# Standard Operating Procedures for: Safety data reconciliation

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# Standard Operating Procedures for: Safety data reconciliation

## PURPOSE

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| This procedure describes the process for reconciling safety data captured in the Pharmacovigilance Database (PVDB) with the data captured in the Clinical Trial Databases, OpenClinica (OC). |

## 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

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| --- | --- |
| **Function** | **Activities** |
| Data Management Team (DMT) | * Safety data reconciliation and identification of discrepancies,
* Reviews the Safety data reconciliation plan,
* Produces the Safety data comparison files,
* Sends and follows-up queries to the site regarding discrepancies identified as inconsistencies in the clinical trial databases, OpenClinica (OC),
* Requests minor corrections in OC as needed.
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| Site Data Entry Personnel | * Data entry into OC,
* Performs corrections in OC following Safety data reconciliation upon request of DMT or Site PI.
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| Internal Monitor  | * Regularly reviews OC outside of reconciliation periods and ensures consistency and medical coherence of the recorded information.
 |
| Pharmacovigilance Officer and deputy (PVO) | * SAE, AESI, pregnancy and overdose data entry into the pharmacovigilance database (PVDB),
* Initiates Safety data reconciliation process,
* Creates and maintains up-to-date the Safety data reconciliation plan for the studies,
* Extracts safety data from the PVDB and sends to the DMT for comparison with OC,
* Manually reviews the comparison files and integrates it in Safety data reconciliation reports,
* Sends and follows-up queries to the site regarding discrepancies identified as inconsistencies in the PVDB,
* Performs corrections in the PVDB,
* Finalizes the Safety data reconciliation reports with manual reconciliation information.
 |
| Site Principal Investigators (PI) and investigators | * Timely responds to queries from the DMT or the PVO.
* Amends the source documents to reflect any correction the site Data Entry personnel needs to reflect in OC, if applicable.
 |
| Study Site Coordinator (SSC)  | * Supports the Site PI in responding to the reconciliation queries and in documenting the related updates.
 |
| Clinical Trial Manager (CTM) | * Approves the Safety data reconciliation plan.
 |
| Central Study Principal Investigators (PI) | * Decide on unsolvable discrepancies.
 |

## 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.

###  Line listing

Extraction of the Pharmacovigilance Database (PVDB) where PVDB entries are presented as lines of text.

### 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.

## PROCEDURE

### Safety data reconciliation plan

Before study initiation, the PVO is responsible for the preparation of a Safety data reconciliation plan highlighting:

* The planning of safety data reconciliations,
* The scope of safety data reconciliations,
* The harmonized definitions or mapping of definitions, and
* The format for reconciliation and query follow-up.

The Safety data reconciliation plan should be reviewed by the DMT and approved by the CTM.

The PVO is responsible to maintain the Safety data reconciliation plan up-to-date in accordance with the study plan and the needs from the trial teams or external bodies (e.g. DSMB, Regulatory Authorities).

### Safety data reconciliation workflow

#### Overview of the process

| **Actions** | **Timelines** | **Responsible functions** |
| --- | --- | --- |
| 1. Safety data reconciliations initiation (for the purpose of data cleaning, QC, coding, etc.)
 | 3 weeks before planned cut-off date per Safety data reconciliation plan | PVO |
| ***…. CUT OFF DATE ….*** |
| 1. PVDB line listing extractions, Quality Check and transmission
 | Within 1 week after cut-off date | PVO |
| 1. OC extractions
 | DMT |
| 1. Merge of data and comparisons (automatic and manual)
 | DMT |
| 1. Discussion on discrepancies and determination of actions (queries)
 | Within 2 weeks after cut-off date or per time frame agreed between the involved functions | DMT, PVO and Site investigators with the support of the Study Site Coordinators as needed. |
| 1. Discrepancies closure
 | DMT and PVO |
| 1. Safety data reconciliation reports archiving
 | Within 1 week after discrepancies closure | PVO |

#### Before safety data reconciliation

In the event that an SAE/AESI/Pregnancy/Overdose occurs, the Site Principal Investigator (PI) or delegate fills an SAE report form (and/or a Pregnancy report form) and submits it to the Sponsor’s Pharmacovigilance (PV) unit within 24 hours of event’s awareness (see SOP PV-001-CT).

Upon receipt of an SAE report form (or a Pregnancy report form), the PVO enters all reported information into the sponsor’s pharmacovigilance database (PVDB; see PV unit SOP PV-TB-P01). The data are processed, checked for quality and consistency, medically reviewed and reported appropriately within time frames allowing for regulatory compliance.

The Site PI also documents SAE/AESI/Pregnancy information in the ‘Adverse Event’ form in the clinical trial databases, OpenClinica (OC)[[1]](#footnote-1). In general, OC completion should occur within 3 calendar days from the visit. The OC data are cross-checked with local paper files for consistency and quality by an internal monitor on a regular basis.

Monthly, the AE/SAE/AESI information from OC is coded by the PVO (refer to the MedDRA coding working instruction, reference PV-TB-I08).

Periodically and in accordance with the Safety data reconciliation plan, the PVO initiates the reconciliation process by sending an email to all involved functions 2 weeks before the planned cut-off date for the reconciliation.

#### During safety data reconciliation

The PVO is responsible for the extraction of safety data from the PVDB up to the cut-off date in accordance with the Safety data reconciliation plan. The PVO checks the line listings and sends them to the DMT.

The DMT extracts the safety data from OC up to the cut-off date.

The contents of both extractions (PVDB vs. OC) are semi-automatically compared using Stata. The DMT creates two comparison files, one for each study.

The PVO includes in two Safety data reconciliation reports the PVDB extractions, the comparison files and the list of discrepancies identified.

The PVO with the support of the DMT is responsible to rate the discrepancies as:

* **Minor**: discrepancy origin is easily identifiable and does not result in a difference in terms of content; e.g. use of a dash instead of a space, typos, and spaces.
* **Major**: discrepancy in content for which a clarification by the Site PI is needed.

For each discrepancy, the PVO with the support of the DMT determines whether correction is needed in OC or in the PVDB. The PVO with the support of the DMT is responsible for reflecting this information into the Safety data reconciliation reports.

The major discrepancies are raised as queries back to the study sites for clarification and resolution. The responsible party, the PVO for changes in the PVDB and the DMT for OC, should send the queries and follow-up on queries (refer to SOP DM-001-CT).

Upon receipt of clarification, the Data Entry Officer (in the name of the Site PI) performs the changes in OC and the PVO in the PVDB. The Site PI or delegate modifies the source documents accordingly if applicable.

In the situations where an SAE would not have been reported as such to the PV unit, the PVO is responsible to **immediately** query the site and requests an SAE report form **within 24 hours of query receipt at the site**.

Same applies in the situations where an SAE is found to be fatal in OC while this information was not reported to the PV unit.

The minor discrepancies are solved directly by the PVO for changes in the PVDB and requested by the DMT for OC (refer to SOP DM-001-CT).

Upon closure of a discrepancy, the PVO with the support of the DMT documents this information in the Safety data reconciliation reports.

If, for any reason, a major discrepancy cannot be solved by the Site PI and the PVO (with the support of the DMT), the central Study PIs are ultimately responsible to decide on the final action regarding this discrepancy. The PVO with the support of the DMT is responsible to document this decision in the Safety data reconciliation reports.

#### After safety data reconciliation

Safety data reconciliation is considered complete when all discrepancies have been solved. The PVO then files the Safety data reconciliation reports and transmits them to the DMT, the Clinical Trial Manager and Central Study Coordinators for their records and/or information. Central study coordinators and internal monitors are encouraged to review the reports.

### Archiving

The Safety data reconciliation plan and the Safety data reconciliation reports are archived by the PVO in the Trial Master File and in the MSF Pharmacovigilance SharePoint.

## REFERENCES

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

## RELATED TOOLS

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| **Related tools for completion of the activities** |
| **Number** | **Title** |
| **1** | Safety data reconciliation plan for endTB interventional clinical trial |
| **2** | MedDRA coding in the endTB clinical trial |

1. The Site PI documents Overdoses in the Drug (ancillary or study drugs) form in OC. [↑](#footnote-ref-1)