Standard Operating Procedure

S52 – URGENT SAFETY MEASURES Version No 4	
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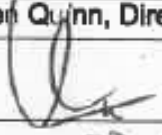
Signature	
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Controlled document

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It is the responsibility of all users of this SOP to ensure that the correct version is being used. If you are reading this in a paper format please go on-line to confirm you have the latest version.

DISCLAIMER

This generic R&D Standard Operating Procedure (SOP) must be followed unless a study specific SOP exists.

Once printed this is an uncontrolled document

Full History			
Version	**Date**	**Reviewed By**	**Reason**
1.0	04/08/2011	Assistant Research & Development Manager	New SOP
1.1	11/04/2014	Assistant Research & Development Manager	Document updated to reflect revised processes and procedures
2.0	18/09/2017	Assistant Research & Development Manager	New template and acronyms. Some changes to process.
3	25/09/2020	Assistant Research & Development Manager	New template and update to reflect current R&D governance structure.
4		Sponsorship Manager	Updates to include national changes to reporting

Associated Trust Policies/ Procedural documents:	R&D SOPs: • S02 Amendments • S31 CTIMP Reporting • S05 Breach of GCP • S22 Safety Reporting
Key Words:	R&D SOP USM
In consultation with: • Quality Assurance Group –August 2023 • Clinical Trial Team Lead Research Nurse - August 2023	

Contents

KEY POINTS OF THIS PROCEDURAL DOCUMENT:

- An urgent safety measure (USM) is an action that the sponsor and investigator may take in order to protect the subjects of a study against any immediate hazard to their health and safety.
- A USM is implemented without prior authorisation from a regulatory body but then must be immediately reported to the relevant regulatory authorities.
- It may be implemented by a Chief Investigator, Principal Investigator or the Sponsor.
- R&D must also be informed as soon as possible (within 24hours).

1. INTRODUCTION

During the course of a Clinical Trial involving an Investigational Medicinal Product (IMP), new safety information in the form of a Serious Adverse Event (SAE) or information received from an external source may necessitate an immediate change in the study procedures or a temporary halt to the study in order to protect clinical trial subjects from any immediate hazard to their health and safety.

If time does not allow for an amendment to be authorised by the Medicines and Healthcare Products Regulatory Agency (MHRA), Research Ethics Committee (REC) and Research Department, this change in procedure can be implemented as an Urgent Safety Measure (USM), by the Chief Investigator (CI) or Principal Investigator (PI), in accordance with the process put in place by the MHRA, and as detailed in this SOP.

This SOP has been produced in accordance with the requirements of The Medicines for Human Use (Clinical Trials) Regulations 2004, The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 and The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009.

2. PURPOSE

If unexpected events relating to the conduct of a trial (or the development of the IMP) sponsored by the Trust occur, there must be arrangements in place for taking appropriate USMs to protect participants against any immediate harm. This SOP will outline the procedures for implementing USMs during the course of a Clinical Trial involving at the Royal Devon University Healthcare NHS Foundation Trust (RDUH).

3. SCOPE

This SOP is applicable to Chief Investigators (CI), delegated trial team members involved in Trust-sponsored CTIMPs, and R&D team members undertaking sponsor activities on behalf of the Trust. Where responsibility is delegated to a Clinical Trials Unit (CTU), this SOP may also applicable to the assigned Trial Manager.

In the unlikely event that Urgent Safety Measures are required in a Trust sponsored non-CTIMP, this SOP will also apply.

For studies hosted by the Trust the PI should follow the procedures outlined by the sponsor of the trial but should report the USM to R&D.

4. DEFINITIONS & ABBREVIATIONS

CI	Chief Investigator
CIMD	Clinical Investigation of a Medical Device
CT	Clinical Trial
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
GOG	R&D Governance Oversight Group
HRA	Health Research Authority
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
QA	Quality Assurance
R&D	Research & Development
RDUH	Royal Devon University Healthcare NHS Foundation Trust
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
Sponsor	An individual, company, institution or organisation which takes responsibility for the initiation, management and financing of a clinical trial. Sponsorship activities may be delegated to the Investigator, CTU and/ or other organisations as appropriate
TMF	Trial Master File
USM	Urgent Safety Measure

5. DUTIES AND RESPONSIBILITIES OF STAFF

For CTIMP studies sponsored by the Trust, the responsibility for notifying the MHRA and REC of a USM is delegated to the CI/PI implementing the USM. For non-CTIMP studies sponsored by the Trust, the responsibility for notifying REC of a USM is delegated to the CI implementing the USM. If the Sponsor implements a USM, then responsibility for notifying the regulatory authorities is that of the Sponsor.

6. PROCEDURES – RDUH Sponsored Trials

6.1 An urgent safety measure is a procedure not defined by the Protocol that is put in place prior to authorisation by the MHRA, REC and Research Department in order to protect clinical trial subjects from any immediate harm to their health and safety.

6.2 Should the CI/PI implement a USM in a CTIMP then the MHRA, REC and sponsor must be notified immediately upon the measures being introduced. Should the sponsor implement a USM, the CI should be informed and then the MHRA, REC must be notified immediately

6.3 **MHRA, REC & Sponsor immediate notification:**

6.3.1 The investigator or sponsor representative implementing the USM must immediately, upon implementing the USM, phone the MHRA's Clinical Trial Unit on 020 3080 6456 to discuss the issue with a safety scientist, ideally within 24 hours. Information you will be asked for on the call:

a. 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
b. The affected IMP(s) - commercial or developmental names
c. Nature of the safety concern and whether it has been reported as a SUSAR
d. Which USMs have been taken and when
e. 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
f. 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.

6.3.2 After discussing the USM with the MHRA assessor via phone (6.3.1) , the investigator or sponsor representative implementing the USM must provide the MHRA with written notification of the measures taken and discussed with the medical assessor, within 3 days from the date the measures were taken.

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. The research ethics committee (REC) that approved the study must also be notified by email within three days. The notice should set out that such measures have been taken and the reasons why.

For trials where 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) by the instigator. More information can be found on the Health Research Authority (HRA) website. No additional notification is required to the REC via this route.

6.3.3 If unable to report a USM to the MHRA via the phone, an email should be sent to clintrialhelpline@mhra.gov.uk within 3 days of taking urgent measures. The subject of the email will be 'USM for trial IRAS ID/EudraCT number'. Please explain in the email the USM implemented, the reason and why it was not reported via phone. An MHRA assessor will be in contact and provide advice regarding further actions.

6.4 **R&D Notification:**

6.4.1 In addition, the reporting Investigator/Sponsor representative will immediately (within 24 hours) inform R&D by email via rduh.randdsafetyreporting@nhs.net about the USM. An Urgent Safety Measure Report Form FRM20_USM Notification Form V2 020817.doc should be attached to the email.

6.4.2 The R&D Department will acknowledge receipt of the email within 24 working hours. It is the responsibility of the Investigator reporting the USM to ensure that a receipt is received and to contact the R&D Department immediately by telephone if a receipt is not received within this timescale. The R&D Department will contact the Investigator reporting the USM on the next working day to discuss the matter further. The Investigator must therefore include in the email contact details where they can be contacted. If the reporting Investigator will be unavailable the next working day then the matter must be discussed fully with a delegated individual and contact details for the delegated individual included in the email.

Please note that a delegated individual must only be in place in exceptional circumstances and that it is expected that the reporting Investigator will be available to discuss the matter.

6.5 Details of any conversation and written notification must be documented in the Investigator Site File (ISF)/Trial Master File (TMF). A copy of the written notification to MHRA and REC should be provided to R&D via the generic safety inbox (rduh.randdsafetyreporting@nhs.net)

6.6 Where applicable, oversight committees (such as the Data Monitoring Committee or Trial Steering Committee) should review information relating to USMs and report any recommendations to all relevant parties.

6.7 **Notification of a substantial amendment**

6.7.1 After the immediate notification (6.3), an amendment tool plus any updated document including the changes agreed with the medical assessor) is also required.

6.7.2 The substantial amendment covering the changes made as part of the USM should be submitted within approximately two weeks of notification to the MHRA by the instigator of the USM (ensuring both the CI and the sponsor representative are copied in as applicable). Any potential reason for delay to submission of the substantial amendment should be discussed and agreed with the medical assessor at the time of initial notification or through a follow up call.

6.7.2 The USM-related substantial amendment must not include changes different from those required as an urgent safety measure. This is due to the fact that unrelated changes may result in rejection.

6.7.3 The substantial amendment should be submitted using MHRA Submissions via the Human Medicines Tile. Please select ‘Clinical Trial’ as the Regulatory Activity and ‘CT - Amendment’ from the Regulatory sub activity dropdown list.
If the trial has gone through the Combined Review process, then the substantial amendment should be submitted via IRAS. More information on how to submit a substantial amendment via IRAS can be found on HRA’s website.

6.7.4 A copy of the complete substantial amendment application must be retained in the ISF/TMF. An acknowledgement must always be requested and followed up if not received. This acknowledgement correspondence must be filed in the ISF/TMF. A copy of the substantial amendment application should also be provided to R&D via the generic safety inbox (rduh.randdsafetyreporting@nhs.net)

6.7.5 Upon receipt of the completed substantial amendment form, the R&D Department will decide whether the amendment might affect the Trust's sponsorship of the study and refer it to the Governance Oversight Group (GOG) if this is considered necessary. External review of the amendment may be obtained.

6.7.6 The Investigator at each site is responsible for ensuring that all other involved parties, such as Pharmacy, are promptly notified that amendments have been made. Refer to R&D/Amendments/S02.

6.7.7 Any correspondence relating to the USM from the MHRA, REC and/or Sponsor must be retained in the ISF/TMF. Correspondence from the MHRA and/or REC must be copied to the R&D Department.

6.8 **For non-CTIMP research**, the procedure above will be followed but MHRA do not need to be informed. Instead the CI must notify REC immediately of any USMs and in any event within three days.

6.9 **For studies hosted** by the RDUH the Sponsor will be notified immediately on their paperwork, and following their process (a copy should be sent to R&D department) so that they can assess and report the USM within the timelines required. For hosted studies the R&D department will review the completed substantial amendment and decide whether the amendment would affect Trust Approval, and refer it to the GOG if considered necessary.

7. DISSEMINATION AND TRAINING

7.1 This SOP and associated templates and forms will be uploaded to the Royal Devon website shortly after having been released.

7.2 All staff whose activities are subject to this SOP should ensure that they take time to read and understand the content of this SOP.

7.3 If applicable, a training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the contents of this SOP.

8. MONITORING COMPLIANCE AND EFFECTIVENESS OF THIS SOP

8.1 In order to monitor compliance with this SOP, the auditable standards will be monitored as follows:

No	Minimum Requirements	Evidenced by
1.	Check R&D have been notified in a timely fashion.	Copy of report & the email correspondence in the safety section of the R&D file
2.	Check that the relevant bodies have been notified of a USM in a timely fashion.	Copy of report & the email correspondence in the safety section of the site file

8.2 Outcomes from audit will be presented to the R&D Governance Oversight Group (GOG) which will monitor any resulting action plans until all issues have been addressed to satisfaction.

8.3 Issues identified via the audit process which require escalation will be referred to GOG.

9. ARCHIVING ARRANGEMENTS

9.1 The original of this document will remain with the R&D Quality Assurance Coordinator. An electronic copy will be maintained on the R&D section of the Q-Pulse document management system and a pdf copy on the Royal Devon website.

9.2 Archive copies must be maintained for any documents which have been superseded. Archive copies in electronic format should be retained indefinitely.

10. REFERENCES

Notification of an Amendment Form, EudraLex - Volume 10 Clinical trials guidelines - European Commission

R&D/Amendments/S02

Forms - Urgent Safety Measure Report Form FRM20_USM Notification Form V2 020817.doc

Health Research Authority (HRA) website

Integrated Research Application System (IRAS)
MHRA Submissions

11. EXAMPLE SCENARIOS

Examples of Urgent Safety Issues might include:

1) Single case reports of a Serious Adverse Reaction with an unexpected outcome (eg death);

2) An increase in the frequency of a Serious Adverse Reaction which is judged to be clinically important;

3) A new event relating to the use or development of the IMP that is likely to affect the safety of the study participants eg:

3.1 An SAE that could be associated with the trial procedures which could lead to a modification of the conduct of the trial;

3.2 A lack of efficacy of an IMP used for the treatment of a life-threatening disease;

3.3 A major safety finding from a completed clinical trial using the same IMP.