# Standard Operating Procedures for

 **Event Validation**

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# Standard Operating Procedures for

# Event Validation

# PURPOSE

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| The primary and secondary endpoints of the endTB and endTB-Q trials are composite endpoints based mainly on sputum bacteriological evolution, but in specific cases also on clinical and radiological findings. To evaluate and assign the treatment outcomes, the 2 following SOPs should be consulted: * SP-026-CT Reporting of Treatment Outcomes;
* SP-032-CT Evaluating bacteriological, radiographic and clinical evolution for outcome classification.

In order to ensure the accuracy of the treatment outcome endpoints in the study and limit the variability across the sites, the Event Validation Group (EVG) must review and validate the treatment outcomes assigned in the endTB Clinical Trials.  |

# SCOPE

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| This standard operating procedure (SOP) describes the organization and performance of central review of treatment outcomes assigned by the Sites for the endTB and endTB-Q trials, to ensure accuracy and standardization in reporting across sites. |

# RESPONSIBLE FUNCTIONS

|  |  |
| --- | --- |
| **Function** | **Activities** |
| **Trial Manager or designee** | * Establish the Event review schedule with the Statistician to issue the listing of treatment outcomes to be reviewed by the EVG.
 |
| **Statistician**  | * Issue a listing of all new treatment outcomes since the previous review.
* Produce a list of treatment outcomes assigned by the algorithm using the information present in the OpenClinica database and compare them to the “Site Investigator Treatment outcome».
* Issue an Event Validation document for each assigned outcome that includes the « Site Investigator Treatment outcome» and the treatment outcomes from the algorithm, a validation page for the EVG conclusion, and bacteriological, radiological and clinical information from OpenClinica for the review.
* Perform final consistency check between the treatment outcomes classified by the algorithm and the “EVG Final Treatment outcome” before database lock.
* Calculate the proportion of discordance between the « Site Investigator Treatment outcome» and those assigned by the EVG.
 |
| **Site Study Coordinator or designee** | * Prepare and make available digital/digitized X-rays for the review, when required by the EVG.
 |
| **Event Validation Group (EVG)** | * Review the treatment outcomes classified by the algorithm as discordant or related to the evaluation of bacteriological, radiological and clinical evolution.
* Assign the outcomes.
* Complete the validation page including the “EVG Final Treatment outcome» worksheet.
 |
| **Site Principal Investigator (Site PI) and/or delegated Site Co investigator (Site CI)** | * Review the discrepancies between « Site Investigator Treatment outcome» and « EVG Final Treatment outcome ».
* Assess potential issues encountered by the Site during treatment outcomes classification and EVG discordant outcomes review and make recommendations for refresher trainings.
 |
| **Site Data Entry** | * Enter the data of “EVG Final Treatment outcome» worksheet in OpenClinica.
 |
| **Site Internal Monitor** | * Perform Source Data Verification (SDV) for the « Site Investigator Treatment outcome» before Event Validation.
* Check for each assigned outcome the presence of the corresponding Event Validation documents (including the “EVG Final Treatment outcome» worksheets) in the patient files.
 |
| **Central Study Coordinator**  | * Share the Event Validation documents containing the “EVG Final Treatment outcome» worksheet with the Site.
 |

# DEFINITIONS and ABBREVIATIONS

For the purpose of event review, the outcomes defined in the endTB and endTB-Q study protocols section 3.2 can be divided into three groups, as follows:

**GROUP A: Outcomes related to death or treatment (change)**

**Week 39, Week 73, Week 104:**

**Unfavorable outcomes**

In the experimental arm and in the control arm if using the shortened regimen, addition or replacement of one or more drugs[[1]](#footnote-2).

* + In the control arm, if using the conventional regimen, addition or replacement of two or more drugs.
	+ Death from any cause.

**Week 73:**

**Unfavorable outcomes**

* + Initiation of a new MDR-TB treatment regimen after the end of the allocated study regimen and before week 73 (relapse).

**Week 104:**

**Unfavorable outcomes**

* + Initiation of a new MDR-TB treatment regimen after the end of the allocated study regimen and before week 104 (relapse).

**GROUP B: Outcomes related to microbiological results only**

**Week 39:**

**Favorable outcomes**

* + A participant’s outcome will be classified as favorable at week 39 if all culture results from samples collected between weeks 36 and 39 are negative and the outcome is not classified as unfavorable.

**Unfavorable outcomes**

* + At least one culture result (from a sample collected between weeks 36 and 39) is positive.
	+ The patient is not assessable because the last available culture result is from a sample collected before week 36.

**Week 73:**

**Favorable outcomes**

* + The last two culture results are negative. These two cultures must be taken from sputum samples collected on separate visits, the latest between weeks 65 and 73.

**Unfavorable outcomes**

* + At least one of the last two cultures, the latest being from a sputum sample collected between weeks 65 and 73, is positive in the absence of evidence of laboratory cross contamination (failure/relapse).
	+ **[**(There is no culture result from a sputum sample collected between weeks 65 and 73) ***or*** (it is positive due to laboratory cross contamination)**]**; ***AND*** **[**the most recent culture is positive in the absence of laboratory contamination**]**.
	+ **[**(The outcome is not assessable because there is no culture result from a sputum sample collected between weeks 65 and 73) ***or*** (it is positive due to laboratory cross contamination)**]**; ***AND*** **[**(there is no other post-baseline culture result), ***or*** (the most recent culture is positive due to laboratory cross contamination)**]**.

**Week 104:**

**Favorable outcomes**

* + The last two cultures are negative. These two cultures must be from sputum samples collected on separate visits, the latest between weeks 97 and 104.

**Unfavorable outcomes**

* + At least one of the last two cultures, the latest being from a sputum sample collected between weeks 97 and 104, is positive in the absence of evidence of laboratory cross contamination (failure/relapse).
	+ **[**(There is no culture result from a sputum sample collected between weeks 97 and 104) ***or*** (it is positive due to laboratory cross contamination)**]**; ***AND*** **[**(there is no other post-baseline culture), ***or*** (it is positive)**]**.

**GROUP C: Outcomes related to the evaluation of bacteriological, radiological and clinical evolution**

**Week 73:**

**Favorable outcomes**

* + **[**The last culture result—from a sputum sample collected between weeks 65 and 73—is negative**]**; ***AND* [**either (there is no other post-baseline culture result) ***or*** (the penultimate culture result is positive due to laboratory cross contamination)**]**; ***AND*** **[**bacteriological, radiological and clinical evolution is favorable**]**.
	+ **[**(There is no culture result from a sputum sample collected between weeks 65 and 73) ***or*** (the result of that culture is positive due to laboratory cross contamination)**]**; ***AND*** **[**the most recent culture result is negative**]**; ***AND*** **[**bacteriological, radiological and clinical evolution is favorable**]**.

**Unfavorable outcomes**

* + **[**The last culture result—from a sputum sample collected between weeks 65 and 73—is negative**]**; ***AND* [**(there is no other post-baseline culture result) ***or*** (the penultimate culture is positive due to laboratory cross contamination)]; ***AND* [**bacteriological, radiological or clinical evolution is unfavorable**]**. (failure/relapse)
	+ **[**(There is no culture result from a sputum sample collected between weeks 65 and 73) ***or*** (it is positive due to laboratory cross contamination)**]**; ***AND*** **[**the most recent culture is negative**]**; ***AND*** **[**bacteriological, radiological or clinical evolution is unfavorable**]**. (failure/relapse)
	+ **[**The outcome is not assessable because (there is no culture result from a sputum sample collected between weeks 65 and 73) ***or*** (it is positive due to laboratory cross contamination)**]**; ***AND* [**(the most recent culture is negative) ***and*** (bacteriological, radiological and clinical evolution is not assessable)**]**.

**Week 104:**

**Favorable outcomes**

* **[**The last culture result—from a sputum sample collected between weeks 97 and 104—negative**]**; ***AND*** **[**either (there is no other post-baseline culture result) ***or*** (the penultimate culture result is positive due to laboratory cross contamination)**]**; ***AND*** **[**bacteriological, radiological and clinical evolution is favourable**]**.
	+ **[**(There is no culture result from a sputum sample collected between weeks 97 and 104) ***or*** (the result of that culture is positive due to laboratory cross contamination)**]**; ***AND*** **[**the most recent culture result is negative**]**; ***AND*** **[**bacteriological, radiological and clinical evolution is favourable**]**.

 **Unfavorable outcomes**

* **[**The last culture result—from a sputum sample collected between weeks 97 and 104—is negative**]**; ***AND*** **[**(there is no other post-baseline culture result) ***or*** (the penultimate culture is positive due to laboratory cross contamination)**]**; ***AND*** **[**bacteriological, radiological or clinical evolution is unfavorable**]**. (failure/relapse)
* **[**(There is no culture result from a sputum sample collected between weeks 97 and 104) ***or*** (it is positive due to laboratory cross contamination)**]**; ***AND* [**the most recent culture is negative**]**; ***AND* [**bacteriological, radiological or clinical evolution is unfavorable**]**. (failure/relapse)
* **[**(There is no culture result from a sputum sample collected between weeks 97 and 104) ***or*** (it is positive due to laboratory cross contamination)**]**; ***AND*****[**(the most recent culture is negative) ***and*** (bacteriological, radiological and clinical evolution is not assessable)**]**.
* Loss to follow-up.

Refer to SOP SP-026-CT *Reporting of Treatment Outcomes* and SP-032-CT *Evaluating bacteriological, radiographic and clinical evolution for outcome classification.*

# PROCEDURE

## 5.1 Materials:

* Listing of participants and endpoints with treatment outcomes to be reviewed;
* Listing of “Site Investigator Treatment outcome”;
* Listing of treatment outcomes as classified by the algorithm;
* Clinical, radiological and bacteriological information;
* Information about all treatment changes;
* Digital/digitized X-rays;
* SOP SP-026-CT *Reporting of Treatment Outcomes*;
* SP-032-CT *Evaluating bacteriological, radiographic and clinical evolution for outcome classification.*
	1. ***Event Validation schedule***

The schedule of outcomes review by site (“batch run”) is established by the Trial Manager and the Statistician based on the number of new treatment outcomes assigned by the Site Investigator since the previous review and the status of SDV of the data relevant for outcome assignment (e.g., culture results, treatment changes, end of treatment and study, death). Event validation should occur at approximately semi-annual intervals for each Site. Frequency may be increased when large numbers of participants are reaching endpoints.

The **Event Validation Group** (EVG) will review/assign the list of events provided by the Statistician. Every effort will be made for the assignment to be blinded.

* 1. ***Outcome review***

An algorithm, written in Stata, will automatically assign the treatment outcomes for outcomes in Groups A and B based on data entered in OpenClinica, specifically looking at the following variables:

* death and all treatment changes for the outcomes in Group A;
* death, all treatment changes of drug classes, and sputum culture results from each sample collected for the outcomes in Group B.

Outcomes in Groups A and B will be classified as “concordant” (if the outcome assigned by the site investigator is identical to the outcome assigned by the algorithm) or “discordant” (if the two outcomes are different). All discordant outcomes in Groups A and B assigned will be reviewed by the EVG.

All outcomes in Group C will be automatically classified by the algorithm as “need evaluation” and will be assigned by the EVG.

At every Outcome batch run, the **Statistician** will:

- Issue a listing of all new treatment outcomes that have become eligible for validation since the previous review. The listing, released per Site, should be used by the sites to identify missing data, complete missing information in OpenClinica and perform Source Data Verification.

- Classify treatment outcomes using the algorithm once the site has cleaned the relevant data and completed data entry and data monitoring in OpenClinica.

- Create an automatic « Event Validation document » for each outcome (see Appendices A2). The « Event Validation document » will include:

* the outcome assigned by the algorithm;
* the “Site Investigator Treatment outcome»;
* a validation page with “EVG Final Treatment outcome» worksheet;
* All deaths, treatment changes, end of treatment and end of study information, sputum culture results from all samples collected;
* Missed visits list
* clinical, radiological and bacteriological information needed to assess the evolution:
* Clinical information will include the following signs/symptoms per patient per visit: body weight, body temperature, ECOG performance status, presence of respiratory symptoms (cough, hemoptysis, thoracic pain, dyspnea) with grade and constitutional symptoms (night sweats, lack of appetite) with grade.
* Radiological information will include chest X-rays conclusions and interpretations (number of lung zones affected, cavities, fibrosis, bullae, pleural effusion, infiltrate, other lesions, extent of disease).
* Bacteriological information will include phenotypic DST results and rapid molecular tests for all drugs.

- Provide to the EVG the listing of all new treatment outcomes (excel file) assigned by the algorithm as part of the batch run and the « Event Validation document » for each treatment outcome to be reviewed. These files will be saved on the endTB SharePoint. When documents are available for review, an email will be sent to the EVG members (with the Trial Manager and Central Study Coordinator in copy).

**Outcomes belonging to Group A and B**

If the outcome assigned by the algorithm is **CONCORDANT** with the one of the Site Investigator:

* The EVG members are not required to validate it.
* The « Event Validation document » is automatically named adding “\_algorithm” at the end of the file name.
* All the “Event Validation documents» with concordant outcomes are made available to the Site in the SharePoint and the Site notified via e-mail.
* The Site Data Entry enters the data in OpenClinica and stores the « Event Validation document/s » in the respective patient file, along with the «Site Investigator Treatment outcome » worksheet/s.
* The Site Internal Monitor checks the presence of the « Event Validation document/s » in the respective patient files.

If the outcome assigned by the algorithm is **DISCORDANT** with the one assigned by the Site Investigator, then the EVG will:

* classify all the discordant outcomes based on the information contained in the « Event Validation document »;
* complete the “EVG Final Treatment outcome» worksheet contained in the « Event Validation document »; and
* discuss all the discordant outcomes with the site Investigators (keeping the Trial Manager, Statistician and Central Study Coordinator in copy).

 As a result of the discussion,

1. If the discrepancy is determined to be due to data incorrectly entered in OpenClinica, the Site Data Entry will modify the data in OpenClinica, the algorithm will be re-run creating a new version of the « Event Validation document ». Then, the EVG Final outcome will be CONCORDANT with that of the Site Investigator.
2. If the Site Investigators change their opinion to agree with the algorithm-assigned outcome, then modifications will be made in the source documents and in OpenClinica accordingly. The algorithm will be re-run creating a new version of the « Event Validation document ». The EVG Final outcome will be CONCORDANT with that of the Site Investigator.
3. If the Site Investigators do not change their opinion concerning the final outcome to be assigned, no modifications will be made in the source documents and in OpenClinica. The algorithm will not be re-run and the Final EVG outcome will be DISCORDANT with that of the Site Investigator.

**Outcomes belonging to Group C**

The **EVG members** will assign all the outcomes belonging to Group C; they will check outcomes of previous time-points already validated and thoroughly assess the following variables present in the « Event Validation document » for each outcome to be reviewed.

* death;
* all treatment changes;
* sputum TB culture results at each visit;
* clinical information on specific signs and symptoms;
* X-rays\*;

\* If requested by the EVG, the **Site SC or designee** provide to the **EVG members** the anonymized chest X-rays for patients with outcomes in Group C. These will be placed in a designated secure section on SharePoint.

In case of queries or uncertainties preventing outcome assignment, the **EVG members** will communicate by email with the Site Investigators (with Trial Manager, Statistician and Central Study Coordinator in copy).

When all the information is clarified, the EVG members will complete the “EVG Final Treatment outcome» worksheet on SharePoint and compare the assigned outcome with the one of the Site Investigator.

If the outcome assigned by the EVG members is **CONCORDANT** with the one of the Site Investigator:

* The “Event Validation documents» is made available to the Site in the SharePoint and the Site notified via e-mail.
* The Site Data Entry enters the data in OpenClinica and stores the « Event Validation document » in the respective patient file, along with the “Site Investigator Treatment outcome» worksheet.
* The Site Internal Monitor checks the presence of the « Event Validation document » in the respective patient file.

If the outcome assigned by the EVG members is **DISCORDANT** with the one of the Site Investigator:

* The EVG members will discuss with the Site investigator the discrepancy (with Trial Manager, Statistician and Central Study Coordinator in copy).

 As a result of the discussion,

1. If the discrepancy is determined to be due to data incorrectly entered in OpenClinica, the Site Data Entry will modify the data in OpenClinica, the algorithm will be re-run creating a new version of the « Event Validation document ». The EVG members will reassign the Outcome and the Final outcome will be CONCORDANT with that of the Site Investigator.
2. If the Site Investigators change their opinion concerning the final outcome to be assigned, modifications will be made in the source documents and in OpenClinica accordingly. The algorithm will be re-run creating a new version of the « Event Validation document ». The EVG members will reassign the Outcome and the Final outcome will be CONCORDANT with that of the Site Investigator.
3. If the Site Investigators do not change their opinion concerning the final outcome to be assigned, no modifications will be made in the source documents and in OpenClinica. The Final EVG outcome will be DISCORDANT with that of the Site Investigator.

**When the final “Event Validation documents» are available:**

* The files are made available to the Site in SharePoint and the Site is notified via email by the Central Study Coordinator.
* The Site Data Entry enters the data in OpenClinica and stores the «Event Validation document/s» in the respective patient file, along with “Site Investigator Treatment outcome»worksheet/s.
* The Site Internal Monitor checks the presence of the “Event Validation documents» in the respective patient files.
	1. ***Outcome reconciliation***

The **Central Data Manager** will:

- Perform monthly reconciliation between “Site Investigator Treatment outcome» (in Treatment Outcome form) vs. “EVG Final Treatment outcome» (in “Event Validation Group (EVG) final treatment outcome” form) in OpenClinica. If discrepant data are found, queries will be sent to sites to request clarification.

- Verify manually queries sent to sites in case of discrepancies, to ensure that a clarification is provided and/or data updated in OpenClinica. In case of persistent discordances, data will be discussed with EVG members.

At the time of Site Closure and before the database lock, to ensure that any changes in the data in OpenClinica since the initial validation did not impact the final validated outcome, the **statistician** will:

1. re-classify all the treatment outcomes usinghe algorithm;
2. coordinate a final check between the outcomes re-classified by the algorithm and the ones entered in OpenClinica as “EVG Final Treatment outcome”.
	1. ***Assessment of proportion of discordances***

The **Statistician** will calculate the proportion of discordance between the “EVG Final Treatment outcome» classification and “Site Investigator Treatment outcome» classification. The EVG will communicate the proportion of discordance to the Trial Manager. In case of more than 10% discordance for a site, the EVG will write a summary of the identified issues. The **Central Study Coordinator** will communicate the result of the review to the central Principal Investigators.

Generally, **less than 10%** discordance is considered satisfactory and does not require actions.

**More than 10%** discordance will require discussions among the central Principal Investigators, site Principal Investigator and Central Study Coordinators to identify potential misunderstanding of the SOPs SP-026-CT *Reporting of Treatment Outcomes* and SP-032-CT *Evaluating bacteriological, radiographic and clinical evolution for outcome classification* and need of refreshing training.

In case of discrepancy between the “EVG Final Treatment outcome» classification and the “Site Investigator Treatment outcome» classification, the “EVG Final Treatment outcome» classification will be used in the statistical analysis. The “Site Investigator Treatment outcome» classification can be used in sensitivity analyses.

# REFERENCES

None

# SUPPORTING DOCUMENTS

* SP-026-CT Reporting of Treatment Outcomes
* SP-032-CT Evaluating bacteriological, radiographic and clinical evolution for outcome classification.

# APPENDIX

|  |  |
| --- | --- |
| **Number** | **Title** |
| A1 | SP-031-CT A1 Treatment outcome validation process - Flowchart |
| A2.1 | SP-031-CT A2.1 Event Validation document W39 |
| A2.2 | SP-031-CT A2.2 Event Validation document W73 |
| A.2.3 | SP-031-CT A2.3 Event Validation document W104 |

1. Addition or replacement of drugs should be reported as number of new (not previously used in the trial regimen) *classes* of drugs added. Drugs removed, dose changes, and drugs restarted after temporary suspension should not be counted as an addition or replacement. As specified in the protocol (section 5.3.3), new drugs within classes already administered (i.e., fluoroquinolones, thioamides, and aminoglycoside/polypeptide) should not count as an addition. New drugs added to conform to new WHO guidance should also not count as an addition. The names of the drugs should not be reported as the EVG should remain blinded to treatment assignment. [↑](#footnote-ref-2)