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Authorized by		Sign	Date
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This page details the version history SOP and the main changes made for each new version.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 27.10.10	J Pacynko	Original SOP approved by R&D Committee on 27.10.10.
Version 2, 12.11.14	J Pacynko	Up-dated - Weblinks, MHRA address, name of R&D Director and contact telephone numbers. Up-dated – methods of submission to REC and R&D
Version 3, 19.02.20	S Moffat	**Changes are shown by wording in red.** Section 3, page 4 Clarification of urgent safety measure Section 4, page 4 Updated – names of R&D Directors Section 4, page 5 Addition of the information the safety scientist will require about the Urgent Safety Measure. Section 4, page 5 Clarifying that notification in writing via email must be done within 3 days of urgent measures being taken and must be followed by submission of a substantial amendment within approximately 2 weeks of the initial notification to the MHRA. Section 4, pages 5 & 6 – Urgent Safety Measures Updating details of how to submit a substantial amendment to the MHRA and REC. Section 4, page 6 – Temporary Halt of a Trial Updating details of how to submit a substantial amendment to the MHRA and REC. Section 4, page 7 – Early Termination of a Trial Update of weblink for the End of Trial form.
Version 4, 03.01.23	S Moffat	**Section 4.1 Urgent safety measures** 4.1.3 - Change of R&D Director's name. 4.1.5 - Updated list of information asked for on the call to the MHRA safety scientist as found on the MHRA webpage. 4.1.9 - Addition of "For trials not approved via Combined Review you will be instructed to send an email to the medical assessor who assessed the USM over the phone,

		clintrialhelpline@mhra.gov.uk." 4.1.10 - Addition of "If at least one of the trials covered by the USM has gone through the Combined Review process, then the USM written notification should be submitted via the Integrated Research" 4.1.11 - Addition of "Please note the USM-related substantial amendment must not include changes different from those required as an urgent safety measure. Inclusion of unrelated changes may result in rejection." 4.1.13 to 4.1.19 – Updated the process of submitting a substantial amendment. 4.1.20 – Updated the email address of R&D QA. **4.2 Temporary halt of a trial** 4.2.2 to 4.2.4 – Updating the process of submitting an amendment for a temporary halt of a trial. 4.2.5 – Updated the email address of R&D QA. **4.3 Restart of a trial** 4.3.2 Amended to "To restart a trial, the investigator (with HUTH R&D) should make the request as a substantial amendment and provide evidence that it is safe to restart the trial **4.4 Early termination of a trial** 4.4.3 to 4.4.5 Updated the process of submitting the End of Trial Notification.

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

1 Purpose

- The purpose of this SOP is to describe the investigator and sponsor responsibilities should it be necessary to take urgent safety measures during the conduct of a HUTH-sponsored CTIMP.

2 Who should use this SOP

2.1 This SOP should be used by:

- All research staff involved with HUTH-sponsored CTIMPs – Chief/Principal investigator, co-investigators, research nurses, clinical support workers, project managers, clinical trial co-ordinators, data managers and administrators etc.
- Clinical trials pharmacy staff – technicians and pharmacists.
- All HUTH R&D staff who manage the sponsorship of HUTH-sponsored CTIMPs.
- Research staff involved with HUTH-sponsored non-CTIMPs may find this SOP a
- useful guide, although the SOP will need to be adapted for the non-CTIMP trial.
- Research staff involved with clinical trials sponsored by an external organisation where the sponsor has no SOP for urgent safety measures. HUTH R&D SOPs are defaulted to in this case.

3 Background

3.1 An urgent safety measure is an action that the sponsor or investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety.

3.2 The legal requirements for urgent safety measures can be found in Part 4 Regulation 30 of The Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031. http://www.legislation.gov.uk/uksi/2004/1031/contents/made

4 Investigator and sponsor responsibilities

4.1 Urgent safety measures (USM)

4.1.1 The investigator or sponsor may take appropriate urgent safety measures in order to protect clinical trial participants against any immediate hazard to their health or safety. The measures should be taken immediately.

4.1.2 These urgent safety measures may be taken without prior authorization from the MHRA, REC or Trust (HUTH R&D). The REC being the research ethics committee that gave a favourable opinion for the trial.

4.1.3 However, the investigator must alert HUTH R&D (sponsor) as soon as possible of the urgent measures taken by contacting the R&D Office telephone number 461883 or 461903 (Mon – Fri 8am – 6pm) or the Trust Switchboard 875875 (out-of-office hours) and

asking for either of the R&D Director Professor Thozhukat Sathyapalan or the R&D Manager James Illingworth.

4.1.4 The investigator or HUTH R&D QA should phone the Clinical Trial Unit at the MHRA and discuss the issue with a safety scientist as soon as possible (ideally within 24 hours of measures being taken). The safety scientist is employed by the MHRA to advise on safety and medical issues. Contact the MHRA CTU via the clinical trials for medicines helpline 020 3080 6456 (Monday - Friday 08:30 -16:30).

4.1.5 The following information will be asked for on the call:

- The IRAS ID and/or the EudraCT number of; a. The trials for which USM action has been taken, b. Other ongoing trials with the same Investigational Medicinal Product(s) (IMP(s)) c. Trials run by a different Sponsor affected by the USM action
- The affected IMP(s) - commercial or developmental names
- Nature of the safety concern and whether it has been reported as a SUSAR
- Which USMs have been taken and when
- The number of UK subjects who are currently receiving the IMP, the number of subjects who received it and the number affected by the USM
- Contact details in case of further questions

4.1.6 Where this information is not available during the initial call it should be provided as soon as possible.

4.1.7 HUTH R&D QA should notify Pharmacy Clinical Trials staff as soon as possible.

4.1.8 The investigator must notify the MHRA, REC and Trust (HUTH R&D) in writing **within 3 days** from the date urgent measures have been taken by email to clintrialhelpline@mhra.gov.uk.

4.1.9 For trials not approved via Combined Review you will be instructed to send an email to the medical assessor who assessed the USM over the phone, clintrialhelpline@mhra.gov.uk.

4.1.10 If at least one of the trials covered by the USM has gone through the Combined Review process, then the USM written notification should be submitted via the Integrated Research Application System (IRAS). More information can be found on the Health Research Authority (HRA) website.

4.1.11 A substantial amendment must also be submitted detailing the changes made as part of the USM within approximately 2 weeks of the initial notification to the MHRA. Please note the USM-related substantial amendment must not include changes different from those required as an urgent safety measure. Inclusion of unrelated changes may result in rejection.

4.1.12 However if the decision is made with HUTH R&D to halt the study due to the urgent safety measures then this can be added to the Amendment Tool and would save submitting another substantial amendment for the temporary halt as described in the next section on temporary halt of a trial.

4.1.13 The Amendment Tool in IRAS should be completed. Guidance for completing this can be found on https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool

4.1.14 In Section 1: Project Information of the Amendment Tool, make sure that you enter the **amendment number (in numerical order of amendments for the trial) and date (when the amendment was completed).** Refer to R&D GCP SOP 01 Version control of essential documents**.**

4.1.15 The Amendment Tool and any updated documents should be sent with a covering letter detailing;

- the urgent measures taken
- the reasons for them
- the measures agreed with the safety scientist.

4.1.16 If the trial has not been submitted via the ccombined review process the amendment should be sent to the MHRA using MHRA Submissions via the Human Medicines tile. This will be submitted by HUTH R&D QA. Please refer to R&D Working Instruction 20 for instructions on how to use MHRA Submissions.
On MHRA Submissions please select "Clinical Trial" as the regulatory activity and then "CT-Amendment" from the drop down list.

4.1.17 If the trial has been submitted via the Combined Review process then the substantial amendment should be submitted via IRAS.

4.1.18 For trials not submitted via the Combined Review process REC must be notified by email within 3 working days of the USM stating the measures that have been taken and the reasons why. Where a substantial amendment is required due to the USM this should be marked as being in response to urgent safety measures and a copy of the USM notification and amended trial documents should be submitted with the amendment.

4.1.19 For trials submitted via the Combined Review process the USM notification should be submitted via IRAS. No additional notification is required to REC. Where a substantial amendment is required due to the USM this should be submitted with any amended trial documents as soon as possible and marked as being in response to urgent safety measures.

4.1.20 The amendment documentation should be emailed to the R&D QA team at hyp-tr.randdqateam@nhs.net. R&D QA will ensure that all relevant amendments are sent to Pharmacy Clinical Trials.

4.2 Temporary halt of a trial

4.2.1 HUTH R&D as sponsor and the Chief/Principal investigator will decide whether the trial should be halted due to the urgent safety measures.

4.2.2 If the decision is made to halt the trial then the investigator or HUTH R&D will notify the MHRA and REC immediately and at least **within 15 days** from when the trial is halted temporarily, by submitting a substantial amendment.

4.2.3 The Amendment Tool in IRAS should be completed. Guidance for completing this can be found on https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool

4.2.4 The process in sections 4.1.17 to 4.1.21 should be followed.

4.2.5 The amendment documentation should be emailed to the R&D QA team at hyp-tr.randdqateam@nhs.net. R&D QA will ensure that all relevant amendments are sent to Pharmacy Clinical Trials.

4.3 Restart of a trial

4.3.1 HUTH R&D as sponsor together with the Chief/Principal investigator will decide if a trial is to be restarted.

4.3.2 To restart a trial, the investigator (with HUTH R&D) should make the request as a substantial amendment and provide evidence that it is safe to restart the trial.

4.3.3 The substantial amendment form should be sent to the MHRA, REC and HUTH R&D as described for the temporary halt in Section 4.2.

4.3.4 An MHRA notice of acceptance, REC favourable opinion and HUTH R&D Confirmation of Capability and Capacity must be obtained for the substantial amendment before the trial can restart.

4.4 Early termination of a trial

4.4.1 If the investigator and HUTH R&D decide not to recommence a temporarily halted trial, the investigator 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.

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

4.4.3 For trials not submitted via the Combined Review process an end of trial form must be submitted to the MHRA using MHRA Submissions via the Human Medicines Tile. Please select 'Clinical Trial' as the Regulatory Activity and 'CT – EOT' from the Regulatory sub activity dropdown list. A copy of the completed EOT form should also be emailed to REC with a covering letter.

4.4.4 For trials submitted through the Combined Review process, then the end of trial declaration should be submitted via IRAS. This automatically submits the notification to the REC and MHRA.

4.4.5 R&D QA will ensure the end of trial form is sent to Pharmacy Clinical Trials.

5 Additional sponsor responsibilities

5.1 To help the investigator to prepare the substantial amendment form and all supporting documents.

5.2 To check when monitoring that the sponsor has been notified of all trial amendments and the decision on substantiality has been made by the sponsor.

5.3 To check when monitoring that MHRA, REC and R&D approvals have been obtained prior to the amendment being implemented.

5.4 To check version control when monitoring. Should the trial amendment have involved amending trial documents (e.g. protocol, consent form, patient information sheet) check that the *latest approved versions* of these documents are being used and examples filed in the Investigator Site File.