University of Hertfordshire UH

Clinical Trials Unit

University of Hertfordshire Clinical Trials Unit (CTU)

STANDARD OPERATING PROCEDURE (SOP): Urgent Safety Measures

Standard Operating Procedure for Urgent Safety Measures at the University of Hertfordshire (UH)

SOP Number: gSOP-29-02	**Effective Date: 2nd December 2024**
Version Number: 2	**Review Date:** 2 - 3 years (or as required)

1. BACKGROUND

This is a University of Hertfordshire (UH) standard operating procedure (SOP).

2. PURPOSE

To outline the procedures to be followed if unexpected events occur relating to the conduct of a UH sponsored or co-sponsored study, that necessitate the Sponsor or Investigator taking appropriate Urgent Safety Measures (USM) to protect trial participants against any immediate hazard to their health or safety.

3. APPLICABLE TO

This applies to all staff involved in clinical research sponsored/co-sponsored by UH or hosted by UH, including, but not limited to: Chief Investigators (CI), Principal Investigators (PI), Research Fellows, Consultants, Statisticians, Clinical Trial Pharmacists, Research Managers, Research Nurses, Clinical Trial Practitioners, Allied Health Professionals, Trial Coordinators, Clinical Studies Officers, Data Managers and Students.

4. RESPONSIBILITIES

For UH sponsored/co-sponsored drug trials, the responsibility for pharmacovigilance is delegated to the CI. The CI should ensure the pharmacovigilance responsibilities are delegated to appropriately trained and qualified individuals and is recorded in a delegation log. The CI shall also ensure that all study personnel involved in conducting UH sponsored/co-sponsored trials attend SOP training sessions provided by the UH CTU and evidence of this is maintained within the study personnel training files.

5. PROCEDURE

USMs are actions which need to be taken to protect participants from any immediate hazard relating to the conduct of the trial or new developments with the Investigational Medicinal Product (IMP), which may affect the safety of the participants.

The CI has the delegated responsibility to take appropriate USMs.

5.1 When to take USMs

- USMs should be taken in a clinical trial when it is considered that they are required in order to protect clinical trial participants from any immediate hazard to their health and safety.
- USMs should be implemented immediately, approvals are not required prior to implementation.

If necessary, treatments and participant recruitment should be put on hold until there is evidence to suggest that the trial is safe to recommence.

Examples of when USMs may be required:

- Single case reports of an expected Serious Adverse Reaction (SAR) with an unexpected outcome (e.g. a fatal outcome).
- An increase in the rate of occurrence of an expected SAR, which is judged to be clinically important.
- Post-study Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur after the participant has completed a clinical trial.
- A new event relating to the conduct or the development of the IMP likely to affect the safety of the participants e.g.,
    - A serious event which could be associated with the trial procedures and which could modify the conduct of the trial.
    - Lack of efficacy of an IMP used for the treatment of a life-threatening disease.
    - A major safety finding from a newly completed animal study.

The CI must notify the main Research Ethics Committee (REC), the MHRA (for Clinical Trials of a Medicinal Product - CTIMPs) and the Sponsor immediately and in any event within three days, in the form of a substantial amendment, of the new events, the reasons for the USMs taken and the reasons why, along with the plan for further action.

5.2 Notifying the REC:

- The CI should notify the main REC that approved the study immediately by telephone.
- The CI must notify the REC of the USMs in writing by email within three days setting out
    - The reasons for the USMs
    - The plan for further action using the appropriate REC safety reporting cover sheet https://www.hra.nhs.uk/documents/1086/safety-report-form-ctimps.docx or https://www.hra.nhs.uk/documents/1087/safety-report-form-non-ctimp.docx.
- If the USM warrants a substantial amendment this must be submitted within three days of implementation (SOP-09 Amendments).

The UH CTU must be notified of USMs using the Notification of Amendment for Urgent Safety Measures form (see Appendix 2).

5.3 Notifying the MHRA

- The CI should telephone the MHRA's Clinical Trials Unit and discuss the issue with a medical assessor immediately, ideally within 24 hours of the measures being taken and no later than three days.
- A medical assessor may contact the CI should further clarification be required.
- This conversation should be documented and filed within the Trial Master File (TMF) for future reference.
- Following the conversation, provide the MHRA with written notification of the USMs taken and discussed with the medical assessor, within three days from the date the measures were taken. For trials not approved via combined review the notification should be emailed to the MHRA, for trials approved via combined review the notification should be submitted on IRAS.
- The CI must notify the MHRA in the form of a substantial amendment, changes resulting from the USM. This should be done within two weeks of notification to the MHRA of an USM. This notification should include:
    - A covering letter detailing:
        - Measures taken.
        - The reason for them.
        - The name of the medical assessor contacted.
    - A notice of substantial amendment form.
    - Any supporting documentation.
- Once all the amendment documentation has been agreed and finalised, the substantial amendment should be submitted, and an email sent to the trial team with all uploaded documents.

Refer to the MHRA and HRA websites to ensure up to date details for safety reporting are followed.

5.4 Notifying the Sponsor

- The CI must notify UH CTU (acting on behalf of the Sponsor) using the Notification of Amendment for Urgent Safety Measure Form and emailing this to uhctu@herts.ac.uk immediately following implementation of measures, setting out:
    - A description of the safety issue.
    - The details of the measures taken.
    - The reasons for the measures.
    - Confirmation that the MHRA and REC have been informed.
    - Confirmation that other PI's have been contacted as required.

- The substantial amendment must be submitted immediately, refer to UH gSOP-09 Amendments.
- The CI should keep UH CTU informed of the progress, outcome or resolution of the actions taken by sending follow-up information.

5.5 Notifying all Sites

- The CI should inform all participating sites and PIs of the implementation of USMs immediately or within a maximum of three days, in writing, by email.
- The local PIs must carry out the actions at participating sites.

5.6 Notifying Trial Participants

- Trial participants must be informed of the USMs and be given the option to continue in the trial with the modified trial procedures or withdraw.

5.7 Documents that must be Retained

- All communications relating to the measures should be retained e.g. emails, memos or letters and filed in the TMF and the sponsor's trial files.

5.8 Temporary Halt of a Trial

- Temporary halt to a trial is sometimes necessary for various reasons, including USMs.
- Temporary halt can apply to the whole trial or at individual site(s), or to all Trust-Sponsored trials using the same IMP; and can halt recruitment and/or interrupt treatments of active participants.
- The notification of temporary halt should:
    - Be submitted to both the REC and MHRA as a substantial amendment within 15 days from when the trial is temporarily halted.
    - Detail what is being halted and reasons for the temporary halt.
- When there is evidence to suggest the trial is safe to recommence:
    - A request to re-start the trial should be submitted as a substantial amendment.
    - Provide necessary evidence.
    - Refer to gSOP-09 Amendments.

5.9 Permanent Halt of a Trial

- Should the Sponsor or Investigator decide the trial will not recommence after temporary halt, an end of trial notification must be submitted to the MHRA within 15 days of the decision.
- Refer to gSOP-21 Trial Closure.

6. RELATED DOCUMENTS

- gSOP-07 Research staff training
- gSOP-18 Site Initiation
- MHRA website for up to date reference on Urgent Safety Measures and temporary halt: https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#10
- HRA website for up to date reference for Urgent Safety Measures: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/
- gSOP-09 Amendments
- gSOP-21 Trial Closure

7. APPENDICES

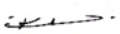
Appendix 1: Definitions
Appendix 2: Notification of Amendment for Urgent Safety Measures

8. VERSION HISTORY/REVISIONS

Version Number	Effective Date	Reason for Change
Version 2	Dec 2024	Review - Included the process for notifying the MHRA (taken from their website) Included URLs for HRA Safety Report Forms and for HRA/MHRA references for USMs

9. AUTHORSHIP & APPROVAL

Author Karen Irvine

Signature  **Date** 2/12/24

Pro-Vice Chancellor (Research & Enterprise) Approval

Signature 

Date 02/12/2025

Signed by Dr Susan Grey, Chair of the Governance of Clinical Studies Group (GCSG), on behalf of the Pro-Vice Chancellor (Research & Enterprise)

10. AGREEMENT

Please detach and retain within <u>your training files</u>

I have read and understood the contents and requirements of this SOP (ref gSOP-29-02) and accept to follow University policies implementing it.

Recipient

Signature: ……Date: ……..

Name & Position: ……

Please retain copy of the signed form for your reference in your training file

Appendix 1: Definitions

Adverse Event (AE)
Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that subject.

Chief Investigator (CI)
An authorised individual who is responsible for the conduct of the whole project in the UK. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. For UH sponsored trials, the CI had been delegated the pharmacovigilance responsibility for identification, recording and reporting of safety events, including submission of Development Safety Update Reports (DSURs) to the MHRA and REC.

Clinical Trial
A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or control) to evaluate the effects of those interventions on health outcomes.

Clinical Trial of investigational Medicinal Product (CTIMP)
A study that looks at the safety or efficacy of a medicine/food stuff/placebo in humans as defined by the Medicines for Human Use Regulations (2004).

Delegated Individual (DI)
An individual delegated by the PI to carry out their task(s).

Pharmacovigilance
The regulations outline procedures for the recording and reporting of safety events (adverse events or suspected unexpected serious adverse reactions) arising from clinical trials.

Principal Investigator (PI)
The investigator responsible for the research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any untoward medical occurrence or effect that at any dose that results in:
• death
• is life-threatening*
• requires hospitalisation or prolongation of existing hospitalisation
• results in persistent or significant disability or incapacity
• is a congenital anomaly or birth defect
• is an important medical event
* "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
All suspected adverse reactions related to an investigational medicinal product (IMP) that is both unexpected and serious.

Appendix 2: Notification of Amendment for Urgent Safety Measures

*Please complete this form and send to the UH CTU Office as soon as possible after implementation of Urgent Safety Measure. This form should only be in exceptional circumstances, for example to protect the participants from an **immediate** hazard to their welfare or safety*

Part A - Where to Send your Request

To: UH CTU Office

Office use only

Date received:

Part B - Your Details

From:

Tel:

Email:

Part C - Sponsor Details

(please tick)

UH-sponsored ☐

UH-co-sponsored (please specify below) ☐

UH-hosted (please specify below)

_____

Part D - Study Details

Trial Name: _____

CTIMP **OR** non-CTIMP

(please delete as

appropriate)

IRAS number:

Chief Investigator: _____

Principal Investigator: _____

Part E – Urgent Safety Measures Details

Description of safety issue:_____
_____
_____
_____

Measures taken:_____
_____

Reasons for the measures: _____

Date effective from:

Has MHRA been informed? Yes No N/A

Has the REC been informed? Yes No

Have other PI's have been contacted as required? Yes No

Chief Investigator Signature: _____

Date:_____