STANDARD OPERATING PROCEDURE

S02 - Submitting Amendments to Regulatory Bodies for Sponsored Studies

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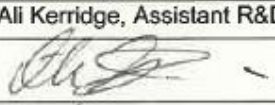
Signature	
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Controlled document

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DISCLAIMER

This generic R&D Standard Operating Procedure (SOP) must be followed unless a study specific SOP exists.

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Full History			
Version	**Date**	**Author**	**Reason**
1.0	30 October 2011	Assistant R&D Manager	First document outlining process
1.1	3 January 2014	Assistant R&D Manager	No significant changes. Corrected general typographical errors and updated web links and format of SOP.
2.0	25 September 2017	Assistant R&D Manager	Rewritten to bring in line with HRA and a clearer scope. New template
3	20 April 2021	Assistant R&D Manager	New template. Significant update to reflect new amendments process

Associated Trust Policies/ Procedural documents:	Research & Development Policy S13 Applying for Ethical Approval S09 Application for CTIMP Sponsorship S52 Urgent Safety Measures S48 Application for non CTIMP Sponsorship
Key Words:	R&D Amendment Non substantial Substantial Clinical trial SOP

In consultation with:

- R&D Facilitator Team (November 2020)
- Quality Assurance Group (November 2020)

Contents

1 INTRODUCTION

Amendments to trial protocols may become necessary during the course of a trial and must be done in accordance with the Clinical Trials Regulations 2004 (Directive 2001/20/EC) and also in compliance with ICH Good Clinical Practice (GCP) Guidance.

The Health Research Authority (HRA) defines a **substantial amendment** as:

> An amendment to the terms of the application, or 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 Health Research Authority (HRA) defines a **non-substantial amendment** as:

> An amendment made to any of the trial documentation including the application forms, protocol or supporting documentation which does not fall into the categories above.

Any amendments to a study (unless an urgent safety measure, refer to SOP 52) are required to be submitted to the following, before implementation:

- The Sponsor (Royal Devon & Exeter NHS Foundation Trust, referred to hereafter as the 'Trust') for review and confirmation of continued Sponsorship
- The required regulatory bodies e.g. Health Research Authority (HRA) (all amendments), the Research Ethics Committee (REC) (if substantial) AND the Medicines and Healthcare products Regulatory Agency (MHRA) if a clinical trial of an investigational medicinal product (CTIMP) or clinical investigation of a medical device CIMD) for review and approval.
- Any notifiable amendment to participating sites for review and confirmation of continued capacity and capability.

2. PURPOSE

This SOP describes the procedure for making amendments to protocols and research-related documentation, both substantial and non-substantial, obtaining sponsor approval of the amendment, submission to the relevant regulatory body (ies) as applicable and approval by the participating sites.

3. SCOPE

This SOP is applicable to all research sponsored by the Trust.

The SOP is applicable to Chief Investigators (CI), delegated trial team members who wish to make amendments to Trust-sponsored research and R&D team members undertaking sponsor activities on behalf of the Trust. Where responsibility for amendments is delegated to a Clinical Trials Unit (CTU), this SOP is also applicable to the assigned Trial Manager.

4. DEFINITIONS

CESP	Common European Submission Platform
CI	Chief Investigator
CIMD	Clinical Investigation of a Medical Device
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GOG	R&D Governance Oversight Group
HRA	Health Research Authority
HCRW	Health and Care Research Wales
HSC	Health & Social Care Organisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
LCRN	Local clinical research network
MHRA	Medicines and Healthcare products Regulatory Agency
NoSA	Notice of Substantial Amendment
R&D	Research & Development
RDB	Research Data Bank
REC	Research Ethics Committee
RTB	Research Tissue Bank
SOP	Standard Operating Procedure
Sponsor	An individual, company, institution or organisation which takes responsibility for the initiation, management and financing of a clinical trial. Sponsorship activities may be delegated to the Investigator, CTU and/ or other organisations as appropriate
TMG	Trial Management Group
TMF	Trial Master File
TSC	Trial Steering Committee

5. DUTIES AND RESPONSIBILITIES OF STAFF

The **Chief Investigator** or his delegated Trial Team Members must inform Trust R&D of all planned amendments and associated updated documents prior to submission to the regulatory authorities unless related to urgent safety measures.

The **Chief Investigator** shall be responsible for preparing an amended protocol and any related documentation, as required, for submission and gain the necessary regulatory approvals (e.g. HRA, REC, and MHRA) and confirmation of capacity and capability from all participating sites, before implementation. All relevant documentation relating to amendments must be filed in the Trial Master File (TMF), superseding any old versions.

The **Sponsor** is responsible for the assessment and authorisation of all amendments prior to regulatory submission.

The **Sponsor** will determine whether an amendment is substantial or non-substantial and may provide advice/ assistance with the preparation of protocol amendments and related documents to the trial team, as required.

The **Trust R&D Office** will ensure that once the applicable regulatory approvals have been granted, all documentation and approvals relating to the amendment are complete and correct before R&D issue a notice of continued capacity & capability.

6. PROCEDURES

6.1 Preparation of the amendment documentation including completion of the Amendment Tool

6.1.1 Once the CI/ Trial team has identified the need for an amendment and discussed with relevant trial personnel e.g. support departments, Trial Management Group (TMG), Trial Steering Committee (TSC), Data Monitoring Committee (DMC) Statistician, they should ensure that all study documents affected by the proposed amendment are updated with clear tracked changes and new version control.

6.1.2 In addition to the updated documentation, the Amendment Tool, downloaded from the IRAS website needs to be completed. The Amendment Tool applies to all project-based research (defined as any of the IRAS Project Filter question 2 categories except for Research Tissue Banks (RTB) and Research Data Banks (RDB)) and replaces the Notice of Substantial Amendment (NOSA) Form and the non-substantial amendment form in use pre June 2020. Note, RTB & RDB amendment applications still require a NOSA or non-substantial amendment form to be completed

Full instructions and training videos are provided on the same web page. On completion, the Tool provides an indication of what type of amendment it is ie substantial or non-substantial, which regulatory bodies need to review it and if sites are required to be informed.

6.1.3 Once the documentation has been completed, all the paperwork and the Amendment Tool must be forwarded to R&D for Sponsor approval prior to regulatory submission.

6.2 Determining the type of amendment and Sponsor review

6.2.1 For Trust-sponsored studies, the CI/ applicant must submit the Amendment Tool and all documents to R&D with clearly tracked changes to highlight the amended wording

6.2.2 The sponsor will confirm the Amendment Tool has been correctly filled in and has correctly attributed the amendment as substantial or non-substantial (as per definitions outlined in Introduction, example provided in Appendix 1) and review any associated documentation, liaising with the relevant personnel to ensure expert review is undertaken (for example, any change to the science of the study should be referred to the R&D Scientific Advisor, costing changes referred to R&D finance).

Review of documentation will include ensuring that the participants' safety and rights are still protected, that changes are made in accordance with the applicable guidelines and legislation, and whether the changes would affect the Sponsor's agreement for continued sponsorship. Changes will also be reviewed to determine if there is any impact on support departments or finances. If re-costing is required, R&D finance will arrange a meeting with the appropriate trial team member to identify and approve these additional costs.

Any comments or changes required will be fed back to the applicant in a timely fashion.

6.2.3 When the sponsor is happy with the amendment, a sponsor representative will approve and lock the Amendment Tool. Locking the Tool will create a PDF version which will be returned to the applicant for online submission (section 6.3).

6.3 Online Submission of Amendments for Regulatory Review

6.3.1 For all types of research, amendments (both substantial and non substantial) and supporting documentation should be uploaded and submitted for review to the relevant regulatory bodies via the IRAS online submission functionality. The online amendment submission functionality requires a separate login to the main IRAS account the applicant will already have. Any applicant that has not used it before may need to set up a new account. Any issues with account set up should be directed to the IRAS Technical Helpdesk for support on: helpdesk@myresearchproject.org.uk

6.3.2 Once logged in, the applicant should refer to the on-screen step-by-step instructions which will guide through the process. The applicant will be asked to enter the IRAS ID, and answer some simple questions about the amendment.

The applicant can then upload all documentation relating to the amendment, and proceed to submit after which the applicant will receive an automated email to confirm submission of the amendment. A copy of this, along with all the relevant amendment paperwork should be kept in the TMF.

6.3.3 Upon submission the amendment will be shared with the relevant regulatory bodies including HRA if it is minor and REC and HRA if it is substantial.

For further details regarding the online submission refer to https://www.myresearchproject.org.uk/help/hlpamendments.aspx

6.3.4 In addition, any substantial amendment to a CTIMP must be notified both to the MHRA before it is implemented, unless it is an urgent safety measure. Note, notification to the MHRA is not required for amendments not meeting the criteria for substantial amendments. NOTE: As of 25 March 2021 all amendments to a clinical trial of an investigational medicinal product (CTIMP) that require notification to the MHRA will no longer require submission of a European Commission “Annex 2” form. Instead, a copy of the completed Amendment Tool should be included as part of notification to the MHRA.

For further guidance about procedures for notifying substantial amendments to the MHRA, please see: https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

Submissions to MHRA are made via the MHRA national portal (replaces the EU CESP system that was used prior to Brexit).

Substantial amendments for review by the MHRA will incur an upfront amendment fee and evidence of payment must be included in the submission.

For further guidance about procedures for notifying substantial amendments to the MHRA, please see: https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

6.3.5 For a CIMD the applicant must notify MHRA Devices of all proposed changes to the investigation (not only those classified as substantial amendments for the purposes of ethical review) and await a letter of no objection from MHRA Devices before implementation. This includes changes made at the request of the REC.

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

Further information can be found on the MHRA website.

6.4

6.4.1 **What happens after submission**

The completed sponsor-approved Amendment Tool will output the recommended amendment category (listed below) automatically

Category:	This category includes any amendment to a research project that has:
A	Implications for, or affects, all participating NHS/HSC organisations hosting the research project.
B	Implications for, or affects, specific 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 provided for information. *Note - Updated Investigator Brochure (IB; Clinical Trials of Investigational Medicinal Products (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	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.

6.4.2 After the applicant has submitted the amendment, it is the duty of the CI / trial team to inform all participating sites of the pending amendment. The completed Amendment Tool with confirmation of amendment category and the amended documents should be shared with the relevant participating sites. When sharing, each NHS R&D Office, LCRN (if network adopted) as well as the local research team should be included. This will enable all participating sites to start assessing the amendment for local continued capacity and capability.

6.4.3 Once the participating NHS organisations in England and/or Wales have been informed they should prepare to implement the amendment whilst the regulatory approvals are being processed. Implementation of the amendment at all participating NHS organisations in England and/or Wales is permitted 35 calendar days from the day on which the organisation(s) were provided with the amendment and any amended documents; so long as:

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

6.4.4 In parallel to informing participating sites, REC and MHRA have 35 days from acknowledgement/ valid receipt to review a amendment. The REC/ HRA letter will confirm the documents received, including dates and version numbers. These should be checked as the approval will be based on the information contained in this letter. MHRA will confirm acknowledgement of a substantial amendment and state the 35 day timeline for review.

6.4.5 Written confirmation will then be provided to approve or reject an amendment by each applicable regulatory body. For an overview of what happens to amendments after submission please refer to the IRAS website (https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx#What-happens-after).

6.5 On Receipt of Regulatory Approval

6.5.1 On receipt of regulatory approvals the CI / trial team should provide a copy of all approval letters and the final approved documents to R&D and any participating sites. R&D will check that document dates and version numbers listed in the approval letter are those of the submitted documents, check any financial and service department impact and liaise as required with the study team to ensure continuing capacity and capability in order to accommodate the amendment. R&D will acknowledge the amendment according to HRA categorisation below.

HRA Categorisation

For Category A or B Amendments

Amendments can be implemented 35 calendar days after the amendment is provided to relevant site unless concerns/ objection raised (conditional on regulatory approval).

For Category C Amendments

The amendment can be implemented as soon as the relevant site is informed (conditional on regulatory approval), unless any concerns or objections are raised

6.5.2 On receipt of ethical and regulatory approval it is the responsibility of the CI/trial team to ensure that all amendment documentation including regulatory approvals is provided to any supporting service departments at RD&E, where appropriate. R&D will also upload a copy of the protocol and relevant documentation to the shared lab drive.

7. DISSEMINATION AND TRAINING FOR THIS DOCUMENT

7.1 This SOP and associated templates and forms will be uploaded to the RDE Research website shortly after having been released.

7.2 All staff whose activities are subject to this SOP should ensure that they take time to read and understand the content of this SOP.

7.3 *If applicable, a training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the contents of this SOP.*

8. MONITORING COMPLIANCE AND EFFECTIVENESS OF THIS SOP

8.1 In order to monitor compliance with this SOP, the auditable standards will be monitored as follows:

No	Minimum Requirements	Evidenced by
1.	Presence of a locked Amendment Tool with categorisation of amendment	R&D file & TMF
2.	Presence of updated versions of documentation with tracked changes as applicable	R&D file & TMF
3.	Presence of relevant regulatory approvals	R&D file & TMF
4.	Presence of R&D acknowledgment if applicable to amendment	R&D file & TMF

8.2 Outcomes from audit will be presented to the R&D Governance Oversight Group (GOG) which will monitor any resulting action plans until all issues have been addressed to satisfaction.

8.3 Issues identified via the audit process which require escalation will be referred to GOG.

9. ARCHIVING ARRANGEMENTS

9.1 The original of this document will remain with the R&D Quality Assurance Coordinator. An electronic copy will be maintained on the R&D section of the Q-Pulse document management system and a pdf copy on the RDE Research website.

9.2 Archive copies must be maintained for any documents which have been superseded. Archive copies in electronic format should be retained indefinitely.

10. REFERENCES

UK policy framework for health and social care research Policy Framework (2017) – https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/

European Parliament and the Council of the European Union (2001) *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Members States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.* Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:EN:PDF

Medicines and Healthcare products Regulatory Agency (MHRA) www.mhra.gov.uk

European Clinical Trials Database eudract.ema.europa.eu

Health Research Authority (HRA) www.hra.nhs.uk

Integrated Research Application System (IRAS) www.myresearchproject.org.uk

Appendix 1: Definitions of substantial and non-substantial amendments

Examples of substantial amendments

- 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 chief investigator
- 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 principal investigator 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;
- any other significant change to the protocol or the terms of the REC application.

Examples of non-substantial amendments:

- 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 chief investigator's research team
- changes to the research team at particular trial sites (other than appointment of a new principal investigator 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.

Changes to contact details for the sponsor (or the sponsor's representative), chief investigator or other study staff are minor amendments but should be notified to the main REC for information.