SAFETY REPORTING

1 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for reporting adverse events and reactions in the clinical drug trials. European reporting requirements are outlined. Specific requirement for other countries are to be outlined in study specific Safety Reporting Specifics form.

This SOP ensures compliance with ICH Guideline for Good Clinical Practice (ICH GCP) and national and international laws and regulations, specified in the SOP Legislation and Guidelines.

2 SCOPE

This SOP is valid for all clinical drug trials sponsored by hospitals that have implemented the NorCRIN SOPs.

3 RESPONSIBILITIES

The sponsor has overall responsibility for ensuring that this SOP is followed.

The sponsor's responsibilities shall be described in the quality system of the sponsor institution. Tasks are delegated according to SOP Roles and Responsibilities in clinical trials implemented in the institution.

Principal investigators at each centre should, while the trial is in progress, continuously record adverse events (AE) according to the current legislation and procedures described in the protocol, and report serious adverse events to the sponsor.

The sponsor is responsible for appointing a medical monitor. The medical monitor has the authority to assess the safety aspects of the clinical trial. The national coordinating investigator/project leader is often apponted medical monitor.

The sponsor is responsible for assessing whether serious adverse events (SAEs) are considered suspected unexpected serious adverse reactions (SUSARs), the submission of SUSARs to authorities through Eudravigilance or by other acceptable means, and informing all participating principal investigators about unexpected serious adverse reactions. The sponsor is also responsible for continuous monitoring of the safety in the clinical trial and annual reporting to the Competent Authorities and Ethics Committees.

The individual health institution in Norway has the responsibility to report events which cause significant personal injury to a trial subject as a result of a medical procedure or other causes of harm to a trial subject. Such incidents must be reported to the Norwegian Board of Health Supervision (Statens helsetilsyn). Events that could have led to significant injury should also be reported.

The medical monitor will be delegated the sponsor tasks described in this SOP. The sponsor may also transfer any or all of the sponsor's trial-related duties and functions to a third party vendor such as a Clinical Trial Unit or a Contract Research Organisation (CRO), but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf. Transfer of duties shall be specified in a written agreement. A Clinical Trial Unit will only be able to enter completed SUSAR reports into Eudravigilance.

4 PROCEDURES

4.1 AEs

All AEs must be recorded in the case report form (CRF) by the Principal investigator (PI) or delegate. In determining whether an AE is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product (IMP).

4.2 SAEs

If the AE is serious (i.e. an SAE), the PI shall within 24 hours report the event to the medical monitor of the sponsor, unless the protocol does not require the SAE to be reported expeditely. Non-expeditable SAEs are recorded and notified to the sponsor per protocol.

The sponsor can rely on the causality assessment made by the reporting investigator or make an additional assessment. The sponsor cannot downgrade the investigator's causality assessment, but can upgrade it.

Expectedness of the SAE should be assessed by the medical monitor using the agreed reference safety information (investigator's brochure or SmPC). When assessing expectedness of a known, already documented serious adverse reaction term, consideration will be given to information on the specificity, frequency, or severity of the reaction.

If the SAE is considered related to the IMP and is also unexpected (suspected unexpected serious adverse reaction, SUSAR) the event must be reported to the drug authorities and the ethics committees, if applicable, see below.

4.3 SUSARs

4.3.1 Minimum information for SUSARs

The initial SUSAR report must contain at least the following information:

- Valid EudraCT number
- Sponsor study number, (e.g. REK reference number)
- One identifiable coded subject
- One identifiable reporter
- One SUSAR
- One suspect IMP

In addition, it is recommended that the following information is provided:

- A full description of the event (or if all the information is not available at the time of the initial report, this could be included in the follow-up), including the event start date, whether or not it is resolved and, if resolved, the date of resolution
- Any relevant medical history or relevant concurrent conditions that are not already listed as part of the event
- An assessment of seriousness and expectedness

- Dates that the suspected drug was administered to the subject, and whether any changes to administration have been made as a result of the event (such as ceasing the medication, or changing the dose)
- Details of any concomitant medications
- In the case of death, the date and cause of death
- Receipt date of the information from the investigator
- Whether the report is an initial report or a follow-up report

Reports should comply with the health facility's privacy policy.

4.3.2 Reporting to Authorities

The medical monitor should send the SUSAR information on CIOMS Form 1 or other equivalent form to the EV user at SUSAR@ous-hf.no for Helse Sør-øst and Helse Nord, similarly SUSAR@helse-bergen.no for Helse Vest and Helse Midt. It is the medical monitor's responsibility to ensure that the form is complete.

In EEA, fatal or life-threatening SUSARs should be reported to the Eudravigilance database within 7 days after receipt by the medical monitor, and with a follow-up information reported within 8 days, whereas all other SUSARs are to be reported within 15 days.

In order to reach the timelines, the medical monitor should send CIOMS forms or equivalent:

- within 72 h (day 3) after the sponsor has gained knowledge of the SAE if the seriousness criteria is death or life-threatening
- within 5 calendar days after the sponsor has gained knowledge of the SAE for other seriousness criteria

If any of the participating countries is outside the EEA submission should be performed as outlined in the Safety Reporting Specifics for the study.

Only unblinded reports should be submitted, so for blinded trials the medical monitor must be independent of the operational study team and be careful not to share unblinded information with study staff.

SUSARs associated with comparators follow the same reporting requirements as for the test IMP. Events associated with placebos will usually not satisfy the criteria for a SUSAR and, therefore, neither for expedited reporting. However, where SUSARs are associated with placebos (e.g., reaction due to an excipient or impurity), the sponsor should report such cases.

For reports of deaths or SAEs also considered efficacy endpoints in trials with high mortality or high morbidity and accepted to be considered as disease related events in the protocol authorised by the competent authorities; systematic unblinding is not required.

Careful assessment should be performed in cases where disease related events appear to be enhanced by the IMP. If the investigator considers disease-related event to also be IMP related and the event is both serious and unexpected then it must be reported as a SUSAR.

In trials with several IMPs, an adverse reaction (AR) must be not expected for all suspected IMPs (according to the separate RSIs) in order for the SAR not to be considered as a SUSAR.

4.3.3 Reporting to collaborating investigators

The PI/NCI shall inform all investigators about all SUSARs. Individual SUSAR reports can be distributed. However, whenever practicable the SUSAR information should be aggregated in a line listing of SUSARs in periods as warranted by the nature of the trial and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the IMP. All principal investigators must confirm receipt of and acquaintance with the new SUSARs.

4.4 Unexpected events and urgent safety measures

In addition to SUSARs all unexpected events that might materially influence the benefit-risk assessment of the IMP or that would lead to changes in the administration of an IMP or in overall conduct of a clinical trial must be notified to the Authorities. Unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as carcinogenicity).

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.

Any urgent safety measures taken must be reported to the Authorities as soon as possible after measures have been taken.

4.5 Reporting of Pregnancies

Pregnancies should be reported by the PI to the sponsor within the same timelines and using the same reporting lines as described in section 4.2. The outcome of the pregnancy should be reported, if possible should information be collected until three months after delivery. Information about a pregnant partner can only be collected upon consent from the partner. If a pregnancy has an adverse outcome (i.e. for the mother and/or the baby), an SAE report must be completed. Information about the baby can only be collected upon consent from the parents.

4.6 Development safety update report (DSUR) / annual reporting

The DSUR should be written in English for possible use in any country. The DSUR template for non-commercial sponsors should be used. For non-commercial sponsors, the annual reporting for non-commercial studies can be used.

If feasible, one single DSUR with data pertinent to all dosage forms and strengths, all indications, and all patient populations under study with the investigational drug, should be written. However, the sponsor is responsible for including at least safety data from the clinical trial(s) for which the organsiation is responsible.

The reporting period for a DSUR is annual from the Development International Birth Date, i.e. the first approval date of the clinical trial. The submission deadline is 60 days after the DSUR data lock point. If Development International Birth Date is not known for an academic sponsored study, DSUR/annual reports should follow the regualtory approval date.

4.7 Reporting overview

WHAT SHOULD BE REPORTED	REPORTER	PERSON/SYSTEM RECEIVING THE REPORT	DEADLINES
AE (including clinically significant abnormal lab values.)	Principal investigator	Medical monitor via eCRF	Record continuously on the trial specific forms (CRF)
SAE	Principal investigator	(medical monitor)	Without undue delay but not later than within 24 hours of obtaining knowledge of the event Usually report in the CRF
Pregnancy	Principal investigator	Sponsor (medical monitor)	Without undue delay, but be aware of consent requirements, cf. Section 4.5.
Fatal and life-threatening **SUSAR** (un-blinded)	Sponsor (medical monitor)*	Eudravigilance / national safety database if applicable	First report: within 7 days. Follow-up report: within 15 days Time limit applies from the day sponsor becomes aware of the event.
Other **SUSAR** (un-blinded)	Sponsor (medical monitor)*	Eudravigilance / national safety database if applicable	First report: within 15 days Follow-up report: as soon as possible.
SUSAR (blinded), and general safety information	Sponsor (medical monitor)	Collaborating investigators	Individual SUSARs or line listings at certain intervals (depending on the type of trial, amount of SUSARs and safety concerns observed).

WHAT SHOULD BE REPORTED	REPORTER	PERSON/SYSTEM RECEIVING THE REPORT	DEADLINES
Urgent safety measures	Sponsor	Competent Authorities in each participating country	Immediately
Significant personal injury to a trial subject as a result of a medical procedure or other causes of harm to a trial subject	Principal investigator	In Norway: Statens helsetilsyn	Immediately, according to institution's internal procedures
Temporary halt or early termination of the trial for safety reasons	Sponsor	Competent Authorities in each participating country	Within 15 days.
DSUR / annual report	Sponsor	Competent Authorities in each participating country	Within 60 days after DSUR data lock point.

* For blinded trials, reporting should be delegated to an independent, qualified person. SOP Randomisation, Blinding and Unblinding

4.8 DOCUMENTATION

Copies of the documents submitted to Competent Authorities either directly or via Eudravigilance should be filed in the sponsor's Trial Master File and in the Investigator's Site File, see SOP Study Files. As a general rule, data in the DSUR should be blinded. However, in some circumstances, unblinding is necessary. If the SUSAR and DSUR contain unblinded data, they need to be stored separately during the trial and filed in the sponsor's Trial Master File only at the end of the trial.

5 NON-COMPLIANCE MANAGEMENT

Non-compliance should be handled according to the procedures for handling non-compliance of the individual institution. Protocol deviations should be reported according to the study protocol or the Protocol Deviation Handling plan.

6 REFERENCES

6.1 External References

- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (CT-3) (June 2011)
- ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- ICH E2F Development Safety Update Report

6.2 Internal References

- SOP Safety Planning
- SOP Randomisation, Blinding and Unblinding
- SOP Study Files
- SOP Protocol Deviation Handling

7 ATTACHMENTS

- DSUR template

8 DEFINITIONS

- SOP Definitions.

9 CHANGES SINCE LAST VERSION

This SOP will replace SOP No.3.4 version 3.2. Included SUSAR reporting to Eudravigilance.