STANDARD OPERATING PROCEDURE 17
Safety

Part 3: Urgent Safety Measures

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Revision Chronology:	Effective date:	Reason for change:
Version 4.0	14 Dec 2023	Biennial review: Flowchart replaced with diagram to summarise requirements and timelines. Consistency check on timelines. Text reviewed to improve flow and reduce duplication. Formatting changes.
Version 3.0	11 Oct 2021	Biennial review: Change to new format. Minor changes to text. Update to timelines. More detail added about discussion with MHRA.
Version 2.0	4 July 2019	Removal of safety reporting process for CTU (now present in parts 1 & 2). Change of title and scope to cover urgent safety measures only. Addition of some specific responsibilities and tasks.
Version 1.6	1 August 2016	Biennial review: Minor clarifications to text. Web links and process flowchart updated.
Version 1.5	26 February 2014	Biennial review: Web links updated. Addition of information on safety reporting for international trials.
Version 1.4	1 December 2011	Update to annual safety reporting requirements. Additional information re: blinding and pregnancy in clinical trials
Version 1.3	1 September 2010	Addition of information re: new MHRA electronic SUSAR reporting system (section 3.3.4.1)
Version 1.2	29 January 2010	Biennial review. Web page links & CTCAE version number updated.
Version 1.1	25 January 2008	Format change. Clarification of reporting process.
Version 1.0	March 2006	

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Part 3 – Urgent Safety Measures

1. Purpose and Scope

This Standard Operating Procedure (SOP) describes how to identify if an Urgent Safety Measure (USM) is required and the process to follow to implement a USM to protect study participants against any immediate hazard to their health and/or safety.

It is applicable to all staff working on University of Warwick (UoW) sponsored research studies.

If the research project is not sponsored by UoW but is managed by Warwick Clinical Trials Unit (WCTU) and appropriately delegated in the collaboration agreement, this SOP should apply. Where this is not the case, externally sponsored studies should follow the relevant sponsor's process and document any deviations from the procedure outlined here.

2. Definitions

Urgent Safety Measure (USM)	A procedure which is not defined by the protocol but put in place with immediate effect to protect study participants from any immediate hazard to their health and safety.

3. Background

For Clinical Trials of Investigational Medicinal Products (CTIMPs), The Medicines for Human Use (Clinical Trials) Regulations make provisions for the sponsor and Chief Investigator (CI) to take appropriate USMs to protect a research participant from an immediate hazard to their health and safety. This can be implemented prior to obtaining approval from the Research Ethics Committee (REC) and the Medicines and Healthcare products Regulatory Agency (MHRA).

4. Procedure

4.1 Responsibilities

CI (or delegate)	• Contact MHRA Clinical Trials Unit and discuss the event with a safety scientist (as required for CTIMPs). • Discuss event with sponsor to determine if a temporary halt to the study is required. • Prepare substantial amendment to detail the USM. • Notify sponsor, REC, MHRA, investigator sites and funder, as applicable. • Monitor implementation of all aspects of the USM. • Notify NHS R&D offices in accordance with local procedures.
Principal Investigator (PI)	• Notify the sponsor/CI immediately (if USM is instigated by the PI/study site). • Confirm implementation of USM at site. • Document conversations with participants. • Undertake and document actions taken to fulfil the USM.
Sponsor	• Retain responsibility and oversight for ensuring USMs are implemented appropriately.
REC	• Receive and review USM information and amendments. • Consider whether the measures taken are appropriate in relation to the potential risks to the participants.
MHRA	• Receive and review USM information and amendments.

	• Consider whether the measures taken are appropriate in relation to the potential risks to the participants.
Data Monitoring Committee (DMC)	• Review information relating to USMs and report recommendations to all relevant parties.
Study/Trial Management Group (S/TMG)	• Discuss and document decisions made regarding implementation of a USM. • Prepare an implementation action plan.
Quality Assurance (QA) Team	• Support study team to review potential USMs and take appropriate actions.

4.2 When?

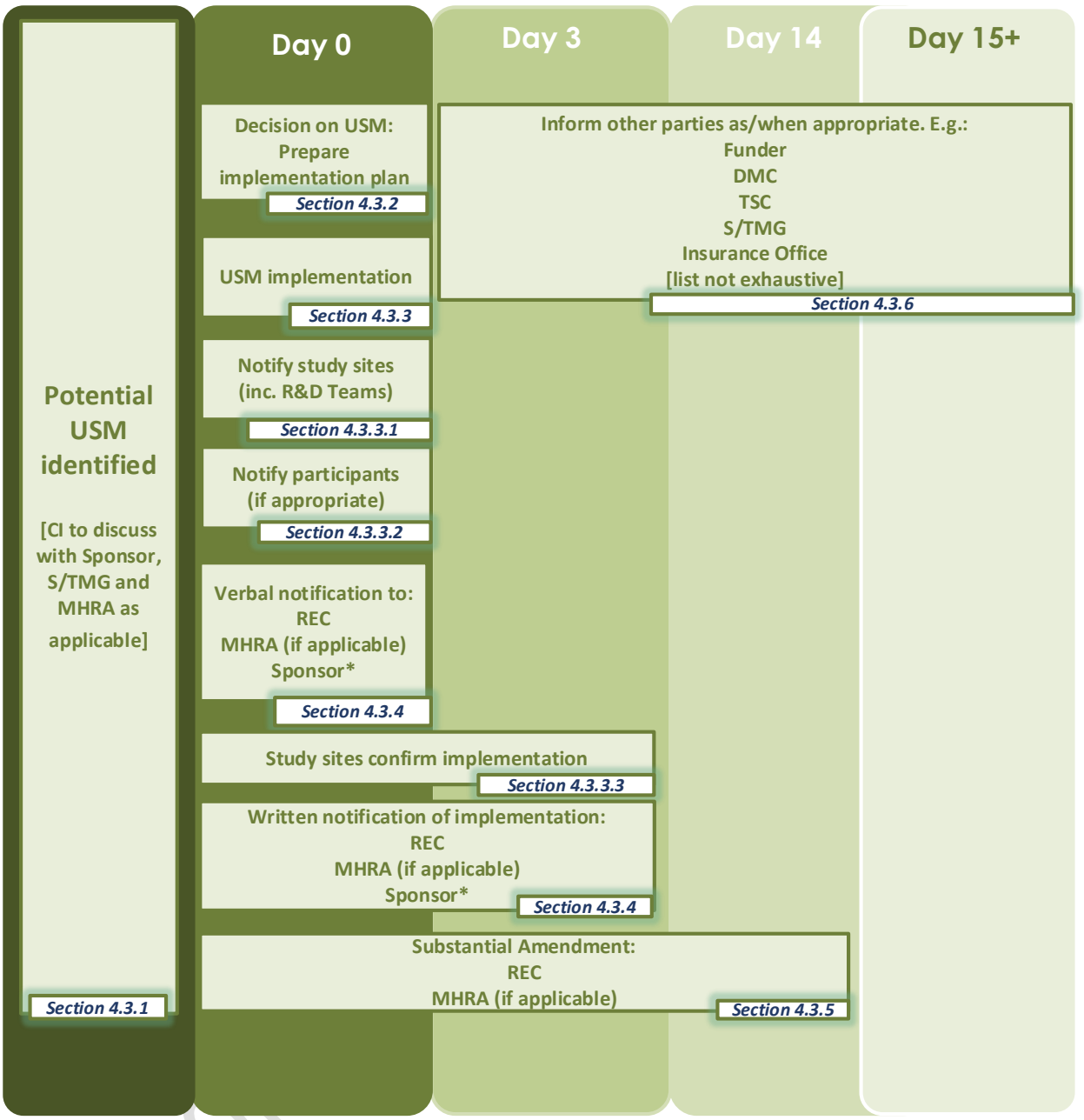
USMs may be identified and implemented at any time during a study. They must be reported immediately (and within three calendar days) to the:

- REC who provided the favourable opinion
- MHRA (if applicable)
- Study sponsor

Initial notification should be via telephone, with notice in writing within 3 calendar days of the USM. This should be followed up by a Notice of Substantial Amendment (NOSA) within 2 weeks of the USM.

4.3 How?

The process is outlined below. Further details can be found in the relevant sections.



**For UoW sponsored studies, verbal notification should go to the Sponsor's Office in Research & Impact Services (R&IS) and written confirmation should be sent to: sponsorship@warwick.ac.uk*

4.3.1 Identification of potential USM

Examples of where a USM may be required:

- Increased rate of occurrence and/or severity of expected Serious Adverse Events (SAEs).
- Expected Serious Adverse Reactions (SARs) where there is an outcome that is not expected.
- Event relating to the conduct of the study
- Event related to the delivery of an Investigational Medicinal Product (IMP).
- Lack of efficacy of an IMP for the treatment of life-threatening condition.
- Significantly higher incidence of death in one trial arm or at an investigator site

This is not an exhaustive list and if there is any potential risk to safety upon gaining information about a process or event, the MHRA and/or REC should be contacted immediately for advice.

If the study is being managed through WCTU, notify the QA team and any other relevant senior member of staff to initiate discussions regarding a decision on implementing an USM.

4.3.2 Decision on USM

Relevant members of the S/TMG, the sponsor's representative (and the QA team if the study is being managed by WCTU) should discuss implementation of a USM and document all discussions detailing actions and decisions. It may also be relevant to involve the DMC in such discussions (refer to SOP 12 Part 3). Advice can be sought from the Health Research Authority (HRA), REC or MHRA if necessary. Once it has been decided that a USM is required, this is considered as 'day zero' and measures should be implemented immediately. Notification to the relevant bodies should be made within the timescales detailed in sections 4.3.3 – 4.3.6. Ensure that all dates of decisions and notifications are recorded and documented. It is good practice to prepare an implementation action plan.

4.3.3 Implementation of USM

USM should be implemented immediately and can be done without the need for agreement or approval from the REC and MHRA. At the study design stage, consideration should be given to the methods to be used to disseminate information to sites and participants and other parties involved. This may include maintaining up-to-date contact lists, methods available for disseminating information quickly, and clearly defined responsibilities in contracts.

4.3.3.1 Notification to investigator sites

The CI or delegate must inform all PIs at collaborating investigator sites immediately in writing by email. The notification must include:

- Reason for USM
- Required actions
- Timelines
- Requirement for confirmation to the CI/delegate within three calendar days, to state that the required actions have been undertaken

The CI or delegate must retain documentation of the notification in the Trial Master File (TMF) and confirm to the Sponsor (and QA team if study is managed by WCTU) when this has been done.

4.3.3.2 Notification to participants

Participants may need to be informed of the USM – this will depend on the design of the study and where it is being hosted. Participants actively receiving the intervention should be informed of the USM by the quickest method, advised of whether additional visits/tests are required, and the timelines and implications of these. All actions should be documented and recorded in the medical notes. Other considerations to make include:

- Do all or some participants need to be re-consented and how will confirmation of re-consent be received and documented?
- Do other study participants that are not receiving the intervention at the time the of the USM need to be informed and how quickly?
- For participants not receiving the intervention at the time of USM, does advice from legal and compliance services and/or ethical advice need to be sought on the approach to notifying?

4.3.3.3 Confirmation of implementation

PIs or delegates at investigator sites should confirm in writing to the study team, within three calendar days that they have implemented any required USMs. Once all sites have confirmed implementation, the CI/delegate should inform the Sponsor (and WCTU QA team if the study is managed through WCTU) and store evidence of the confirmations in the TMF. Any non-response to implementation of a USM within three days of notification to the site should be escalated by the CI/delegate.

4.3.4 Verbal and written notification of USM

Verbal notification of the implementation of any USM should be made to the REC that approved the study within 24 hours of implementation.

For CTIMPs, the implementation should be discussed verbally with a Medical Assessor at the MHRA's Clinical Trials Unit. Document when the verbal notification was made in the TMF. This verbal notification must be followed up with a written notification within three calendar days. This can be done by email and should summarise the measures taken and the discussion with the MHRA's medical assessor. Contact details and information required are available via the link:

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#report-an-urgent-safety-

For international CTIMPs, refer to the reporting requirements for each individual Competent Authority (CA). This process should be clearly outlined at the study outset.

The REC and MHRA are not required to approve an USM but will consider whether the measures taken are appropriate in relation to the potential risks to the subjects.

4.3.5 Notification to REC and/or MHRA via substantial amendment

Formal notification of substantial amendment (SA) should be submitted to REC and MHRA (for CTIMPs) within two weeks of Day 0. Details regarding submission of a SA for USMs is available via:

HRA/REC:

http://www.hra.nhs.uk/research-community/during-your-research-project/safety-reporting/.

MHRA:

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#report-an-urgent-safety-

All substantial amendments should be reviewed and approved by the sponsor (and the QA Team for all WCTU managed studies).

Upon submission of the substantial amendment to the REC and MHRA, sites should be provided with the information for their Investigator Site File (ISF) and Research & Development (R&D) notified.

Where suspension or early termination of the study occurs, refer to SOP 5 Part 3: Communications with Approval Bodies for further details.

4.3.6 Notification to other parties

If not already involved, the funder, DMC, TSC and Insurance Office should be informed of the details of the USM as soon as possible, and documentation of the notification to these bodies must be retained in the TMF.

List of abbreviations

CA	Competent Authority
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
HRA	Health Research Authority
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
NOSA	Notification of Substantial Amendment
R&D	Research & Development
REC	Research Ethics Committee
PI	Principal Investigator
QA	Quality Assurance
R&IS	Research & Impact Services
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
TMF	Trial Master File
S/TMG	Study/Trial Management Group
TSC	Trial Steering Committee
UoW	University of Warwick
USM	Urgent Safety Measure
WCTU	Warwick Clinical Trials Unit