studies. C&V UHB R&D Office staff should receive relevant training (internal and external as necessary) to ensure that national procedures are adhered to in the review and management of amendments.

4. IMPLEMENTATION

The Clinical Board R&D Leads should facilitate implementation by ensuring that all relevant research active personnel within their Boards are aware of the procedure and the implications for their practice.

5. EQUALITY

An equality impact assessment has been carried out on the Research Governance Policy, under which this Procedure falls. No adverse impact has been identified.

6. REVIEW

The Procedure should be reviewed every 3 years, or more regularly if important new legislation so requires.

7. REFERENCES AND RELATED SOPS

The Medicines for Human Use (Clinical Trials) Regulations 2004, (SI 2004 No. 1031) and subsequent amendments.

The UK Policy Framework for Health and Social Care Research (2017)

Research Governance Policy (UHB 099)

Safety reporting in clinical trials of an IMP (CTIMPS) SOP (UHB253)

The UK process for handling UK study amendments:

<https://www.hra.nhs.uk/approvals-amendments/amending-approval/>

www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

<https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx>

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Appendix 1: Definitions of Substantial and Non-Substantial Amendments

Substantial Amendment Definition	Examples (as provided by HRA)
<p>Amendments to the original REC application, to the protocol, or any other supporting documentation that is likely to affect to a significant degree:</p> <ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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 the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study; Significant changes 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 a study following a temporary halt; A change to the definition of the end of the study;

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Substantial Amendment Definition	Examples (as provided by HRA)
	<ul style="list-style-type: none"> Any other significant change to the protocol or the terms of the REC application.
<p>Minor changes to the original REC application, to the protocol, or any other supporting documentation that will NOT affect to a significant degree:</p> <ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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