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This page details the version history and the main changes made for each new version.
The new changes are in red font.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 04.03.11	J Pacynko	Original SOP approved by R&D Committee on 04.03.11 by global email. R&D Committee reviewed SOP on 24.02.11, but meeting not quorate.
Version 2, 10.08.11	J Pacynko	- To emphasize that investigators are required to submit substantial amendments proactively and in a timely fashion to MHRA and/or Ethics. - Up-date HUTH R&D internet links for GCP SOPs & docs. - HUTH R&D GCP SOPs are defaulted to for hosted trials with no SOPs.
Version 3, 12.11.14	J Pacynko	- Internet links up-dated - Creation and submission of the substantial amendment form via IRAS - Minor changes to methods of submission to MHRA, REC and R&D. - Filing all correspondence regarding amendments in the TMF. - 'Extension of the study beyond the period specified in the application form' has been added to non-SA list in Appendix 2.
Version 4, 04.02.19	J Pacynko	- Further detail added on substantiality decision process and documenting the decision. -Added that for single-site trials the R&D monitor will prepare and submit amendments. For multi-site trials, managed by a CTU, the CTU trial co-ordinator will prepare and submit amendments. -Working instructions 11a and 11b contain more detailed instructions on how to prepare and submit substantial and non-substantial amendments and must also be used by R&D QA/CTU trial co-ordinator to green-light amendments. -Methods of submission to REC, HRA and MHRA up-dated. -Confirmation of capacity and capability to incorporate amendment changes is now issued by R&D instead of R&D approval. -If one or more sites of a multi-site trial are temporarily halted, this has to be notified to the MHRA, REC and HRA by submission of a substantial amendment.
Version 5, 09.11.21	S Moffat	- Change of CESP details to MHRA Submissions Portal - Change of IRAS details for submitting amendments - Addition of Appendix 5 – email templates

Please note for definitions of acronyms refer to Appendix 1 of Management of SOPs. Refer to Appendix 2 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.

All the R&D GCP SOPs are available at:
https://www.hey.nhs.uk/research/researchers/gcp-sops-for-hey-sponsored-ctimps/

1 Introduction

1.1 This SOP applies to clinical trials of investigational medicinal products (CTIMPs) sponsored by Hull University Teaching Hospitals NHS Trust.

1.2 During the course of a trial, it may be necessary to make changes to the trial protocol or other trial documents or to the arrangements of the trial.

1.3 Amendments are changes made to a clinical trial after REC favourable opinion and MHRA clinical trial authorisation has been obtained.

1.4 An amendment can either be **substantial** or **non-substantial.**

1.5 It is the Sponsor's legal responsibility to decide whether an amendment is substantial or non-substantial and which approvals are required if the amendment is substantial. It is the Chief/Principal Investigator's responsibility to submit substantial amendments proactively and in a timely fashion.

1.6 The legal requirements for amendments made by the Sponsor can be found in Regulations 24 and 25 of the Medicines for Human Use (Clinical Trials) Regulations 2004 http://www.legislation.gov.uk/uksi/2004/1031/contents/made.

1.7 The European Commission have produced '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 (CT-1, dated 30.03.10)'. This SOP is in accordance with document CT-1. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:EN:PDF

2 Purpose

2.1 The purpose of this SOP is to describe the procedures and responsibilities for notifying, obtaining approvals and implementing amendments to HUTH-sponsored CTIMPs.

2.2 This SOP also describes the procedure for submitting substantial amendments for the temporary halt and restart of a trial and the procedure for the early termination of the trial if the decision is made not to restart.

3 Who should use this SOP

3.1 This SOP should be used by:

- All research staff involved with HUTH-sponsored CTIMPs – Chief/Principal Investigator, co-investigators, research nurses, clinical trial assistants, trial managers, clinical trial co-ordinators, data managers, administrators etc.
- Clinical trials pharmacy staff – technicians and pharmacists.
- All HUTH R&D QA staff who manage the sponsorship of HUTH-sponsored CTIMPs.
- Research staff involved with clinical trials sponsored by an external organisation where the sponsor has no SOP for safety reporting. HUTH R&D SOPs are defaulted to in this case.

4 Sponsor's decision

4.1 The legal and overall responsibility to decide whether an amendment is substantial lies with the Sponsor. The MHRA call this the 'substantiality decision'.

4.2 The R&D QA team, acting as Sponsor representatives, require the CI/PI to notify them of any planned changes to the trial or protocol. This requirement is in the Sponsor/CI/PI formal agreement for the trial.

4.3 R&D QA will then decide whether an amendment to the trial is substantial or non-substantial and if substantial who should be notified, the MHRA or REC or both. R&D may request advice from the CI/PI, REC and/or the MHRA in order to make the decision. The MHRA will give advice without delay and free of charge.

4.4 The substantiality decision will be documented on the Study Tracking/Amendment Log including; date decision made, those involved, whether CI/PI/REC/MHRA were checked with and reason for the decision.

4.5 Appendix 1 gives the HRA and MHRA general guidance on which organization to notify.

4.6 If the amendment is substantial and should be notified to the MHRA only or to the REC only, there is no requirement to send a copy of the amendment for information to the other body.

4.7 An email will be sent to the CI/PI confirming R&D's decision.

5 Who prepares and submits amendments

5.1 For single-site trials, the R&D monitor will prepare and submit the amendments on behalf of the PI. The PI will be required to work with the R&D monitor to amend the documents correctly.

5.2 For multi-site trials, run by a clinical trials unit (CTU), the CTU will be required to prepare and submit the amendments. The CI will need to work with the CTU staff to amend the documents correctly. R&D QA will need to review the documents before authorising amendments.

5.3 For all project-based research, notice of substantial amendment and non-substantial amendment forms are no longer used and have been replaced by the Amendment Tool. Instructions on how to complete the amendment tool and how to submit an amendment online can be found on the IRAS website https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool

6 Non-substantial amendments

6.1 Examples of non-substantial amendments are given in Appendix 3.

6.2 Version number and date of amended documents must be up-dated for non-substantial amendments according to the R&D GCP SOP 01- Version Control

The Amendment Tool replaces the non-substantial amendment form. Amendments, including all supporting documents, should be submitted for review via the IRAS online amendments submission. To access this you must log in to the IRAS Identity Gateway which is a separate log in to your main IRAS account. Guidance can be found on: https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Online-Submission

6.3 **Working instruction 11b**, **the Non-Substantial Amendment Green-light Checklist**, must be used by those staff preparing and submitting non-substantial amendments.

6.4 All non-substantial amendments must be recorded on the Study Tracking or Amendment Log. This log is requested by the MHRA during inspections. The Study Tracking/Amendment Log is kept up-to-date by the R&D monitor or by the CTU trial co-ordinator.

6.5 Changes to contact details for the Sponsor (or the Sponsor's representative), Chief Investigator, Principal Investigator or other study staff on the MHRA/REC application form, are minor amendments but should be notified to the MHRA and the REC that approved your original application for information.

6.6 See the MHRA website (link below) on how to inform the MHRA of changes to the contact person for a CTA.
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#change-your-contact-details

6.7 The non-substantial amendment can only be implemented when HRA approval has been obtained and all green-light checks have been completed by R&D QA. This is the green-light for the amendment to be implemented.

6.8 Please note for non-substantial amendments which require a study wide review confirmation of HRA approval will be received via email (if the amendment affects NHS sites in England and Wales). However for non-substantial amendments that do not require a study wide review the HRA do not send any notification. The automated acknowledgement email received when the amendment is submitted is the approval to implement the amendment according to the categorization information contained in the Amendment Tool. Please see link below for information regarding Amendment categorization.

https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx#Amendment-classifications

6.9 Once the green-light has been issued, the implementation email can be sent to site(s). Please see the links to amendment notification email templates in Appendix 5.

6.10 Up until then, the trial can continue on the basis of the original/previously approved documentation.

6.11 All correspondence regarding the amendment will need to be filed in the TMF.

7 Substantial amendments

Definition

7.1 Amendments to the trial are regarded as substantial where they are likely to have a significant impact on:

- The safety or physical or mental integrity of the clinical trial participants
- The scientific value of the trial
- The conduct or management of the trial
- The quality or safety of any IMP used in the trial

7.2 Examples of substantial amendments are given in Appendix 4.

7.3 Once a substantial amendment has been identified, it is important that the process of preparation and submission is done by the R&D monitor or CTU staff proactively and in a timely fashion. R&D QA staff will review the substantial amendment documents before authorisation.

Preparation and submission

7.4 **Working instruction 11a, the Substantial Amendment Green-light Checklist**, must be used by those staff preparing and submitting substantial amendments.

Notification

7.5 Substantial amendments need to be notified to the MHRA or REC or both (according to R&D's decision) and to the HRA using the Amendment Tool, a covering letter and all amended trial documents according to Appendix 2.

Amendment Tool

7.6 All substantial amendments must be prepared using the Amendment Tool.

7.7 Amendments to REC and HRA will be done via IRAS and must include a pdf version of the completed amendment tool.

7.8 Please note amendments that also require to be submitted to the MHRA no longer require an Annexe 2 form. A copy of the completed and authorized Amendment Tool should now be included in the submission. Please find full instructions on how to use the Amendment Tool on the IRAS website.
https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool

7.9 Where there are changes to study documents (e.g. protocol, patient information sheet, informed consent form, GP letter etc) ensure the version number and date is up-dated according to the R&D GCP SOP 01 Version Control.

Submission

7.10 Substantial amendments to be notified to both the MHRA and REC should be submitted in parallel.

7.11 The completed Amendment Tool form should be transferred via IRAS to the R&D Manager to be authorised electronically on behalf of the Sponsor. Instructions are clearly given in IRAS.

7.12 For REC, amendments, including all supporting documents, should be submitted for review via the IRAS online amendments submission. To access this you must log in to the IRAS Identity Gateway which is a separate log in to your main IRAS account. Guidance can be found on https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Online-Submission.

7.13 The REC co-ordinator sends an email to confirm if the notice of amendment is valid for review or giving the reason why not, usually within **5 working days** of receipt. The REC will issue an ethical opinion on the amendment within a maximum of **35 days** from the date of receipt of a valid notice of amendment.

7.14 For the MHRA, all amendment documents should be sent via the MHRA Submission Portal according to their website using R&D WI 47 MHRA Submission. There are also instructions and training videos on https://www.gov.uk/guidance/register-to-make-submissions-to-the-mhra.

7.15 The MHRA's assessment period is **35 days** from receipt of a valid application. The MHRA email confirming receipt of a valid application or stating the reason if the application is not valid e.g. due to missing documents or incomplete notification of amendment form.

7.16 When the amendment has been assessed the MHRA email a letter of acceptance, or acceptance subject to conditions or grounds for non-acceptance. The letter will specify the options to deal with conditions or grounds for non-acceptance.

7.17 Ensure you send the MHRA letter of acceptance to the HRA as the MHRA do not automatically notify the HRA of their decision.

7.18 The HRA will also assess the amendment. HRA approval brings together the assessment of governance and legal compliance by HRA staff and the independent ethical opinion by REC. Only one application needs to be submitted.

7.19 For R&D, send all the amendment documents to the R&D RDU lead. R&D will forward a copy of the substantial amendment documents to clinical trials pharmacy staff and all other relevant service providers that the amendment affects (e.g. labs, radiology etc) to check the departments have the capacity and capability to incorporate the changes. If the departments are in agreement, R&D will provide confirmation of capacity and capability.

Documenting in Trial Master File (TMF)

7.20 All substantial amendments must be recorded on the Study Tracking or Amendment Log. This log is requested by the MHRA during inspections. The study tracking/amendment log is kept up-to-date by the R&D monitor or CTU trial co-ordinator and filed in the TMF.

7.21 All original signed amendment documents should be kept in the appropriate section in the paper TMF and scanned and saved electronically in the eTMF.

7.22 All correspondence to and from REC, MHRA and HRA regarding the amendment will need to be filed in the TMF. This has been a previous MHRA inspection finding.

This includes:

- Investigator covering emails/letters
- Acknowledgement of receipts from REC and MHRA
- REC favourable opinion and MHRA acceptance
- REC and MHRA rejection emails/letters
- Investigator response emails/letters
- Correspondence to and from the HRA

7.23 The R&D monitor will check that any of the above correspondence which is relevant for pharmacy is forwarded to trials pharmacy staff for their information and to be filed in the Pharmacy Study File.

Green-light and implementation

7.24 The amendment can only be implemented when all regulatory approvals have been obtained and all green-light checks have been completed by R&D QA. This is the green-light for the amendment to be implemented.

7.25 Once the green-light has been issued, the implementation email can be sent to sites.

7.26 Up until then, the trial can continue on the basis of the original/previously approved documentation, unless the rules for urgent safety measures apply.

8 Temporary halt of whole trial or site

Temporary halt

8.1 A temporary halt is a stoppage of either the whole trial or one or more sites, of a multi-site trial, which has not been envisaged in the approved protocol and where there is an intention to resume the trial or site activity.

8.2 The CI/PI must alert R&D QA immediately of any reason to halt either the trial or one or more sites.

8.3 R&D QA and the CI/PI will decide if the trial or site/s should be halted temporarily.

8.4 If the decision is made to halt the trial or site/s then R&D QA or the CI/PI will notify the MHRA and REC immediately and at least **within 15 days** from when the trial/site/s are halted temporarily, by submitting a substantial amendment.

8.5 If the trial is multi-site and being managed by a CTU, the CTU will submit the substantial amendment.

8.6 See R&D GCP SOP 07 – Safety reporting and R&D GCP SOP 09 – Urgent Safety Measures – if the decision to halt the trial was due to urgent safety measures.

8.7 Substantial amendments need to be notified using the Amendment Tool, see above for preparation and submission.

8.8 The Amendment Tool should include a clear explanation of what has been halted (e.g. stopping recruitment and/or interrupting treatment of subjects), the reasons for the temporary halt and whether the whole trial has been halted or just individual sites.

8.9 The Amendment Tool should be sent to the MHRA, REC and HRA as described above for submission.

Restart

8.10 R&D QA together with the Chief/Principal Investigator will decide if a trial or site is to be restarted.

8.11 To restart a trial/site, either R&D QA or the CI/PI should make the request as a substantial amendment and provide evidence that it is safe to restart the trial/site.

8.12 The Amendment Tool should be sent to the MHRA, REC and HRA as described above for submission.

8.13 An MHRA notice of acceptance, REC favourable opinion, HRA approval and Sponsor green-light must be obtained for the substantial amendment before the trial/site can restart.

Early termination of a trial

8.14 If the CI/PI and R&D QA decide not to recommence a temporarily halted trial, the CI/PI, R&D QA or CTU must notify the MHRA, REC and HUTH R&D **within 15 days** of the date of termination by submitting the Declaration of the End of Trial form and including a brief explanation of the reasons for ending the trial.

8.15 The end of trial form is available from: https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#end-of-trial

8.16 The end of trial form should be sent to the MHRA, REC and R&D QA as described above for substantial amendments submission. R&D QA will forward a copy of the end of trial form to the clinical trials pharmacy staff and any other relevant departments/staff.

9 Implementation

- Implementation of this SOP will conform to the process outlined in R&D SOP 01 Management of SOPs.

Appendix 1

Notification of substantial amendments to CTIMPs

It is the legal responsibility of the Sponsor to decide whether a substantial amendment requires MHRA authorisation and/or an ethical opinion. However, Sponsors may wish to take account of the following general guidance, which was agreed between HRA and the MHRA.

(a) Amendments normally requiring authorisation only (MHRA)

- Amendments related to the quality of the IMP
- Changes to non-clinical pharmacology and toxicology data
- Changes to clinical trial and human experience data.

(b) Amendments normally requiring a favourable ethical opinion only (REC)

- Amendments to patient information sheets, consent forms, letters to GPs or other clinicians, letters to relatives/carers, etc (whether generic to the whole study or specific to a particular trial site)
- Change of insurance or indemnity arrangements for the trial
- Change of the Chief Investigator or appointment of a key collaborator
- Change of Principal Investigator at a trial site
- Addition of new trial sites not listed with the original request for authorisation and REC application
- Change to the definition of a trial site
- Any other significant change to the conduct or management of the trial at particular trial sites
- Any other amendments to the terms of the REC application.

(c) Amendments normally requiring both authorisation and a favourable ethical opinion (MHRA and REC)

- Amendments related to the protocol (except those relating only to patient information sheets, consent forms, etc)
- Amendments related to the safety of the IMP
- Any other amendments related to the safety or physical or mental integrity of trial participants, or change to the risk/benefit assessment.
- Change of the sponsor or legal representative of the sponsor.
- Change of the CRO assigned significant tasks
- Change of the definition of the end of the trial.

Appendix 2

Taken from the Gov.uk website: https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#apply-to-change-your-trials-protocol-or-documentation

Apply to change your trial's protocol or documentation

These changes count as a substantial amendment to your clinical trial authorisation. You need to send a notification of amendment form, a revised application form and the following documents to the Medicines and Healthcare products Regulatory Agency (MHRA):

- Covering letter detailing the trial reference numbers (IRAS, CTA number, EudraCT etc) along with Purchase Order Number, outlining the substantial changes (if there have been any non-substantial changes please also outline these separately)
- A pdf copy of the locked Amendment tool. You should ensure that the amendment tool contains a clear description of the substantial amendment and reasons for the proposed changes. Alternatively, for 'bulk' amendments (where the same change affects many trials), the substantial amendment notification form** can be completed and submitted. The form is available here.
- PDF file of the Clinical Trial Authorisation application form* generated in IRAS with changes highlighted, if the amendment affects the information previously submitted.
- Copy of the proposed changes to the protocol or any other documents (e.g. IMPD), showing previous and new wording where applicable supporting data for the amendment, including as applicable:
    - Summaries of data
    - Updated overall risk benefit assessment
    - Possible consequences for subjects already in the trial
    - Possible consequences for the evaluation of results

Appendix 3

Examples of non-substantial amendments

Taken from HRA website
https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-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 at a Non-NHS/HSC site in a CTIMP or a regulated investigation of a medical device);
- 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 (other than a CTIMP or a regulated investigation of a medical device wishing to add a new Non-NHS/HSC site)
- change to the study end date.

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 REC that approved your original application.

Appendix 4

Examples of Substantial Amendments

Taken from HRA website
https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-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 protocol, 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 or key collaborator.
- A change to the insurance or indemnity arrangements for the study.
- Inclusion of a new trial site and investigators (not listed in the original application). Requires favourable opinion from the main REC only. There is no requirement to notify the MHRA.
- Appointment of a new principal investigator at a trial site. Requires favourable opinion from the main REC only. There is no requirement to notify the MHRA.
- 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.

Appendix 5

The following template emails can be used to notify participating NHS organisations in England and Wales of an amendment:

Template email for sponsors to share category A or B amendment documents with sites (regulatory approvals outstanding)
Template email for Category A or B amendment documents with sites – where regulatory approvals in place
Template email for sponsors to share category C amendment documents with sites
Template email for sponsors to confirm implementation of an amendment