STANDARD OPERATING PROCEDURE FOR IMPLEMENTATION OF URGENT SAFETY MEASURES (NWORTH 4.06)

Approvals

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DOCUMENT HISTORY

Version number	Effective date	Authorship	Summary of changes
1	05/10/2011	D. Skelhorn, E. Bedson (based on UKCRC template)	New
2	01/11/2013	D. Skelhorn	Minor changes, section 12b up dated in line with HRA web site, SOP references standardised, Research governance framework for Wales added to references, other reference links updated

1. Table of Contents

2. Purpose

In compliance with the EU Clinical Trials Directive (transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 No.1031, as amended) and Research Governance Framework (2nd edition), procedures for the implementation of urgent safety measures are required for clinical trials involving human participants.

This Standard Operating Procedure (SOP) describes the procedures to be followed when it is necessary to implement urgent safety measures.

3. Scope

This procedure applies when there is a need to address an urgent safety issue relating to the conduct of clinical trials involving human participants. This SOP applies to clinical trials of investigational medicinal products (CTIMP) and non-CTIMPs.

4. Responsibilities

The Sponsor

SI 2004/1031 part 4 30 requires that the Sponsor of a clinical trial ensures there are arrangements for implementing appropriate urgent safety measures to protect participants against any immediate hazard.

The Chief investigator

In practice, the individual best able to take these measures will be the CI, or another identified person or organisation, rather than the Sponsor directly. If the decision making process is to include the trial independent oversight committee/s (Trial Steering Committee or Data Monitoring Committee) this should be identified at the outset and documented accordingly.

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Unless NWORTH has documentation in place, for example signed authority from the Sponsor, acknowledging who retains the responsibility for taking these actions (usually this individual will be the CI) the Sponsor remains directly responsible. Reports will generally be channelled via designated NWORTH personnel; usually this will be the trial coordinator.

Members of the research team

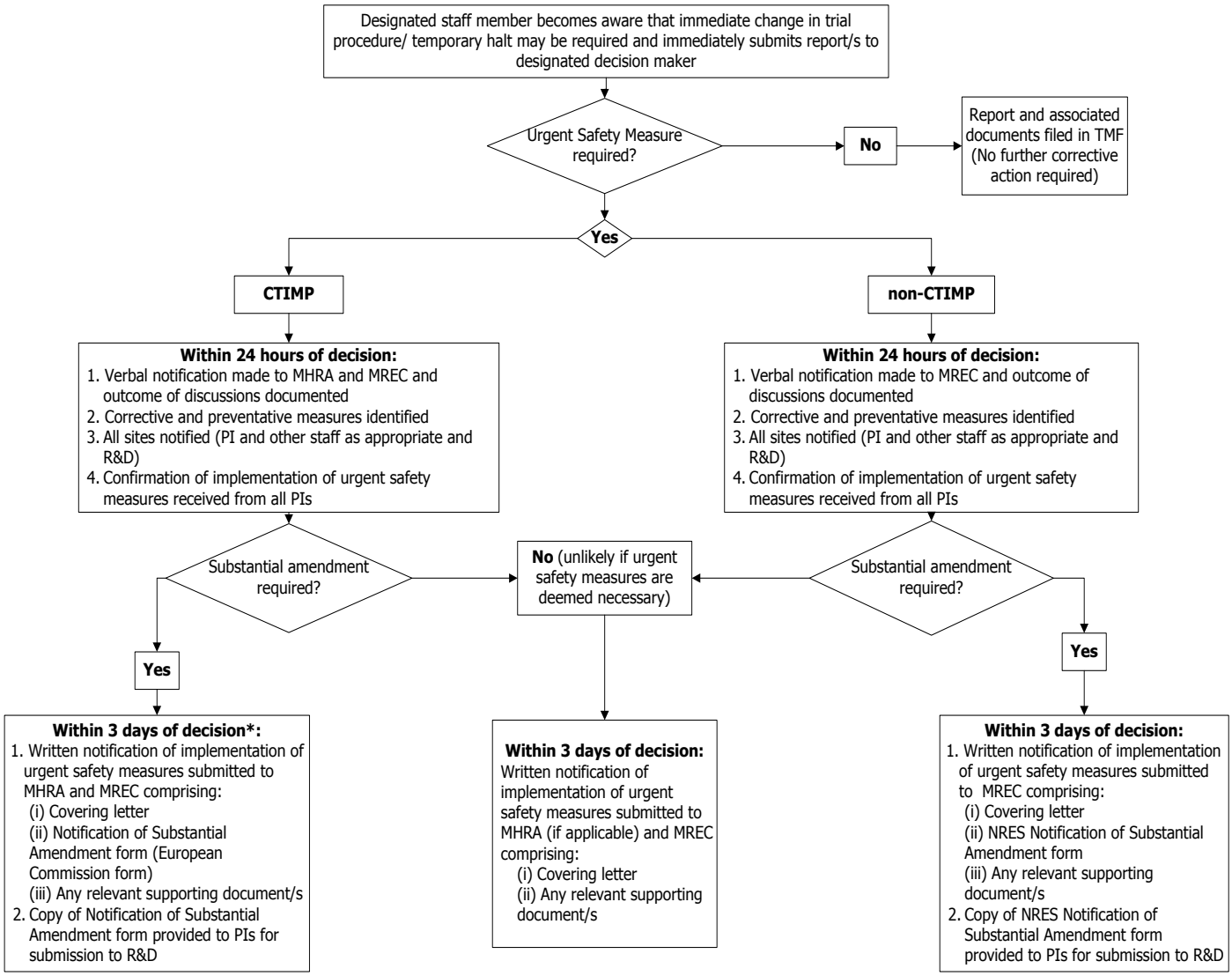
All members of the research team are responsible for reporting (to the sponsor or delegated party) if they believe that the implementation of safety measures is required. NWORTH personnel identified on the delegation log to be responsible for site training, usually this will be the designated trial coordinator, should ensure instructions for reporting of potential urgent safety issues are included during site initiation training (see SOP 3.03 Trial initiation and site set up).

5. Procedure

An urgent safety measure is a procedure which is not defined by the protocol that can be put in place with immediate effect without needing to gain prior authorisation by the REC (and MHRA where applicable), in order to protect clinical trial participants from any immediate hazard to their health and safety. For CTIMPs examples of urgent safety issues may include the occurrence of a single case report of a Serious Adverse Reaction (SAR) that has an unexpected outcome, or a clinically important SAR occurring with greater

frequency than anticipated or a significant hazard, such as lack of efficacy with an IMP used to treat a life-threatening disease. An example of an urgent safety issue that may occur in either CTIMP and non-CTIMPs would be one happening as a result of trial procedures, rather than as a result of an intervention being investigated, for example it may be identified that a trial related assessment exposes participants to unforeseen risk requiring an urgent amendment of trial conduct.

5.1 Procedure Flow Chart



During the development of the trial protocol, the trial management group should ensure that the responsibilities for decision making and implementing of urgent safety measures are both clearly defined and appropriately recorded in the site delegation logs. Training in regard to reporting requirements should be included during site initiation visits.

5.2 Urgent Safety Measures - CTIMP

The following procedure should be followed if a designated NWORTH staff member, usually the trial coordinator, becomes aware of information that indicates an immediate change in a trial procedure, or a temporary halt to a trial may be necessary in order to protect clinical trial participants from any immediate hazard to their health and safety:

1. The designated NWORTH staff member should immediately record the details of the incident on an incident report form (see Appendix 1: Urgent safety measure decision template). They should then inform the CI, Sponsor (via their designated representative), and/or other designated individual (such as nominated senior NWORTH personnel, who has been delegated the responsibility for decision making with regard to urgent safety measures), with full details of the information they have received relating to the incident.
2. The individual designated to make a decision about implementing safety measures considers whether urgent safety measures are necessary to protect participants against any immediate hazard.
3. If trial participants are at risk, the designated individual should inform NWORTH contact that urgent safety measures are to be implemented so that proposed actions can be agreed.
4. The decision making process leading to the implementation of the urgent safety measures are documented (see Appendix 1: Urgent safety measure decision template).
5. For CTIMPs, the sponsor or another delegated individual should phone the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (i.e. within 24 hours). In practice this will ideally be done in parallel to identifying the necessary corrective and preventative measures required and discussions with the medical assessor may inform these actions.
6. The details of the medical assessor spoken to and a summary relating to the outcome of their conversation must be recorded (see Appendix 1: Urgent safety measure decision template).
7. For both CTIMP and non-CTIMPs verbal notification, via telephone, should also be provided to the main Research Ethics Committee and the outcome of these discussions should be summarised (see Appendix 1: Urgent safety measure decision template).
8. The requirement to initiate an urgent safety measure, and the proposed corrective/preventative action, should be communicated to all sites immediately (i.e. within 24 hours of the decision) with acknowledgment of its receipt and implementation received from each Principal Investigator.
9. The implemented urgent safety measures (e.g. amendment to protocol, temporary halt to the trial or premature closure of the trial) must be reported in writing to the MHRA and Ethics Committee within **3 days**. Note that The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009 allows that urgent safety measures implemented during a pandemic may be informed in writing "as soon as possible" rather than within the otherwise required 3 day period.
10. For CTIMP, the MHRA are notified; the substantial amendment should include a covering letter detailing the measures taken, the reason for the measures taken, details of the medical assessor contacted; a Notification of Amendment form; and supporting documentation.

    The MHRA Clinical Trials Unit on 020 7084 2443 or sent by e-mail to clintrialhelpline@mhra.gsi.gov.uk). The amendment should be **marked 'Urgent Safety Measure'.** The amendment should also be sent as PDF documents on a disk to:

    Information Processing Unit, Area 6,
    Medicines & Healthcare products Regulatory Agency,
    151 Buckingham Palace Road, Victoria,
    London. SW1W 9SZ.
    (These contact details are taken from the MHRA website, and should be checked when the implementation of urgent safety measures is considered to be necessary).

11. If delegated to NWORTH to do so, the completion and submission of the substantial amendment form should be arranged by the designated trial coordinator.
12. For CTIMP and non-CTIMP the main REC are notified; Notice in writing should be sent within 3 days and this will be reviewed at a meeting of the main REC or sub-committee.

The main REC do not require this notice to be accompanied by a substantial amendment form, however it should describe corrective and preventative actions, such as intention to submit substantial amendment to protocol, temporary halt of the trial etc. For best practice, notice of the substantial amendment should be submitted within 3 days:

a. For CTIMPs the notice of substantial amendments must use the European Commission form, available on the EudraCT: European Clinical Trials website. The form should be signed by the named applicant and a single hard copy of the relevant form should be submitted to the REC, together with all relevant enclosures.
b. For all other research, there is a notice of substantial amendment form available in IRAS. The system will automatically generate the type of notice of substantial amendment form that is appropriate to the project category. To generate the notice of substantial amendment form in IRAS open your study, highlight the REC application on the Navigate page and then select the Amendment tab and follow the instructions provided. - See more at: http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/preparing-amendments/#sthash.ygt9PQF8.dpuf

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13. For CTIMP and non-CTIMP, NHS R&D should be notified; Principal investigators, or other delegated individual/s, will be supplied with a copy of the appropriate substantial amendment form for submission to R&D departments in parallel to the ethical and regulatory notifications.
14. Arrangements for contacting the individual responsible for decision making with regard to urgent safety measures during extended breaks (for example Christmas and Easter) should be made to ensure appropriate cover is in place.
15. To recommence a temporarily halted trial, NWORTH(via the trial coordinator), if delegated to do so, should make the request as a substantial amendment using the notification of amendment form and providing evidence that it is safe to restart the trial.
16. If a sponsor decides not to recommence a temporarily halted trial, the MHRA and Ethics Committee should be notified within 15 days of this decision, using the End of Trial Declaration form available from http://www.hra.nhs.uk/research-community/end-of-study-and-beyond/ and including a brief explanation of the reasons for ending the trial. This will be undertaken by NWORTH, if it is delegated to do so.

5.3 Urgent Safety Measures – non-CTIMP

Projects that do not involve an IMP do not require authorisation by the MHRA however appropriate governance arrangements are still required. Should urgent safety measures be necessitated in a non-CTIMP project, all of the steps detailed in 5.2 should be followed, other than communication with, and notification of, the MHRA. In addition, for medical devices there should be appropriate vigilance reporting and if it is a clinical investigation of non-CE marked medical devices, MHRA (Medical devices) should be notified .

6. Training plan for SOP implementation

Training will be carried out in accordance with NWORTH training SOP 2.01

7. Glossary of Terms

CTIMP	Clinical trials of investigational medicinal products
Non-CTIMP	Clinical trials assessing interventions other than investigational medicinal products

8. References

1. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0020:EN:HTML
2. Statutory Instrument 2004 No. 1031 The Medicines for Human Use (Clinical Trials) Regulations 2004: http://www.opsi.gov.uk/si/si2004/20041031.htm
3. Research Governance Framework for Health and Social Care: Second edition: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962
4. Research Governance Framework for Health and Social Care in Wales: Second edition: http://www.wales.nhs.uk/sites3/page.cfm?orgid=952&pid=59407
5. International Conference Harmonised Tripartite Guideline Clinical safety data management: Definitionsand standards for expedited reporting E2A : http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

   (October 1994)
6. The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009
7. Medicines and Healthcare products Regulatory Agency http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm#10
8. National Research Ethics Service Standard Operating Procedures for Research Ethics Committees

   http://www.hra.nhs.uk/resources/after-you-apply/knowledgebase-nhs-rec-review-outcomes/nres_sops_v5-1_2012-03-14-2/
9. National Research Ethics Service notice of substantial amendments

   http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/
10. MHRA (Medical devices) http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm

9. Referenced SOPs

UKCRC NWORTH SOP template: Implementation of Urgent Safety Measures
NWORTH Trial initiation and site set up SOP 3.03

10. Appendices

Appendix 1: Urgent safety measure decision template

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Record of decision making: Potential Requirement to Implement Urgent Safety Measures ***THIS FORM TO BE PRINTED AFTER COMPLETION AND RETAINED IN THE TMF***
For <Trial Acronym here>, responsibility for decision making about implementation of urgent safety measure lies with: Sponsor representative: ☐ Chief Investigator: ☐ Other: ☐(specify)_____

Trial name and Acronym:	
EudraCT number (If applicable):	☐ N/A
MREC number:	
Other reference number/s:	☐ N/A
Sponsor:	
Sponsor reference:	
Chief Investigator:	
Date trial commenced:	_ _ / _ _ _ / _ _ _ _
Protocol version and date:	
Date CTU became aware of incident/s:	_ _ / _ _ _ / _ _ _ _
Reported to (check appropriate box):	Sponsor ☐ CI ☐ Other: ☐(specify)_____
Reported by and date:	_ _ / _ _ _ / _ _ _ _

Reason for report: Detailed description of incident/s:

Centre name: _____

PI name: _____

Other involved parties: _____

In this section include details of:

- *Relevant incident/s*
- *The location of the incident/s*
- *Who was involved and the nature of the incident/s*
- *The outcome of the incident/s*
- *Any information given to participants*
- *Any actions planned and/or completed*

Opinion of:
Sponsor representative: ☐ Chief Investigator: ☐ Other: ☐(specify)_____

☐ Urgent safety measures required[1]
☐ Non-urgent intervention/amendment required[2]
☐ No intervention required

Summary of discussions/agreed actions:

[1,] If urgent safety measures are required, designated representative should contact the MREC and MHRA, where applicable, within 24 hours and this should be followed with written confirmation as per SOP
[2] Refer here to local SOPs with regard to decision making and processing of non-urgent amendments to trial conduct

Summarise here e.g. the reasons for urgent safety measures, any agreed preventative and corrective action/s and the plan for further action/s

Designated representative contacted MHRA (if applicable): Yes ☐ N/A ☐

Contact made by	Name of MHRA medical assessor contacted	Date of contact
		_ _ / _ _ _ / _ _ _ _

Comments/ outcome of discussions with MHRA medical assessor:

Designated representative contacted Main Research Ethics Committee: Yes ☐ N/A ☐

Contact made by	Name of MREC representative contacted	Date
		_ _ / _ _ _ / _ _ _ _

Comments/ outcome of discussions with MREC:

Attachments:

List here any relevant attachments, e.g. email correspondence. Ensure they are printed and retained with this summary in the TMF

Record completed by:

Print name and Role	Sign	Date
		_ _ / _ _ _ / _ _ _ _