

Standard Operating Procedure for the Recording, Management and Reporting of Adverse Events

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**Standard Operating Procedure for the Recording,
Management and Reporting of Adverse Events**

PURPOSE

This Standard Operating Procedure (SOP) describes to research staff the procedure for the recording, management and reporting of Adverse Events (AEs), Serious Adverse Events (SAEs), Suspected Serious Adverse Reactions (SSARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) for clinical trials that fall under the UK Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and the European Clinical Trials Directive (EU-GCP-DIRECTIVE). For convenience, this document will use “EU-GCP-DIRECTIVE” to cover the UK legislation and the EU-GCP-DIRECTIVE.

BACKGROUND

The EU-GCP-DIRECTIVE 2001/20/EC and The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) set out the requirements for adverse event management and reporting (pharmacovigilance). To comply with the regulations, which are now law, it is important that organisations undertaking the role of Sponsor have procedures and systems in place to support the recording, verification, reporting, analysis and management of adverse events and serious adverse events (suspected or unexpected).

Below are a number of definitions taken from the Statutory Instrument 2004/1031 in relation to adverse event management that Investigators, research teams and the Sponsor must know.

Definitions

“Adverse Event (AE)”

means any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

“Adverse Reaction (AR)”

means any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

“Serious Adverse Event (SAE), “Serious Adverse Reaction, or Unexpected Serious Adverse Reaction”

means an adverse event, adverse reaction or unexpected adverse reaction respectively that

- (a) results in death
- (b) is life threatening
- (c) requires hospitalisation or prolongation of existing hospitalisation
- (d) results in persistent or significant disability or incapacity or
- (e) consists of a congenital anomaly or birth defect

“Suspected Serious Adverse Reaction (SSAR)”

means an adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out

- (a) in the case of a licensed product, in the summary of product characteristics (SmPC) for that product
- (b) in the case of any other investigational medicinal product, in the Investigator’s Brochure (IB) relating to the trial in question

“Suspected Unexpected Serious Adverse Reaction (SUSAR)”

means an adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out

- (a) in the case of a licensed product, in the summary of product characteristics (SmPC) for that product
- (b) in the case of any other investigational medicinal product, in the IB relating to the trial in question

SCOPE OF THIS SOP

This SOP focuses on the recording, management and reporting of all AEs, ARs, SAEs, SSARs and SUSARs that occur in trial subjects and that require reporting in accordance with the EU-GCP-DIRECTIVE. This document will outline the responsibilities of both the Investigator and the Sponsor. If the Sponsor delegates any duties to the Chief Investigator (CI) or Principal Investigator (PI), the CI/PI must understand and be able to fulfil the duties and responsibilities they have agreed to undertake. The Sponsor will still remain ultimately responsible for any delegated duties. Any delegation of duties must be agreed in a written and signed document between all parties before the trial commences.

For the purposes of this document the term “Sponsor” will be used to describe the person responsible for undertaking the Sponsor’s role for pharmacovigilance in accordance with Part 5 of the Regulations (pharmacovigilance).

Please note that the Sponsor has responsibility for providing the Competent Authority with an annual safety report from the date the trial was first granted authorisation. The requirements and timeframes for the annual report will be described in a separate SOP

RESPONSIBLE PERSONNEL

There are a number of responsibilities that are required when recording and reporting adverse events. Below is a list of responsibilities of both the Investigator and the Sponsor. **Any CI/PI who has agreed to undertake duties for pharmacovigilance delegated by the Sponsor must undertake both Investigator's and Sponsor's responsibilities as described throughout this document.**

Investigator's responsibilities:

- (1) Reporting all SAEs to the Sponsor. The initial report maybe verbal.
- (2) Submitting a detailed written report to the Sponsor following the initial SAE report.
- (3) Providing the Sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety within the agreed timeframes specified in the protocol.
- (4) Assessing each event for causality.
- (5) Supplying the Sponsor and the Research Ethics Committee (REC) with any supplementary information they request.

It is acknowledged that activities (1) and (2) are often undertaken by the study nurse/trial co-ordinator. This is important in urgent situations but every effort must be made by the study nurse or trials co-ordinator to discuss the SAE with the CI/PI.

Sponsor's responsibilities:

The Sponsor allocated to undertake Part 5 of the Regulations (pharmacovigilance) is ultimately responsible for:

- (1) Ongoing safety and evaluation of any Investigational Medicinal Product(s) (IMPs) they are using.
- (2) Promptly notifying any Investigators, REC(s) and Competent Authorities (CAs) (which is the Medicines and Healthcare Products

Regulatory Agency, MHRA for the UK), of any findings that may affect the health of subjects.

- (3) Ensuring they have written SOPs and systems in place to ensure quality standards are met and that personnel are trained for the purpose of data submission, validation, entry and review.
- (4) Keeping detailed written reports of all AEs reported by Investigators and performing an evaluation with respect to seriousness, causality and expectedness.
- (5) Registering users for pharmacovigilance data entry with the European Medicines Evaluation Agency (EMA).
- (6) Reporting all relevant safety information to the relevant REC(s) and CA(s).
- (7) Reporting all SUSARs to CA(s) and REC(s) of concerned Member States associated with comparator product(s) and Marketing Authorisation (MA) holder(s), within given timelines.
- (8) Breaking treatment codes before submitting expedited reports to CA(s) and REC(s) for specific subjects, even if the Investigator has not broken the code. (Note: A system for maintaining the blind for the CI/PI and trial staff may need to be agreed in advance).
- (9) Encouraging the set up of Independent Data Monitoring Committees for clinical trials that have high morbidity/mortality and describing their function in the protocol.
- (10) Submitting the annual safety report to CA(s) and REC(s) (This will be described in SOP, CRN/04/S08/00).

Any or all of the above Sponsor's responsibilities maybe delegated for the purposes of the trial. The Sponsor allocated responsibility for undertaking Part 5 of the Regulations (pharmacovigilance), can choose to delegate the Sponsor's duties to a suitably qualified person within the research team. This person must be named in a written agreement before the trial may commence. It is therefore **essential** that the nominated person is familiar with both the Investigator's **and** the Sponsor's responsibilities for pharmacovigilance recording, management and reporting.

PROCEDURES

1. Decisions and action to be taken by the CI/PI at the trial-planning and protocol writing phase

a) AE recording and reporting:

The CI/PI can decide how to record and report adverse events whether expected or not. The decision can be made **not to** record non-serious AEs (i.e. where the risk/benefit profile of the drugs under study is well established), or to record **only** the more severe AEs (i.e. with drugs which are known to be highly toxic and which cause ARs in a high proportion of patients, such as cytotoxics). In these cases it should be **clearly stated in the trial protocol and the local SOP** what will be recorded and how the reporting is to be managed. It may be decided that **all** non-serious AEs are to be recorded particularly where new drugs are being tested and where the safety-profile has not been established yet. Whatever option is chosen it must be consistent with the purpose of the trial and any toxicity and efficacy end points.

b) SAE recording and reporting:

It is essential to have in place the management and reporting arrangements for SAEs in trials with high morbidity/high mortality diseases, or where the trial primary endpoint could also be a SUSAR. Agreements at the beginning of the trial should be made for such SAEs that can be defined as disease-related and therefore not subject to expedited reporting. Clearly defining such SAEs and the methods for recording them can avoid the need for unnecessary reports later.

The procedures for managing and reporting these SAEs must be clearly defined in the protocol. For these particular trials **the Sponsor** is strongly advised to appoint an Independent Data Monitoring Committee (IDMC) in order to review safety data regularly throughout the trial and when necessary, recommend to the Sponsor whether to continue, modify or terminate the trial. Again, this procedure must be defined in the protocol.

With any recording and reporting, subject confidentiality and adherence to the Data Protection Act (1998) must be maintained on all reports.

2. During the trial

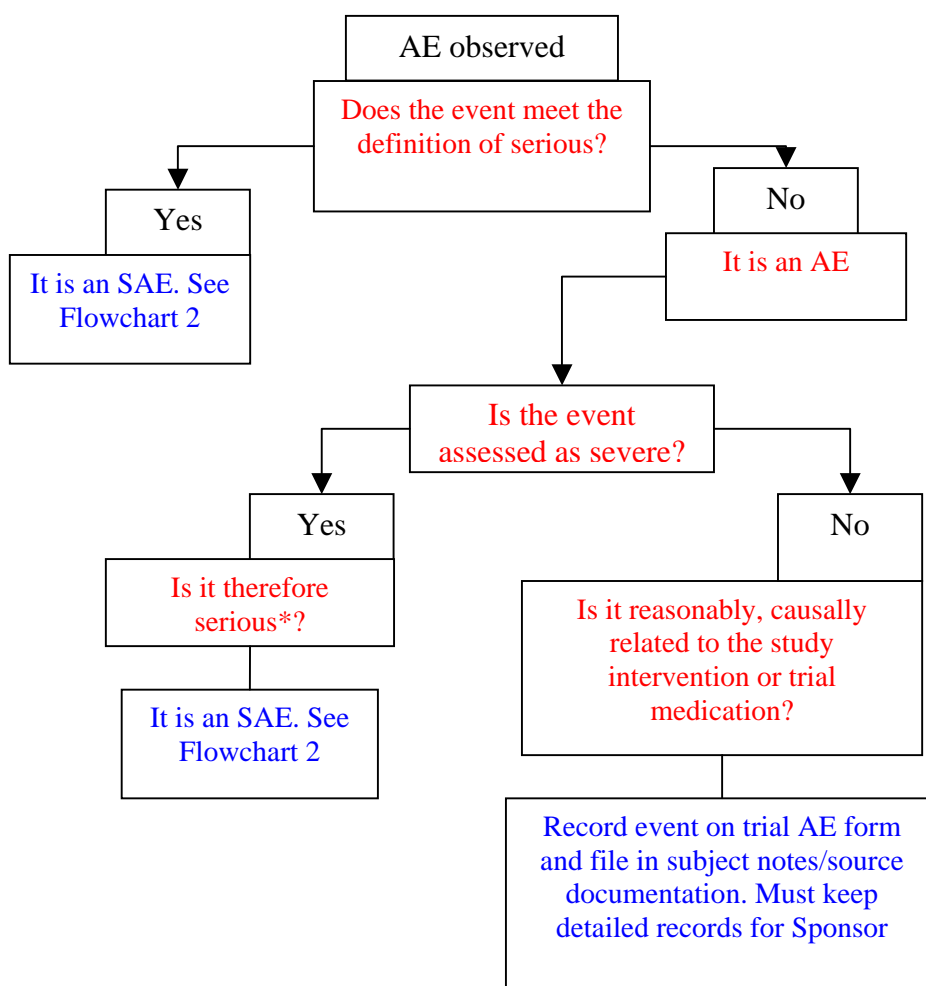
a) The CI/PI's responsibilities and processes for evaluating AEs

Each AE must be evaluated for **seriousness, causality, expectedness** and **severity**. The responsibility for the evaluation of seriousness, causality and expectedness can be shared between the CI and PIs. It may be most appropriate for the treating PI at each centre to evaluate each event, before

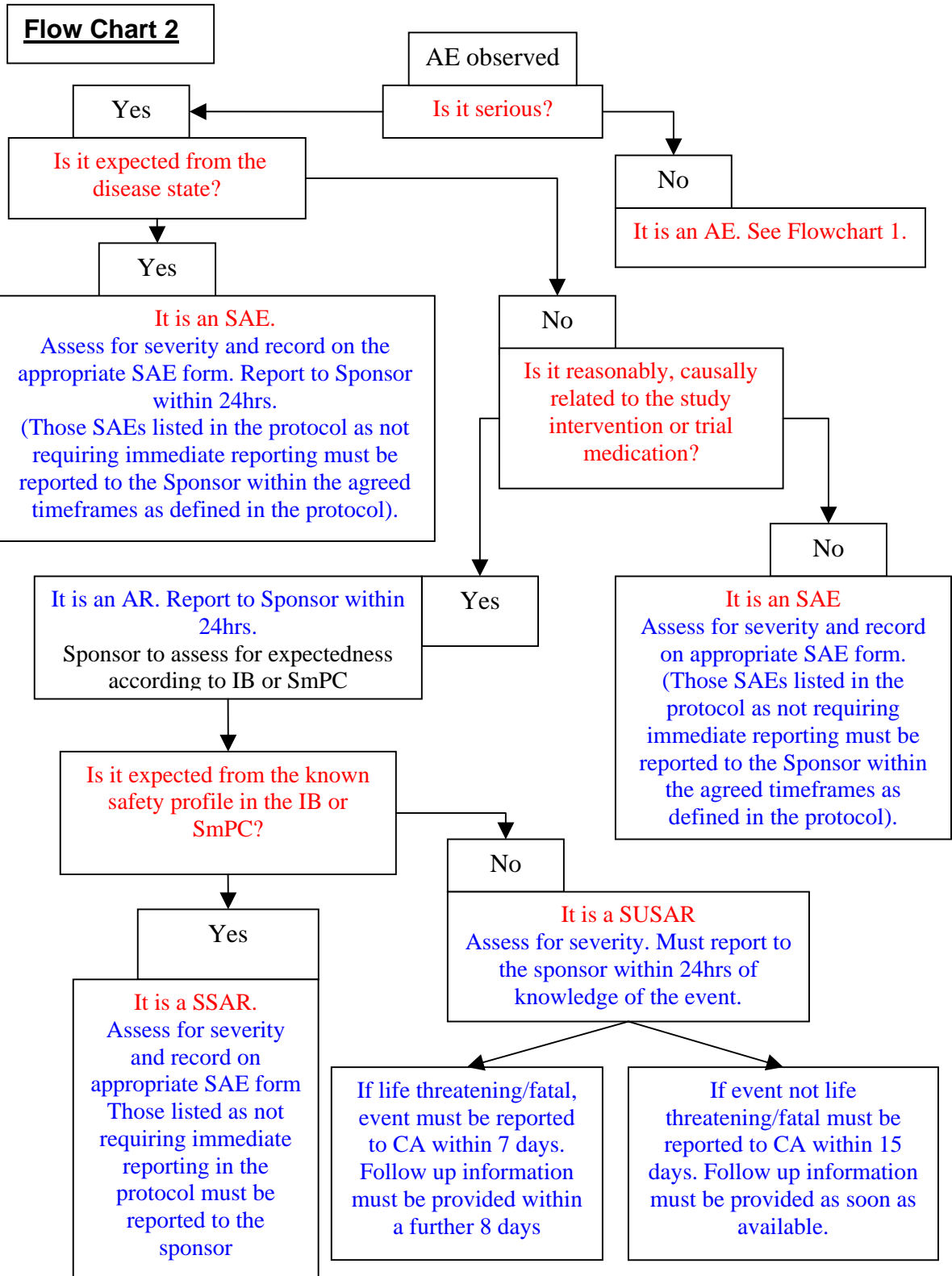
reporting it to the Sponsor. It must be stated in the clinical trial protocol and the local SOP who will take responsibility for the assessment and reporting of such events to the Sponsor and CI simultaneously. As expedited reporting maybe required, this SOP assumes that responsibility of initial assessment and reporting to the Sponsor lies with the PI.

Flowcharts 1 and 2 below will enable Investigators/research personnel to assess AEs and SAEs should they occur during the trial and decide if the event requires further expedited reporting by the Sponsor.

Flowchart 1



* An example would be severe vomiting requiring hospitalisation



b) The CI/PI's responsibilities, definitions and criteria for the evaluation of AEs

i) Evaluation and timeframes for reporting an AE as Serious to the Sponsor:

The CI/PI must assess the AE as serious if the following criteria are met:

- Death
- Is life threatening (when subject is at risk of death at the time of the event, not that death may have occurred if the event was more severe)
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

If the AE is assessed as serious the CI/PI **must** report the event to the Sponsor immediately or within 24hr of being made aware of the event. The initial report can be made verbally but must be promptly followed with a detailed, written report. The CI/PI must record the event with his assessment of seriousness, (along with causality, expectedness and severity) on a trial SAE form provided by the Sponsor (use Alert Report form Appendix 2 if UCL is the appointed Sponsor for Part 5 of the Regulations). Some information may not be available at the time of initial reporting and therefore every effort must be made by the CI/PI to ensure that all the required information for complete reports to be made.

ii) Evaluation of AEs for Causality:

Every effort must be made by the CI/PI to obtain all the required information to determine whether the AE is related to the trial intervention. A suggested 4-point scale maybe used as described below.

Not Related- temporal relationship of the onset of the event, relative to the administration of the product, is not reasonable or another cause can itself explain the occurrence of the event

Possibly Related- temporal relationship of the onset of the event, relative to the administration of the product, is reasonable but the event could have been due to another, equally likely cause

Probably Related- temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is

more likely explained by the drug than by any other cause

Definitely Related-

temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and there is no other cause to explain the event or a re-challenge (if feasible) is positive

Please note the CI/PI is not expected to break the code of blinded studies in order to assess causality. If it is necessary to break the code to ensure patient safety, this maybe done, preferably by an appointed Data Safety Monitoring Committee or Independent person. An AE becomes an AR if the CI/PI assesses the event as “having a reasonable causal relationship to the IMP”. Of the four categories above, “possibly”, “probably” and “definitely” related to an IMP qualifies as an AR. “Not related” would not qualify as a reasonable causal relationship and therefore not qualify as an AR.

iii) Evaluation of AEs for Severity:

It is common practice for events to be assessed for clinical severity (intensity) of the specific event. This must not be confused with “serious” which is a regulatory definition based on subject/event outcome or action criteria.

The CI/PI should describe the event as “mild”, “moderate” or “severe” when assessing severity. This should be included in the written report. **(Note: A severe rating will move an AE to an SAE if hospitalisation is involved).**

iv) Recording of AEs:

The CI/PI must record all AEs (with his assessments of seriousness, causality and severity) onto the trial AE recording form provided by the Sponsor. (A UCL “AE Recording Form” will be available if UCL is the appointed Sponsor for Part 5 of the Regulation when this SOP is revised). The CI/PI must record all AEs on the trial AE record form and file in the subject’s notes/medical records and send copies to the Sponsor. The CI/PI may also be asked to provide his/her evaluation of “expectedness” for such events. This opinion must be recorded on the SAE form before submission to the Sponsor. A copy of the SAE form must be filed in the Trial Master File (TMF) at each site where the SAE occurred for source verification purposes or inspection.

c) Sponsor’s responsibilities for AE recording and reporting

The Sponsor must obtain all AE records from each site and must also perform an evaluation with respect to seriousness, causality and expectedness. Any AE that the Sponsor evaluates as serious, having a possible causal relationship to the trial intervention and is unexpected, will require expedited reporting. This must be reported to the CA(s) and REC(s) according to the

timeframes specified below. The Sponsor must inform the CI/PI of any AE that is re-classified as “serious” or requiring “expedited reporting”.

d) What the Sponsor must do following receipt of SAE report from CI/PI:

On receipt of each and every SAE form the Sponsor must provide an evaluation of “expectedness” for each SAE. Reports have to be considered as “unexpected” if they add significant information on the specificity or severity of an expected event. The expectedness of an SAE/SAR should be determined according to the reference document as defined in the protocol (i.e. IB for non-licensed product or SmPC for a licensed product in the EU assuming that the product is being used in the trial exactly as stated in the SmPC). If the IMP has a Marketing Authorisation in several Member States with different SmPCs, the Sponsor should select one of them as a reference document for assessing expectedness and must identify this in the protocol.

All Suspected Adverse Reactions (SARs) related to an IMP that are both unexpected and serious (SUSAR), are subject to expedited reporting.

Other safety issues also qualify for expedited reporting where they might alter the current risk-benefit assessment of the IMP or that would be sufficient to consider changes in the IMP administration or overall conduct of the trial i.e.

- **New events that relate to the conduct of the trial or the development of the IMP likely to affect the safety of subjects such as an event which could be associated with trial procedures and could modify the conduct of the trial, a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life threatening disease, or a major safety finding from a newly completed animal study.**
- **Single case reporting of an expected SAR with an unexpected outcome.**
- **An increase in the rate of occurrence or severity of an expected SAR, judged clinically important.**
- **Post study SUSARs that occur after the subject has completed a trial.**

If the Sponsor is not in agreement with the “expectedness” decision the CI/PI has made, the Sponsor cannot overrule the CI/PI’s decision. Both opinions must be recorded on the SAE report form. The Sponsor must retain detailed reports of all SAEs reported by the CI/PI.

If the Sponsor has received information from the CI/PI that classes the event as a “SUSAR”, an expedited report form must be completed, signed and dated by the Sponsor prior to submitting to the CA(s) and main REC(s).

Electronic reporting is the preferred method for expedited reporting to the CA(s). The CIOMS-1 (see Appendix 5) form is the widely accepted standard for expedited adverse reaction reporting however, no matter what the form or format used, it is important to capture the basic data elements described in Appendix 4 of this SOP.

For blinded clinical trials, the blind should be maintained unless it was felt necessary to be broken in the interest of subject safety. It is recommended that the blind be broken by the Sponsor for all SARs judged reportable on an expedited basis, before they are reported to the CA(s) for that specific subject (even if the CI/PI remains blinded). If the CI/PI is delegated responsibility by the Sponsor for pharmacovigilance management and reporting, then unblinding should be performed by individuals who are not involved in every day data management.

e) Timeframes in which the Sponsor must submit expedited reports to the CA(s) and REC(s)

i) Fatal/life threatening SUSARs

The Sponsor **must** inform the CA(s) and main REC(s) of fatal or life threatening SUSARs as soon as possible, but no later than **7 calendar days** after the Sponsor has first knowledge of the minimum criteria for expedited reporting. In each case, relevant follow-up information should be sought and a report completed as soon as possible. This should be sent within an **additional 8 calendar days**.

ii) Non- fatal and non-life threatening SUSARs

The Sponsor must report all other SUSARs and safety issues to the CA(s) and main REC(s), as soon as possible but no later than **15 calendar days** after the Sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant information should be given as soon as possible.

iii) Reporting other safety issues

A letter titled "Safety Report" must be sent to the CA(s) and REC(s) for other safety issues also qualifying for expedited reporting (stated on page 12), by the Sponsor. The first page of the report should reference the EudraCT number, title of the trial and the Sponsor's trial protocol code number to which it refers and the points concerned summarised in a short section. Contact numbers of the reporter should also be added for ease of reference.

The Sponsor must retain a copy of the expedited report and associated documentation in the TMF, for source data verification purposes and inspection.

f) Safety Trends

As the Sponsor will be receiving notification of all SARs from all sites, he may be alerted to trends in safety parameters. He must draw these to the attention of the CI and the IDMC (if there is one) and ensure discussions are held and action is indicated to secure the safety of future subjects. Discussions may result in an expedited report being submitted to the CA(s) and REC(s) and the discontinuation of a trial if subject safety is likely to be compromised.

REFERENCES

ICH Harmonised Tripartite Guideline for Good Clinical Practice (1996)

The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument **2004/1031**), implemented on the 1st May 2004

European Commission Document “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use” April 2003 (Final)

European Commission Document “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use” April 2004 Revision 1 CT3

Directive 2001/20/EC of the European Parliament and of the Council of 4th April 2001 on the approximation of the laws, regulations and the 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.

REFERENCED GUIDES/SOPs

Annual Safety Report SOP, CRN/04/S08/00

Guide to Protocol Content and Format to meet ICH GCP Standards,

APPENDICES

Appendix 1 Glossary of commonly used terms

Appendix 2 SAE Alert Report form

Appendix 3 SAE follow-up reporting form

Appendix 4 Data elements for expedited reports

Appendix 5 CIOMS-1 form

Author:
Signature:

Date:

Authorised by:
Signature:

Date:

CONTACTS