**Standard Operating Procedure for**

**Evaluating bacteriological, radiographic and clinical evolution for outcome classification**

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**Standard Operating Procedure for
Evaluating bacteriological, radiographic and clinical evolution for outcome classification**

# PURPOSE

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| This Standard Operating Procedure (SOP) describes the procedures for performing the assessment of bacteriological, radiographic and clinical evolution for outcome classification in the endTB Clinical Trials. |

# SCOPE

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| This SOP is developed for trained healthcare workers assessing the bacteriological, radiographic and clinical evolution of participants in the endTB Clinical Trials for the purpose of outcome classification in the endTB Clinical Trials. |

# RESPONSIBLE FUNCTIONS

|  |  |
| --- | --- |
| **Function** | **Activities** |
| **Site Co-Investigator (site-CI)/Sub-Investigator and Site Principal Investigator (site-PI)** | * Identify cases in which the evaluation of bacteriological, radiographic and clinical evolution is needed.
* Classify the bacteriological, radiographic and clinical evolution as favorable or unfavorable.
 |
| **Event Validation Group** | * Review classification of the outcome.
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# DEFINITIONS and ABBREVIATIONS

**Treatment outcome:** It is the outcome of study treatment which is assigned to each participant at each specified time point and categorized as favorable or unfavorable according to the endTB protocols (section 3.2).

**Bacteriological, radiographic and clinical evolution:** The bacteriological, radiographic and clinical evolution assessment is required for the purpose of outcome definition, according to the protocols of the endTB Clinical Trials, at the study visits of weeks 73 and 104 (see also ***SOP SP-026-CT Reporting of Treatment Outcomes***). The bacteriological, radiographic and clinical status is regularly documented as part of routine clinical care as needed and under scheduled monitoring tests and assessments. This SOP specifically addresses how to use bacteriological, radiographic and clinical evolution for outcome classification at weeks 73 and 104.

**Event Validation Group:** The Event Validation Group comprises central independent medical doctors with experience in the management of MDR-TB patients. The Event Validation Group reviews patient treatment outcomes. Its activities are governed by ***SOP SP-031-CT Event Validation*.**

# PROCEDURE

## *5.1. Material*

Source documents including results of physical examination, X-rays (image and report) and bacteriological results.

***5.2. Evaluation of the bacteriological, radiographic and clinical evolution***

The **Site-CI**, with support from the **Site-PI** if needed,classifies the evolution of the participant’s condition since randomization in the following three categories: bacteriological, radiographic, and clinical evolution.

The assessment of the evolution of the patient under treatment is only required in some specific cases, as defined in the endTB study protocols and in ***SOP SP-026-CT Reporting of Treatment Outcomes***.

*5.2.1. Bacteriological evolution*

**Site-CI,** with the help of the **Site-PI** if needed, classifies the bacteriological evolution according to monthly culture and drug susceptibility test (DST) results as:

* Unfavorable evolution: presence of two or more positive sputum culture results, without evidence of cross-contamination, from sputum specimens collected at different visits (scheduled or unscheduled) at or after the prior outcome assignment; or, acquisition of drug resistance (proven by DST and confirmed by Institute of Tropical Medicine) to any fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin) or other drug(s) that was/were given as part of study treatment in experimental or control arms.
* Unassessable evolution: sputum culture results without evidence of cross-contamination on sputum specimens collected at different visits at or after the prior outcome assignment are unavailable.
* Favorable evolution: if classified neither as unfavorable nor as unassessable.

*5.2.2. Radiographic evolution*

The **Site-CI,** with the help of the **Site-PI** if needed, classifies the radiographic evolution according to the changes on chest X-ray at scheduled and unscheduled visits, using the following criteria:

* Unfavorable evolution: presence of any of the following in the most recent X-ray, compared to baseline:
	+ Appearance of a new lung cavity, or increase of 1 cm or more in the diameter of a pre-existing cavitary lesion, without evidence of association with another concomitant disease.
	+ Significant increase in the extension of lung lesions, i.e., from minimal to moderate or advanced or from moderate to advanced, without evidence of association with another concomitant disease.
	+ Appearance of new lesions that could be suggestive of an active tuberculosis process, without evidence of association with another concomitant disease. For example: new infiltrate(s), pleural effusion(s), mediastinal adenopathy, etc.

**NOTE:** The **Site-CI** and **Site-PI** should systematically consider the possibility of immune response inflammatory syndrome (IRIS) or paradoxical reaction in a patient with occurrence of new radiological lesions or worsening of existing lesions in the 3 months following the introduction of antiretroviral therapy. Radiographic manifestations of IRIS should not be interpreted as unfavorable radiographic evolution.

* Unassessable evolution: no X-ray available after baseline.
* Favorable evolution: if neither classified as unfavorable nor as unassessable.

*5.2.3. Clinical evolution*

The **Site-CI,** with the help of the **Site-PI** if needed, will classify the clinical evolution according to the following criteria:

* Unfavorable evolution: presence of two or more of the following at outcome assignment visit in comparison to baseline:
	+ No weight gain in patients with a body mass index (BMI) < 18.5 at baseline. The criteria of increase in body weight compared to baseline is only to be assessed in patients with BMI < 18.5 at baseline.
	+ 10% weight loss or more in a patient with a BMI ≥18.5 at baseline.
	+ Worsening of the performance status of the patient, measured by any increase in the Eastern Cooperative Oncology Group (ECOG) scale in the absence of any other concomitant disease that could explain the unfavorable clinical evolution.
	+ Worsening (increase of severity) of two or more respiratory signs/symptoms (cough, hemoptysis, thoracic pain, dyspnea) and/or constitutional signs (fever, weight loss, night sweats or lack of appetite), in the absence of any other concomitant disease that could explain the unfavorable clinical evolution.
	+ Occurrence of at least two new symptoms among respiratory signs/symptoms (cough, hemoptysis, thoracic pain, dyspnea) and/or constitution signs (fever, weight loss, night sweats or lack of appetite) in the absence of any other concomitant disease that could explain the unfavorable clinical evolution.
* Unassessable evolution: no clinical examination available after the prior outcome assignment;
* Favorable evolution: if neither classified as unfavorable nor as unassessable.

***5.3. Classification of the bacteriological, radiographic and clinical evolution***

The **Site-CI,** with the support from **Site-PI** if needed, provides a final classification of the evolution of the study participant under treatment, according to the following:

* Unfavorable evolution: participants for whom the evolution is defined as unfavorable in any category among bacteriological, radiographic, and clinical.
* Unassessable evolution: participants for whom the final classification of the evolution is not defined as unfavorable (above), and for whom the evolution is defined as unassessable in all 3 categories among bacteriological, radiographic, and clinical.

**IMPORTANT NOTE**: for all patients who have been assigned an unassessable outcome at Week 39 and for whom there is no further data available (i.e. who discontinued the study and did not perform post-termination follow-up visits) an outcome can be assigned automatically, as follows: a) if the most recent post-baseline culture result is positive, the outcome is unfavorable (outcome number **10** at W73, **11** at W104 as listed in endTB/Q Case Report Form 15); b) if the most recent post-baseline culture result is negative, the evolution is unassessable (outcome number **11** at W73 and W104 as listed in endTB/Q Case Report Form 15).

* Favorable evolution: if neither classified as unfavorable nor as unassessable.

Cases for which the bacteriological, radiographic and clinical evolution assessment is required will be reviewed by the Event Validation Group (See ***SOP SP-31-CT Event Validation***).

If, in the opinion of the **Site PI**, the classification of the evolution according to the above criteria is not correct, the specific reason/s should be documented in free text in the source documents (ie. clinical progress notes) for the review by the Event Validation Group.

# REFERENCES

# None

1. **SUPPORTING DOCUMENTS**

## endTB and endTB-Q Study protocol (specifically section 3.2).

## SOP SP-026-CT Reporting of Treatment Outcomes (endTB Site Study Document).

## SOP SP-031-CT Event Validation (endTB Site Study Document).

## endTB and endTB-Q Case Report Form 15 (endTB Site Study Document).

# APPENDIX

# None