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3.0	**Clare Skinner** **Head of Research Integrity and Governance** Secretariat / Faculty of Medicine and Health, University of Leeds	22/10/2020	
	Steph Britt, **QA Manager (Clinical Trials)** UoL / LTHT Joint Sponsor QA Office (CTIMPs) Research & Innovation Centre	21/10/2020	

Distribution & Storage:

Distribution to:

Investigators and all members of research teams conducting or assisting with a CTIMP trial sponsored by the University of Leeds or Leeds Teaching Hospital NHS Trust.

Location of document:

Paper: Sponsor QA Office, Room 5, Research and Innovation Centre, St James's University Hospital

Electronic: http://www.leedsth.nhs.uk/research/information-for-researchers/key-documents
http://lthweb.leedsth.nhs.uk/sites/research-and-development/resources/Sponsored%20CTIMPs%20%28Quality%20Assurance%29

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Please note: *This SOP should be used and followed in conjunction with other UoL / LTHT SOPs developed for researchers to support study set up and management. These can be found on the LTHT website or by contacting R&I / QA directly. For clinical trials where Leeds is not the trial Sponsor, please refer to any Sponsor SOPs for further information.*

Section A: Introduction

1. This Standard Operating Procedure (SOP) outlines the procedure for the management of amendments made to single-site Clinical Trials of Investigational Medicinal Products (CTIMPs) sponsored by the Leeds Teaching Hospitals NHS Trust (LTHT) or the University of Leeds (UoL).

2. Amendments are changes made to a research study after approval has been given by the regulatory review bodies (e.g. Research Ethics Committee (REC), Medicines and Healthcare products Regulatory Agency (MHRA), and Health Research Authority (HRA)).

3. Amendments may be made to the MHRA Clinical Trial Authorisation application, REC application, trial Protocol, and/or any other documents submitted with the applications to the MHRA and/or REC/HRA.

4. This SOP outlines the process for submitting all amendments to the Sponsor QA Office for review and approval for submission to the appropriate regulatory bodies and obtaining subsequent Sponsor approval to implement the amendment following receipt of all relevant approvals.

Section B: Applicability

1. This SOP is applicable to all members of research teams involved in the amendment process for single-site CTIMPs sponsored by the Leeds Teaching Hospitals NHS Trust (LTHT) or the University of Leeds (UoL).

Section C: LTHT/UoL-Sponsored CTIMP Amendments

1. Classifications of Amendments

1.1. An amendment can be either **substantial or non-substantial** in nature. It is the responsibility of the Sponsor to decide whether an amendment meets the criteria for a substantial amendment, and subsequently which regulatory bodies it must be submitted to for review.

1.2. Therefore, **all amendments** must be submitted to the Sponsor QA Office for review, regardless of the Investigator's opinion regarding the classification of the amendment.

1.3. It is the regulatory responsibility of the Sponsor **and** CI to ensure that the amendment is not implemented until **all** relevant approvals are in place, including ***'Sponsor Authorisation for Amendment Implementation'*** (see Section 5).

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1.4. **Substantial Amendments**

> A **substantial amendment** is defined as an amendment to the terms of the REC/MHRA application(s), 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 trial;
> - The scientific value of the trial;
> - The conduct or management of the trial; or
> - The quality or safety of any Investigational Medicinal Product used in the trial.

1.4.1. Amendments categorised as substantial may require submission to the REC only, the MHRA only (with a notification to the HRA) or to both organisations, depending on the nature of the amendment (see Appendix A for examples).

1.5. **Non-substantial Amendments**

> A **non-substantial amendment** is defined as an amendment that does not meet the criteria for a substantial amendment outlined above (see Appendix B for examples).

1.5.1 Amendments classified by Sponsor QA as non-substantial do not require submission to the REC or MHRA, but as of April 2016 **must be submitted to the HRA**.

2. Submitting an amendment to Sponsor QA

2.1. **Completing a *'CTT05 LTHT/UoL Sponsor Notification of CTIMP Amendment'* form**

2.1.1. Once the need for an amendment has been identified by the research team, a '***CTT05_LTHT UoL Sponsor Notification of CTIMP Amendment'*** form must be completed and submitted to Sponsor QA using the dedicated QA Monitors' inbox (leedsth-tr.qamonitors@nhs.net).

Note: The CTT05 form can be found on the Sponsor QA intranet page and on the R&I website, or alternatively by contacting Sponsor QA directly.

2.1.2. **Section 1** of the CTT05 must be completed by an authorised member of the research team as follows:

- Parts **a) and b)** must be completed with details of the trial (Sponsor number, Sponsor, and Trial Short Name).

- For **part c) Amendment Reference** use the format **Substantial/Non-Substantial *Amendment XX / Document v X / dd-mm-yyyy (Date when submitted to QA)*** *e.g. Substantial Amendment 1/ Protocol v2.0/ 16-03-2016 or Substantial Amendment 2/ GP letter v3.0 / 16-03-2016.* If the amendment relates to multiple documents please list the most significant document changed as the amendment reference.

- For part **d) Amendment Details**, provide a brief summary of the amendment detailing the main changes proposed, including rationale to support the reason(s) for the amendment. In the 'Researcher Opinion (1 or 2)' column, the research team must indicate whether they consider each main change as 'substantial' (1) or 'non-substantial' (2) - see Appendices A and B for examples.

- For part **e)** ensure an updated version number is added to the header / footer of the amended documents. Please see the ***'QCRES_05 Researchers guide to Version Control for Trial Documentation'*** SOP for guidance on appropriate version control.

2.2. **Documents to submit to Sponsor QA with CTT05**

2.2.1. Please ensure the following documentation is sent to Sponsor QA for review in addition to the completed CTT05, as applicable to the nature of the amendment:

- **Clean and tracked versions of <u>all</u> amended documents** (where appropriate a summary of changes between the two versions can be sent in place of a tracked version).
    - Please note that all documents requiring an update **must be QC checked by the research team** <u>prior</u> to submission to Sponsor QA for review to ensure the following:
        a) The updated version number and document date is consistent throughout the document (please see ***'QCRES_05 Researchers guide to Version Control for Trial Documentation'*** for guidance)
        b) All information is correct and final (please ensure that any reviews undertaken by the Chief Investigator, IMP supplier or other required parties (if applicable) are completed and any necessary changes are made <u>prior</u> to submission to Sponsor QA)
        c) That any other documents that may be affected by the amendment are also updated and included within the submission to QA

- **Amendment Tool:**
  All Amendments: An Amendment Tool must be completed, and a draft sent to Sponsor QA upon request. The Amendment Tool template can be found on the Integrated Research Application System (IRAS) help webpage https://www.myresearchproject.org.uk/help/hlpamendments.aspx

Please Note: For amendments requiring submission to the MHRA, Annex 2 of the Amendment Tool must also be completed (this form can be found within the same Amendment Tool template on a separate tab).

- If amended, **updated draft regulatory application forms (REC/IRAS, EudraCT)** with changes highlighted to Sponsor QA either on the form itself or in a summary of changes.

2.3. **Submission to Sponsor QA for review**

2.3.1 Once complete, the CTT05 form, the amendment tool, and the supporting documentation should be emailed to the Sponsor QA Monitors for review using the dedicated QA Monitors' inbox (leedsth-tr.qamonitors@nhs.net).

2.3.2 Please ensure that all relevant support departments (e.g. pharmacy, pathology radiology etc.) are also notified in advance of the planned changes.

2.3.3 Once the amendment has been submitted to the Sponsor QA Office, the Sponsor QA monitoring team (or a delegated member of staff) will confirm receipt of the amendment, review the CTT05 and request any further information within 5 working days of receipt.

3. Sponsor QA approval of amendment

3.1. Once fully reviewed and approved (signed) by Sponsor QA, the CTT05 form will be emailed to the initial sender detailing Sponsor QA's classification of the amendment, and instructions for which regulatory bodies to submit the amendment to.

3.2. Where the Sponsor QA classification detailed on the form differs from that of the researcher's (e.g. when the research team deems the amendment non-substantial, but QA classify it as substantial), **Sponsor QA's decision is final and must be followed.**

3.3. **Requesting signatures on forms by authorised signatories**

3.3.1. Once the CTT05 form has been authorised by Sponsor QA, the research team are then permitted to request authorisation from the appropriate individual to allow for submission to the applicable regulatory bodies. The appropriate signatories are as follows:

- Authorisation of the Amendment Tool for single-site trials **must be given by the Sponsor Representative.**

Note: the trial's Chief Investigator **is not permitted to authorise this form.**

- **Amended REC/EudraCT forms:** Authorisation for changes **must be provided by the Sponsor Representative only.**

4. Submission of amendments for regulatory review

4.1. Once the amendment has been approved by Sponsor QA and authorisations have been obtained on all relevant forms (as per Section 3), it must be submitted for regulatory review as outlined in section 2c) of the QA-reviewed CTT05 form.

4.2. **Submission to the HRA**

4.2.1. Amendments that do not require REC review must still be notified to the HRA via submission of the signed and locked Amendment Tool in IRAS. For amendments that require REC review, the HRA and REC will be notified in tandem following submission in IRAS (please see point 4.3.1 for further information).

4.2.2 From 2nd June 2020, the HRA will no longer categorise the amendment or issue a categorisation email. Categorisation is automatically generated from the information given in the Amendment Tool (it is therefore extremely important that all information included in the Amendment Tool is complete and accurate).

4.2.3 Once completed, the signed and locked Amendment Tool will confirm whether a full review or notification only to the HRA is required:

- For amendments that require full review by the HRA, a HRA approval email will be issued once the review is complete.
- For amendments that require notification only to the HRA, no approval email will be issued. In these circumstances, the automated email received once the pack is submitted on IRAS is the 'approval'.

4.2.4 All interim correspondence **must** be forwarded to the Sponsor QA Assistant (or delegate) within 1 working day.

4.3. Submission to the REC

4.3.1. The signed and locked Amendment Tool must be submitted to the REC via the IRAS portal alongside all supporting documentation (e.g. clean and tracked amended documents,

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cover letter). **REC will share this information internally with the HRA** (please see appendix D).

4.3.2. The REC will issue a letter of acknowledgement confirming if the application is valid.

4.3.3. The REC will give an opinion within 35 days of receipt of the proposed amendment.

4.3.4. The REC may request further information or changes to be made. **Sponsor QA must be notified of any modifications made to the initial amendment via email prior to resubmission**. A new CTT05 form is **not** required to be completed.

4.3.5. Should an 'unfavourable opinion' be given by the REC, a response from the research team should be sent to the REC within 14 days of receipt of this notice, amending the Amendment Tool used for the initial notification and indicating/highlighting the modifications that have been made.

4.3.6. Once the REC have approved the amendment, a 'favourable opinion' (approval) letter is issued. Please forward this onto Sponsor QA within 1 working day.

4.3.7. For amendments relating to a new site or a change of PI only, a letter of acknowledgement will not routinely be issued by the REC.

4.4. Submission to the MHRA

4.4.1. For up-to-date information regarding submitting amendments to the MHRA please use the guidance summarised on the MHRA website (https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues).

4.4.2. Applications to the MHRA for a substantial amendment must be made using the signed and locked Amendment Tool **including** the completed and signed Annex 2.

4.4.3. MHRA amendment submissions must be made through the Common European Submissions Platform (CESP). Please contact the QA Portfolio Coordinator for login details.

4.4.4. Amendments being submitted to the MHRA, but not the REC, must also be submitted to the HRA via IRAS for their information.

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4.4.5. The MHRA will issue an acknowledgement letter and assess the amendment within 35 days of the submission date. Please forward any acknowledgements once received to the QA team within 1 working day.

4.4.6. Post review, the MHRA will issue one of the following letters:

- Acceptance of amendment
- Acceptance of amendment subject to conditions
- Grounds for non-acceptance (usually requires re-submission of the amendment).

4.4.7. All MHRA letters and correspondence must be forwarded to Sponsor QA within 1 working day of receipt.

4.4.8. Sponsor QA must be notified of any resubmissions via email with a clear explanation/justification of the changes made, prior to resubmission. A new CTT05 form is **not** required to be completed for a resubmission.

5. Obtaining *'Sponsor Authorisation for Amendment Implementation'*

5.1. From 27th September 2017* onwards, the Sponsor QA Office will issue a ***'Sponsor Authorisation for Amendment Implementation'*** email to the CI / PI and research team to confirm that all relevant approvals are in place and that the amendment can be implemented at site.

***Note:** *The LTHT R&I department no longer issue Continued Confirmation of Capacity and Capability (CCCC) emails for amendments as of 26th September 2017.*

5.2. **The amendment can only be implemented once the Sponsor Authorisation email has been issued.** In the meantime, the trial must continue on the basis of the current approved documentation.

6. Implementation of amendment

6.1. The amended documentation must be communicated to all members of the research team.

6.2. Previous versions of documents must be clearly marked as superseded in the TMF and kept for audit trail purposes.

6.3. Once all approvals have been received, it is the responsibility of the research team to notify all local departments associated with the trial (e.g. pharmacy, radiology, pathology etc.) of the amendment(s) made.

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6.4. Local departments associated with the trial must confirm if any of the changes affect their trial-specific duties or willingness to support the trial activity (e.g. pathology, pharmacy and radiology etc.).

6.5. All correspondence between the research team and the local departments pertaining to the amendment must be printed and filed in the TMF.

6.6. It is advisable for research teams to create an amendment tracker log to keep a record of all amendments made to the trial (see Appendix C). Such logs must be maintained in real time and filed in the TMF.

Section D: References

MHRA Good Clinical Practice Guide 2012
The European Commission Guidance
Health Research Authority (HRA) http://www.hra.nhs.uk/
QCRES_05 Researchers guide to Version Control for Trial Documentation

Section E: Acronyms

CI	Chief Investigator
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
HoTM	Head of Trial Management
HRA	Health Research Authority
IB	Investigator Brochure
ISF	Investigator Site File
LTHT	Leeds Teaching Hospitals NHS Trust
MHRA	Medicines and Healthcare products Regulatory Agency
NoA	Notice of Amendment
NoSA	Notice of Substantial Amendment
PI	Principal Investigator
QA	Quality Assurance
R&I	Research and Innovation
REC	Research Ethics Committee
SOP	Standard Operation Procedure
SPC	Summary of Product Characteristics
TMF	Trial Master File
UoL	University of Leeds

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Section F: Appendices

Appendix A: Examples of substantial amendments (not an exhaustive list)

- Changes to the design or methodology of the study, or to background information affecting its scientific value; (e.g. adding another trial arm);
- Changes to the primary or secondary endpoints likely to have a significant impact on the safety or scientific value of the trial;
- Use of a new measurement of primary endpoint;
- Changes to the inclusion and exclusion criteria;
- Any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study (e.g. new toxicological or pharmacological data or new interpretation of such data);
- 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;
- Appointment of a new principal investigator at a trial site;
- A change to the insurance or indemnity arrangements for the study;
- Inclusion of a new trial site (not listed in the original application);
- 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 or CTA application.
- Changes to the Reference Safety Information (RSI) (e.g. if the section of the SmPC/IB initially approved as RSI in the original MHRA application is amended)

Appendix B: Examples of non-substantial amendments (not an exhaustive list)

- Minor changes to the protocol or other study documentation, (e.g. correcting errors, updating contact points, minor clarifications);
- Changes to the research team other than the CI or PI *(does not need reporting to Sponsor QA, but must be documented on the staff authorisation / delegation log held in the Trial Master File (TMF));*
- Changes in funding arrangements;
- Changes in the documentation used by the research team for recording study data (e.g. changes to source data collection sheets or Case Report Forms (CRFs));
- Changes in the logistical arrangements for storing or transporting samples;
- Extension of the study beyond the period specified in the application form.

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Appendix C: Example amendment tracker

Amendment code	QA-signed CTT05	REC approval letter	MHRA approval letter	HRA Categorisation	HRA approval	Sponsor Authorisation for Amendment Implementation	Date amendment implemented
E.g. SA-01							

Section G: Previous Versions of Document

Version no.	Valid from	Approved by	Date approved
1.0	20/05/2016	Clare Skinner (Sponsor Representative), Louise Brook (QA Manager)	23/05/2016
2.0	09/04/2018	Clare Skinner (Sponsor Representative), Louise Brook (QA Manager)	27/04/2018
3.0	24/07/2019	Clare Skinner (Sponsor Representative), Steph Britt (QA Manager)	09/01/2020

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