# Standard Operating Procedures for: Safety data collection and reporting at trial sites

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# Standard Operating Procedures for: Safety data collection and reporting at trial sites

## PURPOSE

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| This procedure describes the collection of adverse events (AEs) and other safety parameters, the flow for transmission of this information to the pharmacovigilance (PV) unit, the expedited reporting activities, and the documentation steps at site level. |

## SCOPE

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| This procedure applies to all sites involved in the endTB and endTB-Q interventional clinical trials and to safety data pertaining to all patients enrolled in the endTB and endTB-Q interventional clinical trials. |

## RESPONSIBLE FUNCTIONS

| **Function** | **Activities** |
| --- | --- |
| **Site Co-Investigator (Co-I)** | * Detect, evaluate, record and manage Adverse Events (AEs) and other safety parameters (pregnancies, overdoses); * Timely inform the Site Principal Investigator (PI) and the Site Study Coordinator (SSC) of the occurrence of Serious AEs (SAE), pregnancies, overdoses, and AEs of Special Interest (AESI); * Support the Site PI in filling SAE/Pregnancy Report Forms; * Notify early (if applicable) and collaborate actively on communication, management, implementation, and follow-up of Urgent Safety Measures. |
| **Site Principal Investigator (PI)** | * Detect, evaluate, record and manage AEs and other safety parameters (pregnancies, overdoses); * Support Site Co-Is in managing AEs, pregnancies or overdoses, and patients’ referrals as needed; * Timely inform the Pharmacovigilance (PV) unit of all SAEs, pregnancies, overdoses, and AESI occurring during the trial; * Address all queries raised by the Sponsor including requests for additional information on individual cases; * Forward Suspected Unexpected Serious Adverse Reaction (SUSAR) Reports, Annual Safety Reports (ASR) and Data and Safety Monitoring Board (DSMB) conclusion reports to local Ethic Committees (EC) and National Regulatory Authorities (NRA), as appropriate; * With support from the PV unit, the Central Study PI, the Clinical PI, the Central Study Coordinators and the Clinical Trial Manager (as applicable) address all queries raised by the EC and NRA; * Complete, sign and send SAE/Pregnancy Report Forms to the PV unit; * Notify early (if applicable) and collaborate actively on communication, management, implementation and follow-up of Urgent Safety Measures. |
| **Site Study Coordinator (SSC)** | * Participate on the training of the Site PI and Site Co-I on safety activities; * Support Site PI in verifying the SAE/Pregnancy Report Forms are complete and accurate before transmission to the PV unit; * Support Site PI in addressing queries raised by the Sponsor and in gathering complementary information on individual cases; * Organize translation of expedited reports as appropriate; * Support Site PI in addressing queries raised by EC and NRA; * Maintain proper documentation in relation to safety reporting; * Collaborate actively on communication, management, implementation and follow-up of Urgent Safety Measures. |
| **Pharmacovigilance (PV) Officer and deputy at the PV unit** | * Organize processing of information from the SAE/Pregnancy reports in the Sponsor PV database; * Organize medical review of AESI and SAEs; * Train and support the site on the trial’s safety activities; * Produce submission-ready safety reports including DSMB conclusion reports, SUSAR reports, ASR and other ad hoc reports (in English) for reporting to EC/NRA (as applicable); * Support SSC and Site PI in addressing EC and NRA queries; * Support Central/Clinical Study PI in notification, management, implementation and follow-up of Urgent Safety Measures. |
| **Clinical Trial Manager/Central Study coordinator** | * Participate on the training of the site PI and site Co-I on safety activities; * Support the site on the trial’s safety activities; * Support SSC and Site PI in addressing EC and NRA queries; * Support Central/Clinical Study PI in notification, management, implementation and follow-up of Urgent Safety Measures. |
| **PV Medical Monitor** | * Perform medical reviews (*per PV unit procedure not further described in this SOP*). |
| **Central Study Principal Investigator (PI) and Clinical PI** | * Support the site on the trial’s safety activities; * Support SSC and Site PI in addressing EC and NRA queries; * Notify, manage, implement and follow-up on Urgent Safety Measures. |

## DEFINITIONS and ABBREVIATIONS

### Adverse Event (AE)

Any untoward medical occurrence or worsening of a pre-existing medical condition in a clinical trial subject, administered a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including laboratory test abnormalities), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not considered related to the investigational product.

### Adverse Events of Special Interest (AESI)

Adverse Events of scientific and medical concern with the investigational medicinal product(s), for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate. Such events require further investigation in order to characterize and understand them.

In the frame of the endTB and endTB-Q interventional clinical trials, AESI include the list of conditions mentioned in the Clinical Trial Protocols.

### Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered an Adverse Drug Reaction. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

### Annual Safety Report (ASR)

A periodic safety update report presenting a comprehensive annual review and evaluation of pertinent safety information collected during the clinical trials over the period of 1 year.

### Council for International Organization of Medical Sciences I reporting form (CIOMS)

Standardized international report format for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time.

### Data and Safety Monitoring Board (DSMB)

Independent data monitoring committee established by the Sponsor to assess at intervals the progress of a clinical trial, the safety data and the critical efficacy endpoints, and to recommend to the Sponsor whether to continue, modify or stop a trial.

### Investigational Medicinal Product (IMP)

The pharmaceutical form of an active ingredient being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

### Overdose

Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information or other in-use references (e.g. WHO guidelines). The determination of an overdose will be left to the discretion of the clinical investigator, based on the total dose administered, the emergence of any clinical signs and symptoms suggestive of a toxic administration, as well as his own clinical judgment as it applies to each individual case.

### Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

* is leading to death;
* is life-threatening (defined as a subject at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
* Requires inpatient hospitalization or prolongation of existing hospitalization, with the exceptions described in the Clinical Trial Protocols;
* results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
* results in congenital anomaly or birth defect;
* is otherwise considered an important medical event that may not result in death, be immediately life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
  + Suspected transmission of an infectious agent (pathogenic or nonpathogenic) via the study drug(s) should always be considered an SAE.

A Grade 4 AE or laboratory abnormality does not necessarily indicate an SAE, unless the occurrence meets one or more of the above definitions.

### Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction to a study drug, the nature or severity of which is not consistent with the applicable reference safety information.

### Unexpected Adverse Drug Reaction

An adverse drug reaction, the nature and severity of which is not consistent with the applicable product information (e.g. the Investigator Brochure for an unapproved investigational drug or the package insert for an approved drug).

### Urgent safety measure

Urgent risk minimization action undertaken following the identification of an event/observation which may alter the risk/benefit assessment of the study treatment, including changes in the administration of the IMPs or modification of the conduct of the clinical trials.

## PROCEDURE

### Safety data collection

#### Detection of Adverse Events

The recording of adverse events (AEs) and other relevant safety parameters as defined in the clinical trial (CT) protocols (e.g. pregnancy, overdose) starts from the initiation of study treatment and ends at the last study visit (planned or early discontinuation). This is applicable to all patients irrespective of treatment allocation.

Any untoward medical occurrence in a patient enrolled in the CT qualifies as an AE, including:

* Any symptom, sign, or laboratory abnormality that was not present at baseline, and
* Any worsening of a symptom, sign, or laboratory abnormality already present at baseline.

In addition, overdose of investigational medicinal product (IMP) and pregnancy in an enrolled female patient or in the female partner of an enrolled male patient, are considered relevant safety parameters to be recorded.

The Site Principal Investigator (PI) and Co-Investigator (Co-I) are responsible for:

* Actively looking for AEs when performing clinical examinations and following-up on potential changes in ongoing medical conditions present prior to study start;
* Upon receipt, carefully reviewing lab reports, electrocardiogram reports and other investigations reports for out-of-range/abnormal results;
* At each trial visit, enquiring with the patient about the appearance of any new symptoms or signs since previous visit;
* At each trial visit, enquiring with the patient about contraception use and potential pregnancy;
* Encouraging patients to report any medical event occurring between trial visits to study staff (e.g. nurses, doctors).

The study nurses are responsible for carefully reviewing trial drugs accountability for medication errors and possible overdose.

DOTS corners nurses or counselors are responsible to inform the study nurse on any AE or other safety related information they may learn from patient or observe/notice.

#### Recording Adverse Events and relevant safety parameters in the electronic case report form (eCRF) and study file

The Site Principal Investigator (PI) or Site Co-Investigator (Co-I) is responsible for documenting all AEs in the medical file as well as in the Adverse Event section of the eCRF. AE recording applies to all trial patients, irrespective of the treatment regimen they have been allocated to, and starts upon initiation of study treatment.

AEs (including lab abnormalities) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

* *Example: If a patient experiences chest pain, dyspnea, diaphoresis, and ECG changes, rather than recording each individual symptom, “Myocardial Infarction” should be reported.*

As far as possible, each AE should be evaluated to determine:

* Its **severity grade** according to the provided Severity Grading Scale (grades 1-4; see below).
* Its **duration**,
* Its **causal relationship** to the IMPs (see [table 2](#tab2) below),
* **Action taken** with respect to the IMPs,
* Whether **medication or therapy** was taken/given in relation to the AE,
* Whether it is a **serious** **adverse event (SAE)** (see definition in section 4.9),
* Whether it is an **AE of special interest (AESI)** (see definition in section 4.2).

The assessment of severity is the responsibility of the Site PI or Co-I. A standardized MSF Severity Grading Scale provided by the Sponsor for use in the trial includes all terms from the Division of Microbiology and Infectious Diseases (DMID) grading system and a selection of relevant terms from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) and other references. For those AEs not described in the Severity Grading Scale, the general definition of clinical severity should apply (see [table 1](#tab1) below).

Table 1 General definition of severity

|  |  |  |  |
| --- | --- | --- | --- |
| **Grade 1 Mild** | **Grade 2 Moderate** | **Grade 3 Severe** | **Grade 4 Life-threatening** |
| Transient or mild discomfort (<48 hours); no medical intervention/therapy required. | Mild to moderate limitation in activity -some assistance may be needed; no or minimal medical intervention/ therapy required. | Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible | Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable |

A Frequently Asked Question document is available for further support on the use of the Severity Grading Scale.

Causality assessment is also the responsibility of the Site PI or CoI. When assessing the causal relationship to trial regimen the co-investigator/PI should use one of the following categories:

Table 2 Causality categories definition

| ***Causality category*** | ***Description*** |
| --- | --- |
| **Related** | There is a reasonable possibility that the AE may be related to the drug(s). Elements in favour of a reasonable causal relationship include:   * A favourable temporal relationship, * A positive dechallenge and/or rechallenge, * A plausible pharmacological/biological mechanism of action (whether proven or potential), * Previous knowledge of similar reaction with the drug(s), or * No other evident cause (e.g. previous disease, other drugs). |
| There is insufficient information to evaluate the causal relationship between the AE and the exposure. Conservatively, the AE should be considered related to the drug(s) until a proper assessment is feasible (i.e. upon follow-up). |
| **Not related** | There is no reasonable possibility that the AE is related to the drug(s). This implies that there is a plausible alternative cause for the AE that better explains the occurrence of the AE or that highly confounds the causal relationship between the drug(s) and the AE. |

\*Refer also to the Causality Assessment Aide-Memoire.

Overdoses and pregnancies (exposed via mother or father) should be additionally recorded, indicating which action was taken with the IMPs, whether any therapy/procedure was undertaken, and whether any consequence of these qualify as an AE or SAE (e.g. hepatic injury following overdose or miscarriage following exposed pregnancy). If there is any AE/SAE relating to an overdose or a pregnancy, these should be captured and evaluated as mentioned above.

#### Managing and monitoring Adverse Events and other safety parameters

The Site Co-Investigators must:

* Treat and follow-up all AEs (including lab abnormalities) and overdoses until complete resolution or stabilization of the patient’s condition;
* Follow-up pregnancies until outcome is known, and treat and follow-up any related complication as AEs;
* Follow-up infants born from exposed pregnancies until they reach 12 months of age (evaluation as per local paediatric protocol);
* At each visit, assess any change in the previously recorded AEs with regards to severity, seriousness, causal relationship with the IMPs, intervention required and outcome;
* Liaise with the Site Study PIs if the patient needs to be referred to hospital for investigations and/or treatment;
* Organize hospital referral of patients as required, including the rapid transport of patients in emergency situations;
* Request advice from the Clinical Advisory Committee for difficult cases;
* Arrange the specific follow-up and management of AEs of Special Interest (AESI) as described in the Clinical SOP (SP-018-CT).

The Site Principal Investigators must:

* Approve hospital referral of patients as required;
* Keep regular contact with the patient and the hospital doctors during hospitalization to ensure that all cares are provided according to the patient’s clinical condition and to be informed of any worsening. Ensure that the patient has a study visit before discharge from hospital;
* Ensure all AEs/overdoses/pregnancies are adequately followed-up: support Co-Investigators in getting the required investigations and treatments;
* Ensure that patients are appropriately referred to their treating physician or to an adequate specialist if the AE has not resolved at the end of the trial;
* If pregnancy outcome is not yet known, or if the infant has not reached 12 months of age at the end of trial, ensure follow-up is done (evaluation as per local paediatric protocol).

#### Post-study safety follow-up

The Site Co-Investigators must appropriately refer all patients with ongoing AEs/SAEs, whether they are early discontinued or after last study visit per study schedule.

If possible and if the patient consented for this, the site Co-Investigators continue recording any change/outcome in AESI/SAEs as per the study procedures:

* Within four (4) weeks after patient’s last planned study visit, or
* Within eight (8) weeks after patient’s early study discontinuation visit.

Other AEs that are ongoing at the end of treatment should be given an outcome (e.g. not resolved) at the last study visit or the early termination visit (e.g. not resolved). In the absence of patient’s consent for post-study follow-up, the same applies to AESI/SAE.

Table 3 Post-study safety follow-up for patients with ongoing AESI/SAEs and who consented for post-study follow-up

|  |  |
| --- | --- |
| **Post study safety follow-up** | |
| *Participant status* | *AESI/SAE* |
| Completes treatment and follow-up study periods as per study schedule but has ongoing AESI/SAEs | Followed for outcome for 4 additional weeks or until resolution/stabilization (whichever is later). |
| Has to discontinue the study early and has ongoing AESI/SAEs | Followed for outcome for 8 additional weeks or until resolution/stabilization (whichever is later). |

Pregnancies should be followed-up by the site Co-Investigators, if possible and if patient/patient’s partner consented for this, until an outcome is known, and the infants born from exposed pregnancies reach 12 months of age.

Table 4 Post-study safety follow-up for patients or partners with ongoing pregnancies/delivery <12 months before end of study, and who consented for post-study follow-up

|  |  |
| --- | --- |
| **Post study safety follow-up** | |
| *Mother status* | *Pregnancy/infant* |
| Participant (or participant’s partner) is pregnant or has delivered a baby <12 months before the last study visit. | Followed until pregnancy outcome is known and infant at 6 and 12 months of age (as applicable). |

### Reporting of Serious Adverse Events and relevant safety parameters to Sponsor

#### Expedited Reporting criteria

The Site Co-Investigators must inform immediately the Site PI and the Site Study Coordinator (SSC) of any suspected:

* Serious Adverse Events (SAE) (as defined in section 4.9);
* Adverse Events of Special Interest (AESI) (as defined in section 4.2);
* Pregnancy (exposed via mother or father) during or after IMP exposure; and
* Overdose (as defined in section 4.8).

#### Procedure for Expedited Reporting to Sponsor

Within **24 hours of event’s awareness**, the Site PI with the support of the SSC should proceed with the reporting of the expedited information to the PV Unit, as follows:

|  |
| --- |
| Sequential actions under the Site PI responsibility:   1. Ensure that the AE qualifies for expedited reporting as defined in previous section 5.2.1. 2. Verify that the minimum information required for expedited reporting is known:    1. **Patient identifier** (patient number),    2. Name, address, telephone and/or email of **the person sending the report** (e.g. the Site PI),    3. Nature of the **reportable event** (e.g. hepatitis, anaphylaxis, pregnancy, overdose) or serious outcome (e.g. death in itself without further details is reportable), and    4. **Treatment regimen** the patient has been allocated to. 3. Notify initial information **within 24 hours of awareness** as follows:    * Complete, sign and transmit an SAE (or Pregnancy) Report Form\* together with ***anonymized*** copies of relevant lab and other investigations reports to PV Unit:      + **PV unit**: [PVunit.GVA@geneva.msf.org](mailto:PVunit.GVA@geneva.msf.org) 4. Gather additional information including any missing information from the initial report, and new information such as: event’s outcome, lab results, hospital discharge date, final diagnosis, autopsy report, etc. 5. Notify new information **within 24 hours of new information awareness** as for initial reports:    * Complete, sign and transmit an SAE (or Pregnancy) Report Form\* together with ***anonymized*** copies of relevant lab and other investigations reports to PV unit:      + **PV unit**: [PVunit.GVA@geneva.msf.org](mailto:PVunit.GVA@geneva.msf.org) 6. File all original forms, supportive documents, and correspondences in the patient’s medical file before study end. In parallel, the eCRF should be populated with the same information as described in the endTB and endTB-Q Clinical Trial forms completion guide. |
| In the frame of the endTB and endTB-Q clinical trials, the SAE Report form should be used for all SAEs, but also for non-serious AESI and overdoses (associated or not with AE/SAE). The Pregnancy Report Form should be used for all pregnancies. |

If, for any reason (e.g. technical issue), the electronic (email) transmission of the information cannot be performed, phone transmission of safety information within 24 hours of awareness is possible (+41 22 849 89 74). This type of transmission is not preferred and should always be promptly followed by a written report.

#### Resolution of pharmacovigilance queries

Following expedited reporting of safety information, the Site PI may receive requests for clarification or for additional information from the Sponsor (PV unit). All efforts are made on the Sponsor side to combine such requests as a single query and allocate a reasonable timeline for answering.

Generally, priority requests should be addressed as soon as possible and not later than 24 hours after receipt of the query(ies) at the site. The Site PI, with the support of the SSC, is responsible to timely answer with the appropriate level of details (if available).

All documents must be anonymised before being forwarded to the Sponsor.

### Safety Reporting to Ethics Committees and National Regulatory Authorities

#### Suspected Unexpected Serious Adverse Reaction (SUSAR) Reports

The adverse events that are deemed related to at least one IMP and that are both serious and unexpected (referred as SUSARs for Suspected Unexpected Serious Adverse Reactions) are generally subject to expedited reporting to the National Regulatory Authorities (NRA) and local Ethics Committees (EC) - unless prescribed otherwise in the local regulations.

The PV unit is responsible for providing the Site PI with final submission-ready SUSAR reports (in English and as CIOMS I forms by default), and clearly mentioning the deadline for reporting.

Upon receipt of the CIOMS form, the Site PI (with the support of the SSC) is responsible for translating SUSAR reports (if applicable) and forwarding them to the local EC and to the NRA.

Timelines for reporting are as follows:

* + **Fatal** **or life-threatening SUSAR** must be reported within **7 calendar days** after first knowledge of the case,
  + **Non-fatal and non-life-threatening SUSAR** must be reported within **15 calendar days** after first knowledge of the case.

The PV unit calculates and communicates the deadline for each report, and transmits the report to the site within a timeframe allowing for translation and reporting to EC and NRA (within 4 and 9 calendar days from 1st receipt). The SSC is responsible to track and document receipt acknowledgments from each recipient and transmit those to the PV unit.

If additional individual case safety reports are requested by NRAs/ECs (e.g. all SAEs), the same process applies.

Reporting for each country including recipients, local format/language and timelines is detailed in a Reporting guideline.

#### Annual Safety Reports (ASR)

Annually, a progress safety report (in English and in an internationally accepted format) is issued by the PV unit for reporting to EC/NRA as appropriate.

The Site PI (with support from the SSC) is responsible to ensure proper translation into local language(s) (if applicable) and transmission of the ASR to local EC and NRA.

The PV unit calculates and communicates the deadline for the ASR submission, and transmits the report in an acceptable format and within a timeframe allowing for translation and reporting to local EC and NRA. The SSC is responsible to track and document receipt acknowledgments from each recipient and transmit those to the PV unit.

If more frequent periodic safety reports are requested by NRAs/ECs (e.g. every 6 months), the same process applies.

Reporting for each country including recipients, local format/language and timelines is detailed in a Reporting guideline.

#### Data & Safety Monitoring Board (DSMB) Conclusion Reports

When DSMB meeting minutes are available, the PV unit prepares within 1 week of receipt of the minutes a DSMB conclusion reports in a dedicated format and within a timeframe allowing for translation and reporting, as applicable, to local EC and NRA by the Site PI (with support from the SSC). The SSC is responsible to track and document receipt acknowledgments from each recipient and transmit those to the PV unit.

In the absence of a requested reporting time frame per local EC/NRA, the report shall be submitted within 1 month from the date of finalization of the DSMB meeting minutes.

Reporting for each country including recipients, local format/language and timelines is detailed in a Reporting guideline.

#### Answer to safety requests from Ethics Committees and National Regulatory Authorities

In case of requests for safety information from EC or NRA directly received at the Site, the Site PI (with the support from the SSC) should transmit those **within 24 hours of receipt** to:

* + - **PV unit**: [PVunit.GVA@geneva.msf.org](mailto:PVunit.GVA@geneva.msf.org);
    - **Central Study PI and Clinical PI**: [lorenzo.guglielmetti@paris.msf.org](mailto:lorenzo.guglielmetti@paris.msf.org); [mrich@pih.org](mailto:mrich@pih.org)

Immediate abbreviated communication is acceptable, if proper full request translation can be transmitted afterwards.

The Central/Clinical Study PIs, the Clinical Trial Manager or the Central Study coordinator, and the PV unit are responsible to prepare a response with the collaboration of the Site PI and the SSC. The SSC should organize translation into national language as appropriate and submit the response within the applicable timeframe requested by EC/NRA. The SSC is responsible to track and document receipt acknowledgments from each recipient and transmit those to the PV unit, the Clinical Trial Manager or the Central Study coordinator, and the Central/Clinical Study PIs.

### Urgent Safety Measures

Any urgent action undertaken by the Site PI/Co-Investigators or deemed necessary by the Sponsor in order to protect the patients against a significant safety issue altering study treatment risk/benefit should be communicated immediately between the sites (Site PI, Site Co-investigators, SSC) and the Sponsor (Central/Clinical Study PIs and PV unit), and conversely.

The Sponsor is responsible to organize and coordinate the urgent implementation of risk minimization measures at all investigational sites.

Such safety issues which may alter the risk/benefit of the IMPs or that would be sufficient to consider a change in their administration or in the overall conduct of the clinical trials are additionally to be notified as soon as possible and in written to the NRA and the EC.

The Central/Clinical Study PIs, the Clinical Trial Manager or the Central Study coordinator, and the PV unit are responsible to prepare a notification with the collaboration of the Site PI and the SSC. The SSC should organize translation into national language as appropriate and submit the notification as soon as possible. The SSC is responsible to track and document receipt acknowledgments from each recipient and transmit those to the PV Unit, the Clinical Trial Manager or the Central Study coordinator, and the Central/Clinical Study PIs.

### Archiving

SAE or Pregnancy Report Forms are source documents to be archived as per SOP TF-001-CT.

Individual safety reports (source documents and CIOMS) and proof of receipt acknowledgement from EC/NRA are archived by the PVO as per SOP PV-TB-P01 and by the responsible function as per SOP TF-001-CT.

Periodic safety reports or other safety communications and proof of receipt acknowledgement from EC/NRA are archived by the PVO as per SOP PV-TB-P06 and by the responsible function as per SOP TF-001-CT.

## REFERENCES

* ICH Guideline for Good Clinical Practice (E6R1).
* ICH Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A).
* ICH Development Safety Update Report (E2F).

## RELATED TOOLS

|  |  |
| --- | --- |
| **Related tools for completion of the described activities** | |
| **Number** | **Title** |
| **1** | SAE Report Form and completion guideline |
| **2** | Pregnancy Report Form and completion guideline |
| **3** | Causality assessment aide-memoire |
| **4** | SAE and AESI Reporting flow chart |
| **5** | MSF Severity Grading Scale |
| **6** | Reporting guideline - endTB and endTB-Q interventional clinical trials |
| **7** | FAQ - Severity Grading Scale |