### Study Amendments

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Date</th>
<th>Location</th>
</tr>
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<tbody>
<tr>
<td>Lead Author</td>
<td>Liz Hartshorne, Trials Manager</td>
<td>07-Nov-2018</td>
<td>Signed hard copy stored in approved SOP file with Research Integrity Office</td>
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<tr>
<td>Reviewer</td>
<td>Emma Skinner, Research Integrity Manager</td>
<td>07-Nov-2018</td>
<td>Signed hard copy stored in approved SOP file with Research Integrity Office</td>
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**Effective date**: 07-November-2018  
**Next review date**: 07-November-2020

### Applicability

This Standard Operating Procedure (SOP) applies to all Health and Social Care Research (HSCR)

**Disclaimer**

Once printed from PDF, this document is an unofficial copy.

All SOPs and associated documents must only be accessed through the dedicated SOP area of the Keele University Research Toolkit webpage to ensure the correct version is being used. The user must ensure that they are working to the current version of this document.
### Version History Log

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Reason for change</th>
<th>Implementation plan</th>
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<tbody>
<tr>
<td>1.0</td>
<td>07-Nov-2018</td>
<td>This SOP has replaced the amendments process previously detailed in SOP11 (formerly <em>Regulatory Submissions, V6.0, dated 29-Sep-2016</em>). The information previously in SOP11 relating to initial regulatory submissions has been moved to HSCR SOSOP01. The information relating to amendments has been moved this this SOP. To avoid confusion with other SOPs that reference the old processes, the amendments SOP has been re-coded as SOP50. The Amendments process has been updated to reflect current processes.</td>
<td>This SOP release will be notified via email. Staff are expected to read the SOP when it is released, as applicable to their role. The procedures are to be implemented from the SOP effective date for all studies when submitting applications for amendments to regulatory approvals. A training session will be scheduled following SOP release.</td>
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Section A  Scope and Applicability

A1 This Standard Operating Procedure (SOP) describes the processes for preparing, categorising and submitting all amendments to studies to regulatory bodies, and notifying these to research sites.

A2 This SOP applies to all healthcare research. Some aspects of the SOP will only apply to specific areas of research e.g. notification of substantial amendments to Medicines and Healthcare Products Regulatory Agency (MHRA) for Clinical Trials of Investigational Medicinal Products (CTIMPs). For studies approved by Research Ethics Committees (RECs) other than an NHS REC, please refer to the standard operating procedures of the reviewing REC.

Section B  Introduction

B1 An amendment is a change to a research project after initial approvals have been received. If an amendment is required, it must be determined which of the review body(ies) from whom initial approvals were received need to give approval of the amendment. Different review bodies have different requirements. These are set out in IRAS guidance on notification of amendments.

B2 Amendments are categorised by review bodies as “substantial” or “non-substantial.” It is the sponsor’s responsibility to determine whether an amendment is considered to be substantial or non-substantial.

B3 A substantial amendment is defined 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 any of the following:

- 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

B4 A non-substantial amendment (sometimes termed 'minor amendment') is an amendment which has no significant implications for participants or for the conduct, management or scientific value of the study.

B5 Except when taking urgent safety measures (HSCR SOP20: Safety Reporting and Pharmacovigilance), appropriate approvals must be received before implementing any amendment that is considered to be substantial.

B6 Examples of substantial and non-substantial amendments can be found on the HRA website (and for CTIMPs, examples can also be found in CT1: Communication from the Commission — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial).
## Section C Responsibilities

<table>
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| Chief Investigator (CI)                                              | Development, authorisation and submission of amendments  
|                                                                      | Initial categorisation of amendment  
| Applicant (CI or delegate, e.g. Student Trial Manager (CTU studies),) | Updating study documentation in line with amendments and populating amendment templates / forms  
|                                                                      | Receipt and processing of approvals  
|                                                                      | Notification and implementation of amendment  
| All study team members including CI                                  | Identification of need for amendment.  
| Statistician                                                        | Review of all amendments that affect statistical elements / data integrity of the study  
| Project Assurance Research Integrity (PARI)                         | Final categorisation, review and authorisation of amendments to studies prior to submission to regulatory bodies.  
| Clinical Trials Unit (CTU) Studies only: Senior Trials Manager / Associate Investigator | Review requirement for amendment  
|                                                                      | Review of amendment prior to submissions for sponsor authorisation |
Section D Procedure

D1 Preparing Amendments

D1.1 Any documents that are affected by the amendment must be updated (where applicable) and version control ensured (HSCR SOP02: Document Control).

D1.2 Where it is unclear if the amendment is substantial or non-substantial, advice can be sought from Project Assurance Research Integrity (PARI) by the CI (or delegate). If required, further advice can be sought from the Research Ethics committee (REC), Health Research Authority (HRA) or MHRA. It is important to note that considerations for substantial amendments for approving regulatory bodies may be different, so amendments should be assessed against applicable examples (see section B). For a CTIMP, PARI may contact the MHRA Clinical Trials Helpline for advice if required.

D1.3 Changes to the study should be risk assessed in accordance with HSCR SOP40: Risk Assessment.

CTIMPs only

Key points to note - following MHRA guidance:

- The addition of sites and/or change in Principal Investigator (PI) is considered to be a substantial amendment by the MHRA, however, the MHRA only need to be informed of these changes when the next substantial amendment to the MHRA is submitted. The CI must ensure the addition of any new sites and/or changes in local PIs are submitted to the MHRA before the end of the trial is declared.

- There is no need to notify ‘for information only’ substantial amendments to the MHRA if the information is to be assessed only by the REC.

- There is no requirement to notify the MHRA of non-substantial changes to the protocol or clinical trial authorisation.

- All amendments made to the study documentation, or application form, which do not require approval from the MHRA should be noted in the study documentation and submitted in a subsequent notification of a substantial amendment or before the end of the trial, whichever is the earliest. If no further substantial amendments are expected, all non-substantial amendments should be submitted together as a substantial amendment prior to end of trial. A clear covering letter should be included, explaining the reason for the submission.
D1.4 Procedure for preparation of amendment submissions

Key:
- **Applicant** (CI or their delegate)
- **Project Assurance Research Integrity**
- **CTU studies only**

### Non-Substantial
- **Applicant**
  - Completes non-substantial amendment form available at: [www.hra.nhs.uk/approvals-amendments/amending-approval/](http://www.hra.nhs.uk/approvals-amendments/amending-approval/)
- **CI (or study team member)** identifies need for amendment

### Substantial
- **Applicant**
  - Generates and completes Substantial Amendment form in IRAS
  - **CTIMPs only** (if submission to MHRA is required): Clinical Trial Authorisation Application Form (CTA) updated in its entirety if it has changed since the last submission.

- **CTU studies**:
  - STM must be involved in discussions about amendments to the study, prior to submission for Sponsor review, to enable CTU Operations group to assess whether it is feasible for the amendment to be implemented including (but not limited to):
    - Previously agreed resource
    - Contracts and agreements
    - Trial supplies
    - Regulatory impact
    - Funding

- **CI makes initial assessment of substantiality and applicability of amendment, paying due regard to HRA’s guidance on substantiality / notification (see section B6)**
  - **CTIMPs only**: Amendments may be applicable to REC, MHRA or both. For MHRA, amendments must be categorised as substantial or non-substantial in accordance with: **CT1** (see section B6)
  - Changes to the study must be risk assessed and, if required, the study risk assessment updated (**HSCR SOP40: Risk Assessment**)
    - CI must assess whether the proposed amendment affects the risk/benefit ratio of the study and ensure, where necessary, that justification for continuation of the study is clearly evidenced within the SMF
Non-Substantial

Applicant
- Submits all amended documentation and completed non-substantial amendment form to research.governance@keele.ac.uk

Substantial

Applicant:
- Submits all amended documents to research.governance@keele.ac.uk including evidence of CI assessment of substantiality (e.g. email or completed TEM65: Amendment Summary Template)
- Requests Authorisation of amendment in IRAS

CTU studies:
- CI, STM and all other relevant study team members, particularly the statistician for all amendments that affect any statistical elements of the study, review the amendment submission. The study team members completing this review will vary dependent on the nature and substantiality of the amendment. Evidence of review by each relevant study team member must be retained as part of the TMF.
- TM/SC uses TEM08: Keele CTU Log of amendments and Impact of document changes to log amendment and changes to regulatory approved documents, and assess of the impact of the changes on other documents and/or systems
- All amendments to the protocol should be noted in a change log within the protocol document.

CI authorises amendment in IRAS
Non-Substantial

Sponsor Reviewer reviews proposed amendment usually within 10 working days and follows the EDGE Workflow (_Amendment), which includes (but is not limited to) the following:
- Downloads documentation into Sponsor Electronic File (SPEF, QCD01)
- Confirms amendment categorisation as substantial / non-substantial
- Provides feedback to applicant via email

CI signs non-substantial amendment form and sends (or delegate sends) to research.governance@keele.ac.uk

Sponsor Reviewer
- Signs non-substantial amendment form and returns the signed form to the applicant

Applicant
- Addresses feedback with input from appropriate study team members
- Returns amended documents (with tracked changes, as applicable) to research.governance@keele.ac.uk

CTU studies:
- TM/SC updates TEM08: Keele CTU Log of amendments and impact of document changes (as required)
- Updated protocol signed by the CI (if amended)

Substantial

Applicant requests Authorisations in IRAS

CI authorises amendment in IRAS

Sponsor reviewer
- Downloads all amended documentation into the SPEF (QCD01)
- Notifies Authorised signatory via email that the amendment requires authorising in IRAS

Sponsor Authorised Signatory
- Authorises the amendment in IRAS, usually within 5 working days
D2 Submission of Amendments and receipt of approvals

D2.1. Once all authorisations have been received, documentation can be submitted to the appropriate review body(ies) in accordance with their requirements.

D2.2. CTIMPs only: the addition of new NHS participating organisations and/or changes to Principal Investigators should be submitted separately to other amendments to expedite the review process. Multiple new NHS sites may be grouped into a single amendment submission.
D2.3. Procedure for submission of amendments and receipt of approvals

**Non-Substantial**

- **Applicant** emails to HRA (hra.amendments@nhs.net):
  - signed non-substantial amendment form
  - amended documents (if applicable)
  - for CTU studies: TEM65: Amendment Summary (where applicable)


- **Applicant** follows procedures as described on:
  - HRA website ([https://www.hra.nhs.uk/approvals-amendments/amending-approval/](https://www.hra.nhs.uk/approvals-amendments/amending-approval/))

- **Applicant** receives HRA categorisation and approval of amendment.

**Substantial**

- **Applicant** emails to REC (and HRA if REC outside England - see IRAS guidance([https://www.myresearchproject.org.uk/help/hipamendmentssresearch.aspx](https://www.myresearchproject.org.uk/help/hipamendmentssresearch.aspx))):
  - PDF copy of the authorised Notice of Substantial Amendment form from IRAS
  - all amended documents and covering letter (if applicable)
  - for CTU studies: TEM65: Amendment Summary (if applicable)

- Detailed guidance on review of amendments for studies approved by the REC/HRA can be found on the HRA website ([https://www.hra.nhs.uk/approvals-amendments/amending-approval/](https://www.hra.nhs.uk/approvals-amendments/amending-approval/)).

- **Applicant** receives REC favourable opinion and HRA approval of amendment.

**MHRA - CTIMPs only (if applicable)**

- **Applicant** submits via CESP:
  - Updated XML and PDF of Clinical Trial Authorisation application
  - Covering letter
  - PDF copy of the authorised Notice of Substantial Amendment form from IRAS
  - all relevant amended documents
  - for CTU studies: TEM65: Amendment Summary (if applicable)


- **Applicant** receives confirmation of receipt of valid application.

- **Applicant** receives MHRA Notice of Acceptance.

MHRA assess within 35 days of receipt of valid application.
**Applicant**
- Checks correct study documentation is referenced and any conditions of approval are complied with.
- Emails copies of all approval letters and approved documents to research.governance@keele.ac.uk (NB. Site approvals of amendments must be managed by the CI (or delegate) and do not need to be sent to PARI.)
- Files approval documentation in the **Study Master File (HSCR SOP06)**
- Updates applicable study registries e.g. CPMS, ISRCTN, clinicaltrials.gov, as required (HSCR SOP49: Study Registration)

**Important:**
If an application to amend a study is rejected by any regulatory body, the amendment must not be implemented unless the amendment has been resubmitted and approved.

**Applicant** confirms the following prior to implementation:
- All applicable regulatory approvals have been received.
- For amendments categorised by HRA as Category A and B; participating NHS/ISC organisation(s) agree / do not object to amendment (https://www.myresearchproject.org.uk/help/hlpmendmentsresearch.asp x#What-happens-after)
- For CTU studies: **FOR34: CTU Amendment Green Light Form** should be completed, if applicable. To confirm all processes have been completed prior to implementation of an amendment at an individual site, **FOR35: Research Site Amendment Green Light Form** and/or **FOR36: PIC site amendment green light form**, or a tracker, may be used

**Sponsor Reviewer**
Follows the EDGE Workflow (**Amendment**), which includes (but is not limited to) the following:
- Download the study documentation into the SPEF
- Update the project attributes within the EDGE record if required
- Update the Sponsor Risk Assessment (if required)
D3 Implementing Approved Amendments

D3.1 Following receipt of the categorisation email from the HRA, participating sites should be notified by the CI (or delegate) in accordance with HRA categorisation of the amendment and following the procedure as described on the IRAS website.

D3.2 Amendments must not be implemented until all applicable approvals are in place.

D3.3 For CTU Studies, FOR34: CTU Green Light Approval Form must be used prior to implementation of substantial amendments (except for those that concern only changes to site and PI information which does not require this).

D3.4 For studies outside Keele CTU, consideration should be made for the activities as described on the FOR34: CTU Green Light Approval Form.

D3.5 Amendments to studies should be considered in the context of the study as a whole and may result in amendments to approved documents, contracts, trial level SOPs and other tools.

Section E References

CT1: Communication from the Commission — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial.


CESP - https://cespportal.hma.eu

ISRCTN - https://www.isrctn.com/

CPMS - https://cpms.nihr.ac.uk/