STANDARD OPERATING PROCEDURE

S52 – URGENT SAFETY MEASURES

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Controlled document

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DISCLAIMER

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

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Full History			
Version	**Date**	**Author**	**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.

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 –Sept 2020
- Clinical Trial Team Lead Resarch Nurse - August 2020

Contents

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 an IMP at The Royal Devon & Exeter NHS Foundation Trust (RDEFT).

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

CI	Chief Investigator
CT	Clinical Trial
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
GOG	Governance Oversight Group
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LRM	Local Management Research
MHRA	Medicines and Healthcare Products Regulatory Agency
PI	Principal Investigator
QA	Quality Assurance
R&D	Research & Development
REC	Research Ethics Committee
RDEFT	Royal Devon & Exeter NHS Foundation Trust
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
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

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 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. If the MHRA need more information a medical assessor will contact you. Details of this conversation must be documented in the Investigator Site File (ISF)/Trial Master File (TMF).

6.3 For studies hosted by the RDEFT 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.

6.4 For sponsored studies, the reporting investigator will immediately email (via generic safety reporting email) a Notification of Urgent Safety Measure Report Form hyperlink to the R&D Department. The R&D Department will acknowledge receipt of the notification 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 USM Report Form contact details where he/she can be contacted.

6.5 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 USM report form. 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.

6.6 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 The Investigator (or Sponsor representative if the Sponsor is implementing the USM) shall then immediately, and no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures. MHRA will tell you how to do this when you speak to them, but it will usually be by email. Written notification in the form of a substantial amendment (annex 2) is also required. The substantial amendment should include a covering letter detailing the measures taken, the reason for them and the name of the MHRA medical assessor contacted; a Notification of Clinical Trial (CT) Amendment form (EudraCT Public Website Documentation page) and any additional supporting documentation.

6.8 A copy of the complete substantial amendment application must be retained in the ISF/TMF together with evidence of posting (recorded delivery is recommended). An acknowledgement must always be requested and followed up if not received. This acknowledgement correspondence must be filed in the ISF/TMF.

6.9 For those studies sponsored by the RDEFT, 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.

6.10 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 GOGif considered necessary.

6.11 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.

6.12 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.

6.13 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.

7. DISSEMINATION AND TRAINING

7.1 This SOP and associated templates and forms will be uploaded to the RDE Research 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 EFFECTIVESS 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 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 RDE Research 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

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.