SAFETY PLANNING

1 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the planning steps related to safety required for the practical clinical trial conduct in Norway or as an international project in order for the Sponsor to fulfil its duties according to national and international regulations.

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.

The sponsor is responsible for appointing a medical monitor. The medical monitor has the responsibility to assess the safety aspects of the clinical trial. The principal investigator for single centre trials / national coordinating investigator for multicentre trials (PI/NCI) can take on the role as medical monitor if the trial is not blinded for that person. For blinded trials, the medical monitor should be unblinded.

PI/NCI is anticipated to assume the coordinating activities on behalf of the sponsor according to this SOP. The PI/NCI will ensure that a complete oversight of clinical trial requirements is obtained for the applicable participating countries/sites. The PI/NCI is responsible for outlining the safety reporting requirements for the clinical trial and ensure that the reporting requirements can be fulfilled via Eudravigilance notifications or via local/national databases/notification systems. In multinational studies SUSARs should be submitted directly to EudraVigilance.The sponsor may transfer any or all of the sponsor's trial-related duties and functions to a third party vendor such as a Clinical Trial Unit providing this service, 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.

When outsourced to a CTU, dedicated staff at the applicable Clinical Trial Unit will perform the EudraVigilance registration and reporting of SUSARs when delegated such tasks by the sponsor. An agreement between the sponsor and the Clinical Trial Unit should be made before the trial starts. The medical responsibility remain at the sponsor, the Clinical Trial Unit will only submit the data.

4 PROCEDURES

4.1 Study Conduct Planning

Before a clinical trial can commence, a complete overview of requirements must be in place to ensure they are all fulfilled. Country and site specific differences must be collected, see below for multinational studies. The

sponsor checklist could be used as guidance. All participating sites, independent of country, must sign a clinical trial agreement before study start.

4.1.1 National studies

The sponsor checklist could be used as guidance, see above.

4.1.2 Multinational studies

For multinational studies there should be one person responsible for coordinating the entire study, the Coordinating Investigator. In most instances it will be the NCI in the sponsor institution who will hold this role.

For multinational studies the NCI or sponsor representative in each country should ensure that local requirements are complied with. Each NCI must complete and sign the NCI Disclosure and Commitment form, which gives the Coordinating Investigator an overview of specific requirements to fulfil in the particular study. The Agreement Multicenter Trial must detail the delegation of tasks in accordance with feedback in the Disclosure and Commitment form and according to sponsor's wish for organisation. The agreement will outline the responsibility split between the sponsor organisation and the investigator sites' organisations, see SOP Samarbeidsavtaler, informasjonsrutiner og delegering av oppgaver.

4.2 Preparations for Safety Reporting

A medical monitor with responsibility for review and evalution of SAEs, SUSAR and annual safety reporting should be appointed for the study and preferably mentioned in the protocol. The name of the medical monitor must be listed in the Safety reporting specifics form and preferrably in the protocol.

The form Safety Reporting Specifics must be completed prior to study start. Reporting requirements per country and site must be obtained.

SAE relatedness assessment must always be done by the investigator. The medical monitor can rely on this assessment or can do an additional assessment, see SOP Safety Reporting.

Expectedness assessment is the responsibility of the medical monitor, see SOP Safety reporting. The Reference Safety Information must be specified in the Safety reporting specifics form.

For blinded trials, the medical monitor or an independent person at e.g. the clinical trial unit should be nominated as an unblinded person with access to the randomisation code as SUSARs are to be submitted to the authorities are unblinded,. The name and contact details of the unblinded person must be listed in the Safety reporting specifics form. The unblinded person must never reveal the code to blinded staff. If the reporting is delegated, the randomisation code needs to be available for them before the clinical trial starts. The communication between the independent person and the personnel reponsible for SUSAR reporting to the authorities, if these are not the same, should be documented. The medical monitor is responsible for all the medical information on a SUSAR report. The independent person will only unblind and send to applicable authorities according to Safety Reporting Specifics and inform the medical monitor.

For multinational studies including countries requiring SUSARs reporting through Eudravigilance, the sponsor must appoint a Responsible Person (RP) for Eudravigilance (see Eudravigilance registration and SUSAR reporting). The role is described in the Eudravigilance Registration Manual, item 3.6.2. The role is administrative

and has an obligation to manage/maintain access for users in the organisation. The overall responsibility remain at the sponsor. The RP can appoint a "trusted deputy" to do the technical job managing the users. There can only be one RP in each organisation. The person that approves the research procedures in the organisation, typically the research director, is recommended to approve/appoint the RP. A person in close connection to clinical research support is recommended to hold the role as RP.

If the sponsor does not have a Eudravigilance (EV) trained person available, the sponsor representative must enter into an agreement with an organisation having EV trained staff (e.g. a Clinical Trial Unit or a CRO) to ensure proper SUSAR reporting. The sponsor represantative is responsible for forwarding potential SUSARs to the Clinical Trial Unit. EV reporting is done according to the working instruction Eudravigilance registration and SUSAR reporting.

For studies where the SAE information is entered into a different database than the trial data, the frequency of the SAE reconciliation should be specified in the Safety Reporting Specifics form see also SOP Data management. .

4.3 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 Topic E 2 A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

4.4 Internal References

- SOP Safety Reporting
- SOP Data management

5 ATTACHMENTS

- Safety Reporting Specifics Form
- Eudravigilance registration and SUSAR reporting
- Data Processing Agreement SUSAR reporting

6 DEFINITIONS

- SOP Definitions.

Abbreviation	Term	Definition
DMC	Data Monitoring Committee	Independent group of experts external to the study assessing the progress, safety data and, if needed, critical efficacy endpoints of the clinical study
DSUR	Development Safety Update Report	A pre-marketing periodic report which covers safety information of drugs.

EV	Eudravigilance	System for managing and analysing information on suspected adverse reactions to medicines which have been authorised or being studied in clinical trials in the European Economic Area (EEA).
SUSAR	Suspected Unexpected Serious Adverse Reaction	

7 CHANGES SINCE LAST VERSION

Version 1.1. This SOP replaces SOP no. 2.16 version 1.0. The medical monitor needs to be unblinded.