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Urgent Safety Measures

Clinical Trials

SOP Reference ID:		Noclor/Spon/S08/01	
Version Number	1.0	**Effective Date:**	1st March 2016

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Standard Operating Procedure: Urgent Safety Measures

Version History

SOP Reference ID	Effective Date	Reason for Change
SOP CA019 Version 1.0	18/11/2011	
Noclor/Spon/S08/01	01/03/2016	Newly created Noclor SOP (applicable to all Noclor partner NHS Trusts). New numbering system adopted so this SOP has been assigned first version. New SOP format and revised content.

Authorship and Authorisation

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Standard Operating Procedure: Urgent Safety Measures

1. Purpose

An Urgent Safety Measure (USM) is a measure 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 for CTIMPs) in order to protect clinical trial participants from any immediate hazard to their health and safety.

In compliance with the EU Clinical Trials Directive (transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 No.10312, as amended) and Research Governance Framework (2nd edition), procedures for the implementation of USMs 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 an USM in a clinical trial sponsored by a Noclor Partner NHS Trust.

2. Scope

This SOP should be followed by Chief Investigators (CIs) that are responsible for setting up and managing clinical trials [Clinical Trials of Investigational Medicinal Products (CTIMPs) and non-CTIMPs] to ensure that when an USM is initiated that it is implemented and notified in accordance with sponsor procedures and regulatory requirements (where relevant).

3. Abbreviations

CI	Chief Investigator
CTIMP	Clinical Trial of Investigational Medicinal Product
PI	Principal Investigator
SOP	Standard Operating Procedure
TMF	Trial Master File

4. Procedure and Responsible Personnel

USMs may be instigated by either the Sponsor or an Investigator (Chief or Principal); they apply when actions are taken regarding the whole study.

Investigators must act immediately if they find a safety issue during a clinical trial to protect subjects from any immediate threat to their health and safety. Principal Investigators (PIs) are delegated this responsibility through their contractual agreement (mNCAs) with the sponsor.

The clinical trial protocol (and supporting trial procedures where relevant) should document the procedures for Investigators to follow for implementing and notifying USMs. For CTIMPs, (PIs) should be trained in the USM procedures at the Site Initiation Visit (SIV).

Examples of when an USM may be required in a CTIMP:

- Serious adverse reactions with an unexpected outcome (e.g. death) – suspend recruitment as USM
- A major safety issue identified from other studies (clinical or non-clinical) or from other usage of the investigational medicinal products (IMP) – suspend recruitment as USM

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	Procedure	Responsible Personnel
4.1	The Chief Investigator (CI) should be the first point of contact for Principal Investigators (PIs) to discuss any concerns over safety or proposed /implemented USMs [if time permits the PI should discuss such actions with the CI prior to implementation of measures]. All safety concerns should be taken seriously and addressed by the CI directly. Details and outcomes of all discussions must be clearly documented in the TMF (even when the concern raised turns out to be inconsequential).	All/Chief Investigator (CI)
4.2	**Initial verbal notification of USMs** **4.2.1 CTIMPs** 4.2.1.1 Where there is an immediate threat to safety, the CI should contact the MHRA's Clinical Trial Unit directly (and within 24 hours) to discuss the safety issue with a safety assessor. 4.2.1.2 The CI must communicate the outcome of discussions with the MHRA safety assessor immediately to the Noclor Sponsor Representative[1] (by telephone and followed-up with email). 4.2.1.3 The CI must inform the REC that provided the favourable opinion by telephone within 24 hours of the safety hazard/USM 4.2.1.4 If the CI is not contactable in situations where there is an immediate threat to safety the PI must contact the MHRA's Clinical Trial Unit directly (and within 24 hours) to discuss the issue with a safety assessor. The PI must communicate the outcome of discussions with the MHRA safety assessor immediately to the CI and the Sponsor Representative (telephone and followed up with email). **Refer to MHRA website for current contacts details for the clinical trial helpline.** *[1]The CI should attempt to contact the Noclor Sponsor Representative to discuss concerns over safety or proposed /implemented USMs prior to verbally notifying the regulatory authorities/REC but only if time permits.* **4.2.2 Non-CTIMPs** 4.2.2.1 The CI should notify the REC (that gave the favourable	Chief Investigator (CI)/Principal Investigator

	opinion) and the Noclor Sponsor Representative verbally within 24 hours of the hazard/USM	
4.3	**Written Notification of USM** **4.3.1 CTIMPS** 4.3.1.1 The CI must follow up the verbal notification of an USM with written notification within 3 days of the safety hazard/USM 4.3.1.2 This notification should be a written account of the telephone conversation with the safety assessor (names and dates/times of telephone call should be documented) and include details of what measures have been taken, the reason for the measures, a summary of advice given/plans for further action 4.3.1.3 The MHRA safety assessor will communicate how they (the MHRA) should be notified in writing during the initial telephone call (this is usually by email to the clinical trial helpline with email 'Subject' as Urgent Safety Measure). 4.3.1.4 The USM written notification should also be sent to the REC and Noclor Sponsor Representative in parallel (i.e within the 3 days) 4.3.1.5 Where a substantial amendment is required this should be processed according to SOP Noclor/Spon/S07/0X **4.3.2 Non-CTIMPs** 4.3.2.1 The CI must follow-up verbal notification of an USM with written notification within the 3 days of the hazard/USM. Written notification should be sent to the REC and the Noclor Sponsor Representative. The written notification should detail what measures have been taken, the reason for the measures and the plans for further action 4.3.2.2 Where a substantial amendment is required this should be prepared according to Amendment SOP (Noclor/Spon/S07/0X)	Chief Investigator (CI)
4.4	The CI in discussion with the Noclor Sponsor Representative[1] will need to consider the following actions at the time of identifying/notifying the USM: 4.4.1 Whether a temporary halt to trial is required (allowing time to assess the situation /safety data). Refer to Temporary	Chief Investigator (CI)/Noclor Sponsor Representative

	Halt SOP Noclor/Spon/S09/0X 4.4.2 Notify all Investigators who need to implement the same measures (Noclor Sponsor Representative must be copied in on all communications). PIs should notify their local R&D departments according to local policies/procedures 4.4.3 The specific event(s) /immediate hazard that has instigated the USM must also be reported according to trial safety reporting procedures and local incident reporting policy (as relevant) 4.4.4 Where an USM has been instigated at a specific site the PI must record details of the USM on the Protocol Deviations, Violations & Non-Compliance to GCP log (Noclor/Spon/T04/01) as Category 4. 4.4.5 Review of risks and associated mitigation plans for the trial to continue. Refer to Risk Assessment SOP (Noclor/Spon/S03/0X) 4.4.6 Agree to next steps/further action required e.g amendment to protocol 4.4.7 The rationale for the urgent safety measure should be made available to trial subjects. Investigators should provide written information (as prepared by CI) to the trial subjects and document discussions in their medical notes. In addition subjects must be given the option to re-consent to continue the trial with modified trial procedures or withdraw from the trial [1]*If any decision-making processes for a specific trial involves one of the trial oversight committees (TSC or IDMC) this should be documented in the protocol and the relevant Committee Charter as appropriate*	
4.5	The CI is responsible for keeping the sponsor, investigator sites and other parties as relevant (such as funder) fully informed of progress with any action plans/ outcomes /decisions relating to USMs and the future of the trial.	Chief Investigator (CI)
4.6	Where a temporary halt has been implemented the procedures for re-start further to the temporary halt must be followed. Refer to Temporary Halts SOP (Noclor/Spon/S09/0X).	Chief Investigator (CI)
4.7	If the study does not recommence after the USM the end of study should be notified. For CTIMPs, this would be defined as an early termination to the	Chief Investigator (CI)

	trial and must to be notified to the MHRA and Research Ethics Committees (REC) within 15 days of the decision being made not to re-start. Refer to End of Study Notification, Close-Out and Reporting SOP Noclor/Spon/S11/0X	
4.8	The details of all telephone calls, meetings, correspondence /emails, the timings of events, decision-making pertaining to a specific safety concern/USM should be documented (including date, time, who was spoken to and the outcome of discussions) and retained in the TMF.	Chief Investigator (CI)

5. Deviation from SOP

Noclor Sponsor SOPs define working methods which should be adhered to. However, occasionally for specific projects it may be necessary to deviate from the Sponsor SOP.

Formal written explanations/justifications of such deviations must be approved by Noclor Sponsor Representative prior to implementation (or they will be considered a non-compliance to sponsor procedures requiring reporting according to SOP Noclor/Spon/S10/0X).

The deviation from Sponsor SOP should be recorded on the SOP Deviation Form (Noclor/Inter/T12/0X) and sent to the Sponsor Representative for review. A copy of the completed and signed form should be filed with the TMF.

6. SOP Storage and Archive

The details of this SOP should be included on the study specific document inventory log (Noclor/Spon/T07/0X).

The Chief Investigator (CI) is responsible for retaining and archiving controlled copies of Sponsor SOPs (and the associated training records) that have been worked to for the duration of a trial in the Trial Master File (TMF).

7. Associated Documents

Document Reference ID	Document Type	Document Title
Noclor/Spon/S03/0X	SOP	Risk Assessment (Sponsored Research)
Noclor/Spon/S07/0X	SOP	Amendments (Sponsored Research)
Noclor/Spon/S09/0X	SOP	Temporary Halts (Clinical Trials)
Noclor/Spon/S11/0X	SOP	End of Study Notification, Close-Out and Reporting (Sponsored Research)
Noclor/Spon/T04/01	Template	Protocol Deviations, Violations & Non-Compliance to GCP Log

8. Appendices

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9. Confirmation of Training

This SOP will be provided to the Chief Investigator (CI) of a clinical trial that is being sponsored by a Noclor Partner NHS Trust and he/she will have the opportunity to ask specific questions to the author of the SOP.

The CI must e-sign the confirmation of self-training below prior to the study commencing.

The CI is responsible for ensuring that members of his/her study team are trained in the sponsor procedures (SOPs) that are relevant to their specific roles and responsibilities on the study.

I,

confirm that I have read and understood the content of this SOP and will work according to it.

Controlled copies of Sponsor SOPs should be filed in the relevant section of the Trial Master File (TMF). If this SOP replaces a previous version, the previous version should be retained in the TMF and marked through as superseded.

The SOP details should be added to the document inventory log (Noclor/Spon/T07/0X).

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10. SOP Training Log

All members of the co-ordinating trial team concerned by this SOP (according to the role and responsibilities they are being delegated by the CI and as they appear on the co-ordinating trial team delegation log) should sign the SOP training log.

	Full Name	By signing below I confirm that I understand and agree to work to this SOP	
		Signature	Date

This training log should be filed in the relevant section of the TMF.