# Safety Monitoring Plan

# endTB (Evaluating Newly approved Drugs for multidrug-resistant TB): A Clinical Trial

# Protocol Number: NCT02754765

# &

# endTB-Q (Evaluating Newly Approved Drugs in Combination Regimens for Multidrug-Resistant TB with Fluoroquinolone Resistance (Q)): A Clinical Trial

# Protocol Number: NCT03896685

|  |  |
| --- | --- |
| **Reference:** | PV-TB-D23 |
| **Date:** | 8-May-2020 |
| **Version:** | 4.0 |
| **Countries:** | Georgia, Kazakhstan, Lesotho, Peru, South Africa, Pakistan, India, Vietnam |

# Table of Contents

[Safety Monitoring Plan 1](#_Toc40272677)

[Table of Contents 2](#_Toc40272683)

[1. Safety data collection and transmission to the Sponsor’s Pharmacovigilance Unit 3](#_Toc40272684)

[2. Pharmacovigilance database 3](#_Toc40272685)

[3. Safety data processing and medical review 3](#_Toc40272686)

[4. Individual case safety reports submission 5](#_Toc40272687)

[5. Annual Safety Reports 6](#_Toc40272688)

[6. Other periodic reporting activities 6](#_Toc40272689)

[6.1 Data & safety Monitoring Board 6](#_Toc40272690)

[6.2 Answers to queries from National Regulatory Authorities or local Ethics Committees 6](#_Toc40272691)

[7. Databases reconciliation 6](#_Toc40272692)

[8. Safety signal management and urgent safety measures 7](#_Toc40272693)

[List of abbreviations and definitions 8](#_Toc40272694)

[List of references 9](#_Toc40272695)

[Pharmacovigilance contact information 11](#_Toc40272696)

# Safety data collection and transmission to the Sponsor’s Pharmacovigilance Unit

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

Any untoward medical occurrence in a patient enrolled in the clinical trials qualifies as an AE, including any symptom, sign, or laboratory abnormality that was not present at baseline, and any worsening of an abnormality already present at baseline.

Safety data collection and transmission to the Sponsor’s Pharmacovigilance Unit (PV Unit) is under the responsibility of the Site Principal Investigator and Site Co-Investigators. The PV Unit receives immediately, **within 24 hours of first awareness on site**, via email and on dedicated ***anonymised*** Report Forms:

* All **serious AEs (SAEs)** whether or not deemed related to one or several investigational medicinal product(s) (IMPs),
* Non-serious AEs defined per protocol as pertaining to **areas of special interest**,
* Any **overdose** of an IMP, and
* **Pregnancy** in an enrolled female patient or in the female partner of an enrolled male patient.

Safety data collection is ongoing during the whole study duration and may be maintained post-study for patients who consented for per protocols’ post-study safety follow-up. Details on the process are available in the dedicated Standard Operating Procedure (ref. PV-001-CT).

# Pharmacovigilance database

The Pharmacovigilance Database for the clinical trials is MSF Basecon SafetyBase Interchange®. Maintenance and updates are contractually delegated to the IT-specialized company Basecon under the responsibility of the PV Unit (database administration procedure; ref. PV-TB-P02).

The Pharmacovigilance database will include all individual case safety reports for study patients experiencing SAEs, AEs of interest, overdoses and pregnancies (patient and partner).

Of note, the same database is used as a central repository of safety data from other DR TB projects (e.g. endTB program, MSF DR TB projects) and other clinical trials (e.g. TB-PRACTECAL), centralizing safety information on DR TB medications and allowing for signal detection.

# Safety data processing and medical review

The flow and timelines for data processing and medical review are common to the clinical trials covered by the PV Unit.

### Individual Case Safety Report receipt, validation and triage

Within 1 calendar day of first receipt by the Sponsor’s PV unit, all Report Forms on SAEs, AEs of interest, overdoses and pregnancies received from the Site are checked for completeness and prioritized by the MSF Pharmacovigilance Officer (or deputy) based on seriousness and the Site Investigator’s causality assessment.

“Day 0”, i.e. the clock start date for regulatory reporting, is determined as the date of first receipt by the Sponsor of a valid Individual Case Safety Report (ICSR) including the following minimum information: 1) a study patient or partner (for partner’s pregnancy), 2) the list of Investigational Medicinal Products (investigational regimen or standard of care), 3) the reporter, and 4) a reportable event.

Valid ICSRs are sent for medical review and in parallel processed in the Pharmacovigilance database. The PV Unit immediately liaises with the site for additional necessary information if a report is invalid.

The timeline for each activity depends on the type of case and is summarized in Table 1. The detailed process is available in procedure PV-TB-P01.

### Medical review

The PV medical monitor is responsible to perform the medical review of each SAE and AEI reports. This activity comprises evaluating for each adverse event-investigational medicinal product pair: the expectedness and the Sponsor’s assessment of the causality.

Cases considered as potential Suspected Unexpected Serious Adverse Reactions (SUSARs) are directed to a special review committee, the Medical Review Board.

### Medical review Board - SUSAR assessment

The Medical Review Board (MRB) is a medical/safety oversight committee of international DR TB experts appointed by the PV Unit to review all potential SUSAR cases reported to the PV Unit from any DR TB project/study covered by the PV Unit (terms of reference; PV-TB-D19).

The MRB reviews and confirms SUSARs (i.e. confirm expectedness and causality assessment per Sponsor) and assess the overall impact on the individual patient and on the conduct of all reporting DR-TB projects. This evaluation is part of overall signal detection activities of the PV Unit (ref. PV-TB-P05).

In addition, the MRB advises on the management and risk minimization actions for any Significant Safety Issue, which is identified by the PV unit or project/trial teams, and may alter treatment risk/benefit.

Serious and unexpected adverse events deemed related to IMP(s) by the Site Investigator **and/or** the Sponsor qualify as SUSARs.

MRB meetings occur on a fixed schedule allowing compliance with expedited reporting timelines. The Pharmacovigilance Officer (or deputy) can at any time convene an ad-hoc MRB meeting for Significant Safety Issue assessment.

### Case processing, quality control and follow-up

In parallel with medical review and MRB SUSAR assessment, each ICSR is entered in the Pharmacovigilance Database. Source data verification of database entry against the Report Forms is performed by the Pharmacovigilance Officer (or deputy).

Once the cases have been medically reviewed and processed, reportable ICSRs are extracted from the database and submitted to National Regulatory Authorities, Ethics Committees, Data & Safety Monitoring Board and drug manufacturers, as applicable (see section 4); other cases are completed.

The PV Unit follows-up regularly with the site on individual cases until resolution or stabilization of SAEs/AEIs, or until a pregnancy outcome is known and at 6 and 12 months after the baby is born.

Follow-up information is reported, processed and medically reviewed using the same process as for the initial report (ref. PV-TB-P01).

Table 1 Overview table of timelines for clinical trial individual case safety reports transmission from site, processing, medical review and submission

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Activity** | **Responsible** | **Reporting deadline in ‘calendar days from Day 0’** | | | | |
| **SUSARs** | | | **SAEs *(non-SUSARs)*** | **Non serious AEIs, overdoses, pregnancies** |
| **Fatal/Life-threatening** | **Other** | |
| **Transmission of reportable information on an SAE/Pregnancy Report Form** | Site PI and Co-Investigators | Within **24 hours** of first awareness on Site | | | | |
| **Validation & triage** | PV officers | Within 1 calendar day of first receipt at Sponsor (=Day 0) | | | | |
| **Medical review** | PV Medical monitor | 1 | | 2 | 5 | 10 *(or 5 if reportable)* |
| **MRB SUSAR assessment** | MRB | 3 | | 7 | N/A | N/A |
| **Data entry in the PV database** | PV officers | 2 | | 7 | 8 | 30 *(or 8 if reportable)* |
| **Source data verification** | PV officers | 3 | | 8 | Monthly random sample, QC | |
| **Reporting of a CIOMS I form to Site Investigators** | PV officers | 4 | | 9 | 9 *(only in country where reportable)* | |
| **Submission of CIOMS form to DSMB and drug manufacturers\***(as applicable) | PV officers | 4-7 | | 9-15 | N/A | |
| **Submission of CIOMS form to local Ethics Committees and National Regulatory Agencies\*** | Site PI | 4-7 | | 9-15 | 9-15 *(only in country where reportable)* | |
| \*Of note, where applicable, format and timelines are adapted as per local requirements if less than 7/15 calendar days from Day 0. By default ICH E2A applies as the minimum standard for expedited reporting. | | | | | | |

# Individual case safety reports submission

By default and in accordance with ICH E2A, Suspected Unexpected Serious Adverse Reactions (SUSARs) are subject to expedited reporting to the National Regulatory Authorities (NRA) and local Ethics Committees (EC). The PV Unit provides the Site Principal Investigator with international submission-ready SUSAR reports (in English and as CIOMS I forms by default) for translation and submission. Timelines for reporting are in Table 1. The PV Unit with the support of the Site Study Coordinator tracks and documents receipt acknowledgments from each recipient.

If additional individual case safety reports are requested by NRA and local EC (e.g. all national SAEs), the same process applies. If different timelines apply, the most stringent timeline is applied.

The PV Unit directly transmits the SUSAR reports to the Data & Safety Monitoring Board. Receipt tracking and documentation is performed by the PV Unit.

Transmission of individual cases to drug manufacturers is performed in accordance with all valid contractual agreements under the responsibility of the PV Unit. By default, SUSARs with the new drugs (bedaquiline and delamanid) are shared (refer to Table 1). Receipt tracking and documentation is performed by the PV Unit.

# Annual Safety Reports

An Annual Safety Report, in the format of a ‘Development Safety Update Safety Report’ (ICH E2F), is prepared by the PV Unit and reviewed by the PV medical monitor. The Site Principal Investigator submits the report to NRA and Local EC within 60 calendar days from database lock. Receipt acknowledgement is tracked and documented by the PV Unit and the Site Study Coordinator. If more frequent reporting or different formats are required by the NRA or the local EC, the same process applies.

The MRB receives Annual Safety Reports for safety oversight and signal detection purpose (refer to section 8).

# Other periodic reporting activities

## Data & safety Monitoring Board

The PV Unit provides the Data & Safety Monitoring Board (DSMB) with:

1. SUSAR reports in an expedited manner (section 4),
2. Individual case narratives for DSMB periodic reports (ref. DSMB charter),
3. Interim AEI line listings (ref. DSMB charter),
4. Information on valid safety signals or recommendations from the Medical Review Board (section 8),
5. Information on situations described as triggering a DSMB review in the DSMB charter,
6. Any *ad hoc* listing, analysis or information in collaboration with the Central Data Manager and the rest of the Central Coordination Team.

Where applicable, the PV Unit transfers the DSMB conclusion reports in an acceptable format and within a timeframe allowing for translation and reporting to local EC and NRA by the Site Principal Investigator. The PV Unit with the support of the Site Study Coordinator tracks and documents receipt.

## Answers to queries from National Regulatory Authorities or local Ethics Committees

Requests for safety information from EC or NRA directly received by the Site, should be transmitted by the Site Principal Investigator to the PV Unit and the Central Study/Clinical Principal Investigators within 24 hours of receipt. The PV Unit collaborates on the preparation and submission of responses (ref. PV-001-CT).

# Databases reconciliation

Every 3 months, as per the endTB and endTB-Q Clinical Trials Reconciliation Plan schedule, safety data from the Pharmacovigilance database and the endTB and endTB-Q Clinical trials databases (Open Clinica) are reconciled to ensure coherence and completeness of the information. Detailed process is explained in the Standard Operation Procedure PV-002-CT.

# Safety signal management and urgent safety measures

Safety signal detection within the pharmacovigilance system for DR TB projects/clinical trials is an ongoing process occurring at each step of safety data management and during periodic safety analyses.

A safety signal is any information arising from one or multiple sources, which suggests a new potentially causal association, or a new aspect of a known association between an exposure and an event or set of related events, either adverse or beneficial (rarely), that is judged to be of sufficient likelihood to justify verification.

The Medical Review Board (MRB) is responsible for evaluating all potential safety signals brought to its attention or detected internally during SUSAR or periodic/cumulative analysis review.

The MRB is responsible for the preparation of communication to all concerned investigators/clinicians, ECs (central and local), NRAs (or Ministries of Health), DSMB, manufacturers, partners, and for ensuring the implementation and follow-up of any risk minimization measure. Of note, activities may be delegated as appropriate, e.g. implementation of risk minimization activity delegated to the trial Central Coordination Team.

Throughout the process, if a safety signal is considered a potential Significant Safety Issue (see definition below), the PV officers will convene an immediate ad-hoc MRB meeting (within 3 calendar days of signal detection). Signal validation and recommendation on signal management and risk minimization actions relating to any valid Significant Safety Issue altering treatment risk/benefit should occur within 3 calendar days of signal detection.

Any urgent action deemed necessary to protect patients against a Significant Safety Issue [Urgent Safety measures] should be communicated immediately (within 24 hours of identification of the need for urgent communication, i.e. from signal validation) to the sites/clinics (Site PIs, Study Site Coordinators – *in turn responsible to communicate further as appropriate*), and additionally be notified as soon as possible and in writing to all investigators/clinicians, ECs (central and local), NRAs (or Ministries of Health), DSMB, manufacturers, and partners.

The PV Unit tracks and documents each step of safety signal management and communication, urgent and non-urgent (ref. PV-TB-P05).

# List of abbreviations and definitions

**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 Interest (AEI):** 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, AEI 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.

**“Day 0” or “clock-start” date**: Date of receipt of a valid ICSR setting the clock start date for expedited reporting (if applicable).

**Individual Case Safety Report (ICSR):** Format and content 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.

**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 non-pathogenic) 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.

**Significant safety issue**: Any event or observation which may alter the risk/benefit assessment of the treatment and/or impacting public health, necessitating immediate changes in the administration of the drugs or important modification of the conduct of the CT/program. This includes major findings from clinical/non-clinical studies (published, from partners or internal), findings from drug manufacturers, WHO or internal review, safety issue relating to trial procedures, etc.

**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 trial.

# List of references

| **Type** | **Ref no.** | **Title** |
| --- | --- | --- |
| PV Unit Standard Operating Procedures | PV-TB-P01 | Safety Data Collection, Processing and Reporting at MSF Pharmacovigilance unit |
| PV-TB-P02 | Safety Database Administration |
| PV-TB-P03 | Data Entry Conventions |
| PV-TB-P04 | Compliance Measurement |
| PV-TB-P05 | Safety Signal Management and Safety Communication |
| PV-TB-P06 | Periodic Safety Reports for Clinical Trials Sponsored by MSF |
| PV-TB-P07 | Audits and inspections |
| PV-TB-P08 | Quality Document Management System |
| PV Unit Standard Report Forms | PV-TB-F01 | SAE Report Form |
| PV-TB-F02 | Pregnancy Report Form |
| PV Unit Standard and Project –specific Reference Documents | PV-TB-D01 | SAE Report Form completion guideline |
| PV-TB-D02 | Pregnancy Report Form completion guideline |
| PV-TB-D03 | Causality assessment aide-memoire |
| PV-TB-D04 | PVDB user training certificate template |
| PV-TB-D05 | CAPA template |
| PV-TB-D06 | Compliance report template |
| PV-TB-D07 | Safety Data Management at MSF PV unit flow chart - TB |
| PV-TB-D08 | Narrative & Company comment templates |
| PV-TB-D09 | DSUR template |
| PV-TB-D10 | Study Periodic Safety Reports (covering <1 year) template |
| PV-TB-D11 | PV Unit Standard Operating Procedure Template |
| PV-TB-D12 | TB Severity Grading Scale |
| PV-TB-D13 | Individual Case Safety Reports Quality check Guidance |
| PV-TB-D18 | Safety data reconciliation plan endTB and endTB-Q interventional clinical trials |
| PV-TB-D19 | Medical Review Board - Terms of Reference |
| PV-TB-D20 | MSF Pharmacovigilance unit organogram |
| PV-TB-D21 | FAQ Severity Grading Scale |
| PV-TB-D22 | Reporting guideline - endTB and endTB-Q interventional clinical trials |
| PV-TB-D23 | Safety monitoring Plan - endTB and endTB-Q interventional clinical trials |
| PV-TB-I08 | MedDRA coding working instruction - endTB and endTB-Q interventional clinical trials |
| endTB and endTB-Q clinical trials Standard Operating Procedures | PV-001-CT | Safety data collection and reporting at trial sites |
| PV-002-CT | Safety data reconciliation |

# Pharmacovigilance contact information

Completed and signed SAE (or Pregnancy) Report Form are reportable to the PV Unit **within 24 hours of first event’s awareness on site**:

* + - **PV unit**: [PVunit.GVA@geneva.msf.org](mailto:PVunit.GVA@geneva.msf.org); (refer to the locally approved version of the protocol)