UNIVERSITY OF LINCOLN

# CLINICAL GOVERNANCE - STANDARD OPERATING PROCEDURE

## CLINICAL TRIAL AMENDMENT

### CG-QMS SOP CG12

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| **Version History** | **Reason for change** |
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NOTE: All SOPs are subject to regular review.

Please ensure that the version of this SOP is the most up-to-date.

**OUT OF DATE DOCUMENTS MUST NOT BE USED AND HARD COPIES SHOULD BE DESTROYED**

## 1. PURPOSE

To outline the process for preparing an amendment to a clinical trial or clinical study ethics application or a clinical trial authorisation (CTA) application.

## 2. SCOPE

This SOP applies to all University of Lincoln (UoL) sponsored clinical research or where LinCTU (Lincoln Clinical Trials Unit) are providing trial support in accordance with the Clinical Governance – Quality Management System (CG-QMS) and/or as agreed in any service level agreement(s).

## 3. BACKGROUND

3.1 Amendments are changes made to a research project after approval from a review body has been given. If an amendment is required to the research project, it is the responsibility of the Chief Investigator (CI) to determine whether notification to the review bodies is required.

3.2 The CI also has overall responsibility for ensuring that the amendment is implemented.

**NHS / HRA amendments**

3.3 Amendments to a Research Ethics Committee (REC) and/or Heath Research Authority (HRA) application, NHS / HSC R&D application are through completion of an Amendment Tool and submitting via online amendment submission (through IRAS).

3.4 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 and Research Databases).

**Clinical Trial Authorisations (CTA) / Clinical Trials of Investigational Medicinal Products (CTIMP) amendments**

3.5 For CTA/CTIMP amendments that require submission to the Medicine Health Regulatory Authority (MHRA), the Amendment Tool must be completed alongside the Annex 2 form according to the instructions below.

**UoL ethics amendments**

3.6 An amendment form should be completed in LEAS.

**Lincoln Clinical Trials Unit (LinCTU)**

3.7 LinCTU may support the CI in submitted study / trial amendments in accordance with the agreed terms and conditions of a signed service level agreement (SLA)

**Urgent safety measures**

3.8 Urgent safety measures may be implemented immediately where participant safety is concerned.

## 4. CROSS REFERENCES

4.1 CG-QMS SOP CG11 Serious Breach

4.2 CG-QMS RF CG12-RF01 Amendment Log

4.3 HRA Amendment Tool

4.4 Annexe 2

4.5 MHRA Clinical trials for medicines: manage your authorisation, report safety issues

## 5. PROCEDURE

**AMENDING A HRA / NHS ETHICS APPLICATION**

The Chief Investigator or delegated nominee / LinCTU staff shall:

5.1 Decide whether the amendment is substantial or non-substantial. Consult the research governance manager as required.

A substantial amendment is defined as 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 study.
- The conduct or management of the study.
- The quality or safety of any investigational medicinal product (IMP) used.

A non-substantial amendment is defined as a change to the details of the study which will have no significant implications for participants, the scientific value, conduct or management of the trial, or quality and safety of the Investigational Medicinal Product in a CTIMP.

Note: Non-substantial amendments do not need to be approved by the REC or MHRA. NHS R&D shall be notified of all non-substantial amendments as they occur and these shall be categorised as per the UK Amendment Tool. The applicant, on completion of the Amendment tool, shall receive notification of the relevant categorisation, who it should be sent to and whether the amendment can be implemented immediately, or if a 35-day implementation date applies.

5.2 Amend the protocol and any supporting documentation required. Highlighting or otherwise tracking any changes and change the version number and date of the document.

5.3 Uniquely identify the amendment such as (A= Amendment): Ann/yy (where 'nn' is the next number for that amendment and yy is the year in which the amendment was made)

5.4 Download the latest version of the Amendment Tool. Once downloaded, complete the Amendment Tool (or Notice of Substantial Amendment form in the case of RTB and RDB projects) in IRAS.

5.5 Submit the Amendment Tool along with any revised / new document to sponsor@lincoln.ac.uk for review.

A member of the research governance team shall review the amendment and advise whether any changes are required. The declaration section will then be completed by the sponsor or person with explicit delegated authority from the sponsor (authorised delegate). Amendments must not be submitted without prior authorisation from or on behalf of the sponsor.

5.6 Once agreed, all supporting documentation for the amendment should be gathered and submitted

The online amendment submission functionality requires you to log in to the IRAS Identity Gateway, which is separate login to your main IRAS account. Information about accessing this is provided at:

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

Refer to the on-screen step-by-step instructions and create new amendment, upload all documentation relating to the amendment and proceed to submit.

Upon submission you will receive an automated email to confirm submission of your amendment. The amendment will be shared with REC and/or for study-wide review as applicable.

**5.7 Urgent safety measures of a CTA**

In order to determine whether the action you are taking is an Urgent Safety Measure (USM) please refer to section 3.9 and 3.10 (142-150) of guidance document CT-1.

Call the MHRA's Clinical Trials Unit on 020 3080 6456 to discuss the issue with a medical assessor, ideally within 24 hours of measures being taken. Please call no later than 3 days from the date the measures are taken.

SUSAR's should be reported in accordance with SOP CG11 Serious Breach.

## AMENDING A UOL ETHICS APPLICATION

5.8 The CI or delegated nominee / LinCTU staff shall:

Prepare the amendment in accordance with (steps 5.1-5.3 above) and complete an amendment sub-form in LEAS. Guidance for submitting an amendment may be found at https://lncn.ac/amendment

The amendment may then be submitted via LEAS.

## AMENDING A CLINICAL TRIAL AUTHORISATION (CTA)

5.9 Complete the Amendment Tool in accordance with 5.1-5.6 above.

An Annex 2* may still be used to notify the MHRA of 'bulk' amendments (identical changes to multiple studies at one time)

*Available under the 'Annex 2' tab of the Amendment Tool which is enabled only when the information entered into the amendment tool tab indicates that an Annex 2 notification is required. Refer to the on-screen guidance when completing this form.

Note: The Annex 2 form will need to be signed. This can be done by either adding in an image of the signature to the excel form prior to locking the form, or sign and scan the pdf (using signature function in Adobe). When complete, click 'Lock for submission' which will generate a locked pdf copy of the completed Annex 2 form.

5.10 Further guidance on submitting an amendment to the MHRA may be found here:

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#suspend-or-terminate-a-trial

5.11 Submit an amendment tool/annexe 2 notification of amendment form, a revised application form and the following documents to the Medicines and Healthcare products Regulatory Agency (MHRA):

- covering letter outlining the substantial and any non-substantial changes
- signed Amendment Tool / notification of amendment form (Annex 2) from the European Commission website
- updated PDF versions of the clinical trial application form (Annex 1) generated in IRAS if it has changed since the last submission
- reasons for the proposed changes
- proposed changes to the protocol or other document (eg investigational medicinal product dossier), showing previous and new wording
- supporting data for the change, including:
    - summaries of data
    - updated overall risk-benefit assessment
    - possible consequences for subjects already in the trial
    - possible consequences for the evaluation of results

Note: Amending a Clinical Trial Authorisation may incur a fee. Invoices for Clinical Trial Authorisation applications, and Substantial Amendment applications are sent directly to the applicant (The applicant is the person listed in section C1 of the Annex 1 form, or section D1 of the Annex 2 form) shortly after a valid submission has been established. Non-payment may also result in suspension of any licence or authorisation

Clinical trial submissions should be made through MHRA submissions.

Further guidance on submitting an amendment to the MHRA may be found here:

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#suspend-or-terminate-a-trial

## MODIFYING AN AMENDMENT

5.12 Where the REC gives an unfavourable opinion of a substantial amendment, the sponsor or CI may submit a modified amendment taking account of 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. Modified amendments must not be submitted using the online portal. REC email addresses can be looked up on the HRA website.

## RECORDING THE AMENDMENT

5.13 The CI, or delegate, must log all amendments in a trial specific substantial and non- substantial amendment log using RF CG12-RF01 Amendment Log and stored in the Trial Master File (TMF).

5.14 A copy of the amendment should be provided to all participating sites, and the site-specific amendment log should be updated and stored in the Study Site File.

5.15 It is the responsibility of the CI to notify any other relevant individuals (e.g. Principal Investigators (PIs) if a multisite research project) or organisations (e.g. drug supply company, labs, pharmacy etc) that all necessary approvals have been received before an amendment can be implemented.

**TEMPORARY SUSPENSION**

**Suspending a HRA / NHS ethics application**

5.16 This should be processed as a substantial amendment in accordance with 5.1-5.6.

**Suspending a CTA (CTIMPs):**

5.17 Temporary suspensions of CTIMPs require notification to the MHRA immediately or at least within 15 days of the suspension.

5.18 The notification should be made as a substantial amendment using the notification of amendment form, clearly explaining what has been stopped and the reasons for the suspension.

5.19 Substantial amendments relating to temporary suspension must be submitted using MHRA Submissions via the Human Medicines Tile. Please select 'Clinical Trial' as the Regulatory Activity and 'CT – Amendment' from the Regulatory sub activity dropdown list.

5.20 To restart a trial that has been temporarily suspended, you must make the request as a substantial amendment using the notification of amendment form, providing evidence that it is safe to restart the trial.

**IMPLEMENTING AN AMENDMENT AT NHS ORGANISATIONS IN ENGLAND**

5.21 NHS ethics: 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.

5.22 MHRA: Will assess your application within 35 days. Healthy volunteer trials and Sponsor-determined phase I trials in non-oncology patients may qualify for a shorter assessment time (average 14 days). State in the heading of your covering letter if you think your trial is eligible.

5.23 Following the implementation of the Amendment Tool and Online Submission for amendments, the applicant will receive an automated acknowledgement email confirming the submission has been successful. A copy should be sent to the sponsor.

5.24 The Amendment Tool outputs include confirmation of the category of the amendment.

5.25 If all relevant regulatory approvals are in place and there has been no objection from site, category A and B amendments can be implemented after 35 days.

Category C amendments can be implemented as soon as any regulatory approvals are received – there is no need to wait 35 days.

Category A and B amendments may be implemented sooner than 35 days in cases where all regulatory approvals have been issued and where the NHS/HSC organisation has confirmed that the amendment may be implemented prior to this date.

5.26 Upon receipt of the amendment, the coordinating function of the lead nation will notify the coordinating function of any other participating nation(s) – where applicable.

## 6. FLOWCHART

None required.

## 7. APPENDIX 1

Examples of substantial amendments:

- changes to the design or methodology of the study, or to background information likely to have a significant impact on 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 stud
- 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
- 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.

*For the purposes of a CTIMP you must submit a substantial amendment to the MHRA. You must not include any other changes with this amendment. You can't submit any other substantial amendments until you have confirmation from the MHRA that the Sponsor has been changed.

Examples of non-substantial amendments:

- inclusion of a new trial site (not listed in the original application) (CTIMP)
- appointment of a new principal investigator at a trial site (CTIMP)
- 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
- 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 approving ethics committee.