

Standard Operating Procedure

Handling of Adverse Events in Clinical Trials

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1. ABBREVIATION

AE	Adverse Event
ASST-PG23:	Azienda Socio-Sanitaria Territoriale - Papa Giovanni XXIII
CA:	Competent Authority
CIOMS:	Council for International Organizations of Medical Sciences
CRF:	Case Record Form
DSUR:	Development Safety Update Report
EC:	Ethics Committee
EVCTM:	EudraVigilance Clinical Trial Module
FROM:	Fondazione per la Ricerca Ospedale Di Bergamo
IB:	Investigator's Brochure
ICSR:	Individual case safety report
IMP:	Investigational Medical Product
MR:	Medical Reviewer
PM:	Project Manager
PV:	Pharmacovigilance
SAE:	Serious Adverse Event
SADR:	Serious Adverse Drug Reaction
SOP:	Standard Operating Procedure
SUSAR:	Suspected Unexpected Serious Adverse Reaction
TMF:	Trial Master File

2. SCOPE

This Standard Operating Procedure (SOP) describes responsibilities and activities to appropriately manage Serious Adverse Event (SAEs)/ SADR occurred during the conduct of interventional clinical trials with Investigational Medicinal Products (IMPs) to comply with applicable regulations.

3. FIELD OF APPLICATION

This SOP applies to personnel of Fondazione per la Ricerca Ospedale di Bergamo (FROM) or Azienda Socio-Sanitaria Territoriale - Papa Giovanni XXIII (ASST-PG23) involved in the pharmacovigilance (PV) activities related to clinical trials with IMPs.

Third parties can be involved and delegated in the PV activities as reported below; in this case activities, related responsibilities and SOPs to be used should be defined in an *ad hoc* agreement between the parties.

4. RESPONSIBILITIES

Operational Director (FROM sponsored/supported trials)

- Negotiates and approves the agreement with the third party delegated by FROM for some PV activities.

Clinical Operations Coordinator (FROM sponsored/supported trials)

- Discusses and approves the safety management documents drawn up by the Project Manager (PM) for each clinical trial (e.g. Safety Data Exchange Agreements, Adverse Events handling manuals).

Project Manager/ ASST-PG23 Investigator acting as Sponsor

- Ensures that the protocol includes procedures for handling (i.e. recording, assessing and reporting) of Adverse Events (AEs).
- Review and/or drafts the safety management documents describing the procedures of safety data exchange with the third party delegated for some PV activities according to the agreement (FROM sponsored/supported trials).
- Provides the third party with the Serious Adverse Event (SAE) evaluation form (FROM sponsored/supported trials).
- Provides the third party with any updated documents and information needed for the delegated tasks (e.g. trial protocol, Investigator's Brochure/IB, updated lists of investigational sites and Ethical Committees, trial approvals, etc.) (FROM sponsored/supported trials).
- Oversees the performance of the third party (FROM sponsored/supported trials).
- Provides all data concerning safety to the third party delegated for developing Development Safety Update Report (DSUR) (FROM sponsored/supported trials).
- Drafts the DSUR ASST (PG23 Investigator acting as Sponsor)
- Reviews the final draft DSUR.
- Informs the investigators about SUSARs by means of the periodic distribution of line listing, according to the Safety Management Plan and/or related agreement.
- Draft the Adverse Events management manuals for the Investigator(s), reporting the procedures of safety data exchange during a clinical study, with special attention to the transmission of Serious Adverse Events.
- Archives the safety management documents in the Trial Master File (TMF).
- Organizes the Data Monitoring Committee, if requested.
- Informs the Company(ies) providing the Investigational Medical Product (IMP) about SAE/ADR and pregnancy occurrence, according to the related agreement or safety data exchange documents in use (if applicable).

Medical Reviewer (MR)/ ASST—PG23 Investigator acting as Sponsor

- Reviews the SAE/SADR issued by the Investigator and assesses the expectedness of a SAE.
- Reviews and approves the Suspected Unexpected Serious Adverse Reaction (SUSAR) line listing.
- Approves the final annual DSUR.

ASST-PG23 Representative (ASST-PG23 sponsored trials)

- Collect SUSAR Forms issued by Investigator acting as Sponsor.
- Notifies SUSARs to EV and national Competent Authority(ies) (CA) through the EudraVigilance Clinical Trial Module (EVCTM).
- Notifies SUSARs to the ASSTPG23 Ethics Committee (EC). who released the single opinion (i.e. in Italy).
- Notifies the DSUR, issued by the Investigator acting as Sponsor, to the EC and CA.

Third Party (FROM sponsored/supported trials)

- Reviews AEs recorded by investigators in the Case Report Form (CRF).
- Collects SAE reports.
- Assesses preliminary the SAE report, and collects additional information to complete and/or clarify SAE/SADR information reported by the Investigator.
- Forwards the complete SAE report in CIOMS format to the attention of the FROM MR for medical review and the final assessment of the causality and expectedness of the event.
- Provides (in case of first collaboration) FROM with the prove of registration in EudraVigilance as non-commercial Sponsor.
- Notifies SUSARs to EV and national Competent Authority(ies) (CA) through the EudraVigilance Clinical Trial Module (EVCTM).
- Notifies SUSARs to the ASST-PG23 EC who released the single opinion (i.e. In Italy) .
- Provides FROM with a copy of SUSAR notification and the receipt of the notification in EVCTM.
- Drafts the DSUR and submits it to the PM for revision.
- Notifies the DSUR to the EC and CA.
- Provide Investigators with SUSARs and the periodic line listings (e.g. every 6 months).

Clinical Research Associate

- Ensures that Investigators are aware of safety reporting obligations.
- Provides training to the site staff on safety reporting.
- Verifies that all AEs are duly reported in the CRF by Investigators according to the protocol / Safety Management Plan.

- Ensures that all SAEs occurred at a site are reported by the Investigator to FROM and/or to the third parties delegated for PV activities in due time according to the protocol/safety management documents.
- Ensures that safety data collected by the site are accurate, complete and consistent with source documents.
- Supports the PM in case of safety pending issues with a site.

5. PROCEDURES

The purposes of the safety activities under the responsibility of FROM/ASST-PG23 are the following:

- collect information on the safety profile of an IMP
- make CAs aware of SUSARs occurred in a specific trial
- make the EC who has released the single opinion (i.e ASST-PG23) aware of SUSARs that have occurred in its territory
- to provide CA and ECs with the annual DSUR
- to provide investigators with periodic line listings of SUSARs.

All drugs, even those with a marketing authorization, that are used in a trial as comparators are considered IMPs. These comparators are subject to the same reporting requirement of the IMPs. Products used in the trial according to the protocol but falling outside the definition of IMP are defined as Non-IMPs. ADRs related to these products are subject to reporting.

5.1 Definitions

For convenience of FROM/ASST-PG23 staff involved in PV activities some definitions are reported here below according to the following regulatory documents:

- *Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3').*
- *Directive 2001/20/EC 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.*

Adverse Event

Article 2(m) of Directive 2001/20/EC.

Any untoward medical occurrence in a patient or clinical trial subject administered medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with a use of medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR)

Article 2(n) of Directive 2001/20/EC.

All untoward and unintended responses to an investigational medicinal product (IMP) related to any dose administered.

Note: This definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the IMP.

The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Serious Adverse Event (SAE)

Article 2(o) of Directive 2001/20/EC.

Any untoward medical occurrence or effect that at any dose:

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

Unexpected Adverse Reaction

Article 2(p) of Directive 2001/20/EC.

An adverse Reaction, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorized investigational product or Summary of Product Characteristics for an authorized product).

Note:

- the term “severe” is often used to describe the intensity of an event or reaction (e.g. mild, moderate or severe) and should not be confused or interchanged with the term “serious”. Seriousness is defined by the features (the presence of one or more) reported above in SAE definition (a, b, c, d, e).
- the term “unexpected” means that the nature and severity of AE is not consistent with the applicable product information (e.g., IB for investigational agent or SmPC).

5.2 Safety management documents

Since the safety assessment of an IMP involves many activities that are responsibility of different roles taking part to a clinical trial (i.e. Investigators, Sponsor, third parties delegated for PV activities), it is important at beginning of the study to identify all involved parties and responsibilities, modalities of collaboration and relevant timelines to be respected according to the applicable regulation.

The information can be included in the trial protocol or in specific safety management documents depending on the complexity of the trial. The safety management documents can be identified as:

- Adverse Events Handling Manual or Safety Management Manual, detailing the process of safety information exchange between Investigators and the Sponsor (i.e. FROM/Third Party or ASST-PG23).
- Safety Data Exchange Agreements (SDEA) detailing the process of safety information exchange between FROM/ASST-PG23 and third party (for trials sponsored or supported by FROM) or between FROM/ASST-PG23 and the pharmaceutical company supplying the IMP(s).

The safety management documents are drafted by the PM and shared with the FROM Clinical Operations Coordinator and the third party delegated for the PV activities. The Clinical Operations Coordinator is responsible for approving them before the trial start.

The SDEA that can be part of the agreement is usually proposed by the Company providing the IMP according to own procedures and/or by the third party delegated for PV activities. In this case the SDEAs are reviewed by the PM and then approved by the Clinical Operations Coordinator.

The procedures and the timeframes for AEs, SAEs and pregnancies reporting by investigators to FROM/ASST-PG23 Investigator acting as Sponsor and/or third party must be specified in the clinical trial protocol or in the Safety Management Manual (or AE handling manual). Particularly the following items should be taken into consideration:

- Definitions of SAEs requiring expedited reporting by the investigator according to the applicable regulations and trial-specific requirements.
- Reporting period for an individual patient:

AEs: from the informed consent signature to the end of study.

SAEs: from informed consent signature to the end of the observation period following the last IMP dose defined in the protocol, whichever occurs later; the duration of the observation period should be not less than 4 weeks since last IMP dose and should be defined considering the IMP's half-life and expected time to adverse reactions occurrence.

Pregnancies: from informed consent signature to the end of study, if not differently specified in the protocol and/or related agreement.

- Causality scale to be applied for assessment of relationship to the tested IMP(s) and relevant WHO definitions (i.e. definite, probable, possible, unlikely, unrelated).
- Instructions for reporting SAEs and pregnancies in female patients/partner of male patient, including fax number and emergency telephone contact number.
- Timelines for SAEs and pregnancies reporting by the Investigator.

5.3 Handling of SAEs

Notification of all AEs identified in the protocol as subject to the SAE reporting procedure must be sent by the Investigator detecting the SAE to FROM PM/Third Party or to Representative of ASST-PG23 within 24 hours after the Investigator becomes aware of it.

For SAEs that were ongoing or for which insufficient information was available at the time of initial reporting, a follow-up report should be provided by the Investigator as soon as new significant information becomes available and in any case within 8 calendar days from first notification, to allow FROM/Third Party

or ASST-PG23 to respect the SUSAR notification timelines. This requirement should be specified in all protocols. Follow-up reports are to be processed according to the same procedure as the initial reports.

The investigator should fill in the **Serious Adverse Event Report Form (T.CLI10.01/2)** to be delivered to FROM PM/Third Party or Representative of ASST-PG23 according to the instructions provided in the study protocol or in the safety management manuals.

For SAE Report Form completed within the eCRF, this process also includes the transmission (by mail or fax) of printed copy of the electronic SAE form dated and signed in original. When requested (and defined by SDEA/manuals) the investigators will transmit CIOMS form on behalf of printed electronic SAE form. Emergency procedures for notification by phone should be in place in case the normal procedure cannot be followed.

Upon receipt of a SAE Report, the following activities are to be carried-out by the involved party:

- check the completeness/accuracy of the following information:
 - protocol identification number
 - patient identification number
 - reporter's name and institution
 - adverse event definition
 - suspect IMP name
- if minimum information is missing/incomplete/illegible, immediately request the site to send a corrected/completed SAE report
- each SAE is identified by a progressive number starting from 1 (i.e. SAE-1, SAE-2 etc) assigned to the initial report. Each Follow-Up (F-up) report is identified by the Event and date of FU issue
- submit the **SAE Evaluation Form (T.CLI10.02/2)** completed with the relevant information to the MR for FROM sponsored or supported trials
- deliver a copy of the SAE Report to the Company(ies) providing the suspected IMP(s).

The FROM MR/ASST-PG23 Investigator acting as Sponsor completes the SAE Evaluation Form providing position on:

- **Seriousness**: to be assessed according to the Article 2(o) of Directive 2001/20/EC and trial-specific requirements, if any.
- **Relatedness**: an event is to be considered related to the IMP if a causal relationship to the treatment is at least reasonable possible (i.e. the relationship cannot be ruled out). For the purpose of SUSAR reporting, a SAE is considered study treatment-related if it is assessed as definitively, probably or possibly related. In combination trials, it should be specified in the protocol whether relatedness is to be assessed separately for each IMP or for the combination overall. If relatedness is assigned separately for each IMP, a SAE is considered study treatment-related if it is related to at least one of the tested IMPs.
- **Expectedness**: this evaluation is required only for events which are considered serious and related to the study treatment by the investigator and/or by FROM. "Expected" is meant from the perspective of

previously observed, not on the basis of what might be anticipated from the pharmacological properties of an IMP.

A SAE is to be considered unexpected if not included in the reference document of the concerned IMP as follows:

- For IMPs with no marketing authorization or authorized IMPs not used according to the terms and conditions of the marketing authorization: the event is not listed as an expected IMP-related event in the IB or in the SmPC (in case of simplified IMP Dossier).
- For marketed IMPs used according to the terms and conditions of the marketing authorization: the event is not present in the list of expected adverse drug reactions reported in the SmPC; if the IMP has a marketing authorization in more than one Country with different SmPCs, the PM selects the one to be used in the trial as the reference document for expectedness evaluation.
- In combination studies, if none of the reference documents include a list of expected events for the tested combination as such, expectedness is to be assessed for each individual IMP considering the list of expected events relevant to the IMP administered as single agent.

The aspects to be considered in the determination of expectedness should include not only the nature of the event but also its severity, seriousness, and outcome, if these are specified in the reference document. Fatal serious adverse drug reactions are to be considered unexpected by default.

After notification of a SUSAR and until the relevant reference document is updated, additional occurrences of the same event have yet to be considered as unexpected.

The FROM MR/ASST—PG23 Investigator acting as Sponsor reports on the SAE Evaluation Form any queries to be addressed to the investigational site and indicates whether a follow-up report is required. Urgent queries should be immediately transmitted to the investigational site.

If a SAE seems to fulfil the SUSAR definition and/or the third party envisages a possible need to take urgent actions to protect the safety of study patients, the FROM MR/ ASST—PG23 Investigator acting as Sponsor are to be involved within 1 business day of SAE receipt and requested to urgently review the case and discuss the potential need to take actions to protect the study patients against any immediate hazard.

If urgent actions are to be implemented to protect patients' safety, these can be applied upon their notification to the concerned IRBs/IECs and CAs without waiting for regulatory approval. In this case the PM sends a communication to all investigators participating to the trial, while the third party delegated by FROM informs the concerned ECs/ CAs. These activities are in charge of the Investigator acting as Sponsor in case of trials sponsored by ASST-PG23 (i.e. for those FROM support is not requested).

The halting of the trial or other actions taken have to be notified to CAs/ECs according to the applicable regulations and in any case within 15 calendar days of the action implementation. After a temporary interruption, patient accrual/treatment can be resumed only after the concerned ECs have given a favourable opinion and only if the CAs have not raised grounds for no acceptance of the recommencement.

The completed SAE are managed as described below:

a) No actions required:

the PM/ ASST—PG23 Investigator acting as Sponsor files the copy of SAE Report and SAE Evaluation Form in the TMF of the concerned trial.

The third party files these documents in its own archives/safety database.

b) Queries have to be addressed to the investigational site:

the PM/ ASST—PG23 Investigator acting as Sponsor requests clarification to the site where the SAE occurred.

c) The SAE requires expedited reporting, the third party on behalf of FROM of the ASST-PG23 Representative on behalf of the ASST—PG23 Investigator acting as Sponsor transmits SUSAR to the CA through EV. A copy of the EV acknowledgements are transmitted to the PM/Investigator acting as Sponsor as soon as available, as well as the EV output of the Individual Case Safety Report (ICSR) in E2B format.

The third party/ASST-PG23 Representative forwards the SUSAR report to ASST-PG23 EC who has released the single opinion and to the EC where the SUSAR occurred.

5.4 Handling of Exposure in Utero Reports

Any pregnancy assessed in a female patient or, when feasible, in a partner of male patient enrolled in clinical trial should be reported by the Investigator to FROM or to the ASST—PG23 Investigator acting as Sponsor within 24 hours from when the investigator becomes aware of it by using the **Exposure in Utero Report Form (T.CLI10.03/2)**.

If the MR/ ASST—PG23 Investigator acting as Sponsor determines that a SAE occurred in connection with a pregnancy, this is to be notified as required for any other SAE report.

All **Exposure in Utero Report Forms** are to be transmitted to the EC of the concerned investigational site within 7 calendar days of its receipt by the Sponsor (FROM or ASST-pg23) regardless if the pregnancy was associated to a SAE or not.

The PM transmits the form to the third party by email and is responsible for ensuring that the pregnancy is followed up as well as the child's outcome.

5.5 Annual safety reporting (DSUR)

Annual safety reporting to CAs and ECs will be drafted as DSUR according to ICH –E2F- Development Safety Update Report guidelines.

The DSUR can be drafted by the third party for FROM sponsored or supported trials or by the ASST—PG23 Investigator acting as Sponsor.

The FROM PM is responsible for informing the third party on the deadlines for DSUR transmission and for coordinating the relevant activities. The third party drafts the document. The FROM PM and the FROM MR review the DSUR for accuracy and consistency.

The DSUR could also be prepared in collaboration with the Company(ies) providing the IMP, if specified in the agreement between the parties, but FROM/ ASST—PG23 Investigator acting as Sponsor remains ultimately responsible for the report content and proper transmission.

The third party delegated by FROM or the ASST-PG23 Representative is in charge for DSUR transmission to the concerned CAs and the concerned ECs.

5.6 Archive

The PM/ ASST—PG23 Investigator acting as Sponsor is responsible for ensuring that all documents about the IMP(s) safety and relevant correspondence are filed in the appropriate section of the TMF.

6. REFERENCES

- Decreto Legislativo 24 giugno 2003, n. 211 "Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico" Determinazione 20 settembre 2012 "Adozione delle linee guida CT-3 (giugno 2011) della C.E. di attuazione della Direttiva 2001/20/CE, delle linee guida ICH E2F (settembre 2011) e istituzione di una banca dati nazionale relativa al monitoraggio della sicurezza dei medicinali in sperimentazione clinica. (Determinazione n. 9/2012).
- Misure per l'attuazione della Determinazione AIFA n. 9/2012 relativa al monitoraggio della sicurezza dei medicinali in sperimentazione clinica (31/01/2014).
- Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') - (2011/C 172/01).
- Directive 2001/20/EC 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.
- ICH – E2A - Note for guidance on clinical safety data management: definitions and standards expedited reporting (CPMP/ICH/377/95).
- ICH – E2F - Development Safety Update Report (EMA/CHMP/ICH/309348/2008).

7. TEMPLATES

T.CLI10.01/2 SAE Report Form

T.CLI10.02/2 SAE Evaluation Form

T.CLI10.03/2 Exposure in Utero Report Form

8. VERSION HISTORY

Version	Date	Reason for revision
1	30 Sept 2016	Starting document.
2	22 Jun 2020	General review of the document.