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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	<p>Changes are shown by wording in red.</p> <p><u>Section 3, page 4</u> Clarification of urgent safety measure</p> <p><u>Section 4, page 4</u> Updated – names of R&D Directors</p> <p><u>Section 4, page 5</u> Addition of the information the safety scientist will require about the Urgent Safety Measure.</p> <p><u>Section 4, page 5</u> 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.</p> <p><u>Section 4, pages 5 & 6 – Urgent Safety Measures</u> Updating details of how to submit a substantial amendment to the MHRA and REC.</p> <p><u>Section 4, page 6 – Temporary Halt of a Trial</u> Updating details of how to submit a substantial amendment to the MHRA and REC.</p> <p><u>Section 4, page 7 – Early Termination of a Trial</u> Update of weblink for the End of Trial form.</p>

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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

- 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

- 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.
- 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/ukxi/2004/1031/contents/made>

4 Investigator and sponsor responsibilities

4.1 Urgent safety measures (USM)

- 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.
- 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.

- 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 Directors Professor Anthony Maraveyas or Professor Mahmoud Loubani** or the R&D Manager James Illingworth.
- 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).

The following information will be asked for on the call:

1. EudraCT number (including for other trials which may potentially be affected) of the trials for which USM action has been taken.
2. EudraCT number of other ongoing trials with the same Investigational Medicinal Product.
3. Whether any other trials with a different sponsor may be impacted and whether the concerned investigators have been made aware.
4. The affected IMPs (including alternative/commercial names).
5. Nature of the safety signal, and whether have there been any SUSARs.
6. What immediate safety actions have been taken and when.
7. 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.
8. Contact details in case of further questions.

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

- HUTH R&D QA should notify Pharmacy Clinical Trials staff as soon as possible.
- 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**. **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.**
- Note that 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 substantial amendment form and would save submitting another substantial amendment for the temporary halt as described in the next section on temporary halt of a trial.
- The Substantial Amendment Notification form can be created in IRAS by using the *Create Notice of Substantial Amendment* button in the Amendments tab.
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- In **part E.1** of the substantial amendment form, 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](#).**
- The substantial amendment form and any supporting documents should be sent with a covering letter detailing;
 - the urgent measures taken
 - the reasons for them
 - the **safety scientist** contacted.

- The amendment should be sent to the MHRA using the CESP system. This will be submitted by HUTH R&D QA. Please refer to R&D Working Instruction 20 for instructions on how to use CESP.
On the CESP system please select “Regulatory Activity Type: Clinical Trial”. **Do not** select “Urgent Safety Restriction Procedure”.
- The substantial amendment form, any supporting documents and a covering letter in pdf format should be emailed to the REC co-ordinator.
Please note you cannot submit amendments via IRAS.
- The amendment documentation should be emailed to the R&D QA team at research.development@hey.nhs.uk. R&D QA will ensure that all relevant amendments are sent to Pharmacy Clinical Trials.

4.2 Temporary halt of a trial

- HUTH R&D as sponsor and the Chief/Principal investigator will decide whether the trial should be halted due to the urgent safety measures.
- 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 notification of amendment form**.
- The Substantial Amendment Notification form can be created in IRAS by using the *Create Notice of Substantial Amendment* button in the Amendments tab.
- The form should include a clear explanation of what has been halted (e.g. stopping recruitment and/or interrupting treatment of subjects) and the reasons for the temporary halt.
- Substantial amendments relating to temporary suspension and urgent safety measures must be submitted using the CESP system. This will be submitted by HUTH R&D QA. Please refer to R&D Working Instruction 20 for instructions on how to use CESP
- The substantial amendment form, any supporting documents and a covering letter in pdf format should be emailed to the REC co-ordinator.
Please note you cannot submit amendments via IRAS.
- The amendment documentation should be emailed to the R&D QA team at research.development@hey.nhs.uk. R&D QA will ensure that all relevant amendments are sent to Pharmacy Clinical Trials.

4.3 Restart of a trial

- HUTH R&D as sponsor together with the Chief/Principal investigator will decide if a trial is to be restarted.
- To restart a trial, the investigator (with HUTH R&D) should make the request as a substantial amendment using the substantial amendment notification form and providing evidence that it is safe to restart the trial.
- The substantial amendment form should be sent to the MHRA, REC and HUTH R&D as described for the temporary halt.

- 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

- 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.
- 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>
- The end of trial form must be submitted to the MHRA using the CESP system. This will be submitted by HUTH R&D QA . Please refer to R&D Working Instruction 20 for instructions on how to use CESP.
- The end of trial form should be emailed to the REC co-ordinator.
- R&D QA will ensure the end of trial form is sent to Pharmacy Clinical Trials.

5 Additional sponsor responsibilities

- To help the investigator to prepare the substantial amendment form and all supporting documents.
- 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.
- To check when monitoring that MHRA, REC and R&D approvals have been obtained prior to the amendment being implemented.
- 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**.