# Standard Operating Procedure for

# Reporting of Treatment Outcomes

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**Table of contents**

[1. PURPOSE 2](#_Toc176189574)

[2. SCOPE 2](#_Toc176189575)

[3. RESPONSIBLE FUNCTIONS 2](#_Toc176189576)

[4. DEFINITIONS and ABBREVIATIONS 2](#_Toc176189577)

[5. PROCEDURE 3](#_Toc176189578)

[5.1 Material 3](#_Toc176189579)

[5.2 Definition of overall culture results at each visit for outcome assignment 3](#_Toc176189580)

[5.2.1 Not assessable culture result 3](#_Toc176189581)

[5.2.2 Overall culture result at any visit 4](#_Toc176189582)

[5.2.3 Special considerations for Week 73 and 104 outcomes 4](#_Toc176189583)

[5.2.4 Post-termination follow-up visits 4](#_Toc176189584)

[5.3 Treatment Outcome Assignment Procedures 4](#_Toc176189585)

[5.4 Special Circumstances 5](#_Toc176189586)

[5.4.1 Outcomes that should be assigned as soon as they occur (and should apply to all subsequent endpoints) 5](#_Toc176189587)

[5.4.2 Special Requirements in case of Death 5](#_Toc176189588)

[5.4.3 Unfavorable due to Unassessable at Weeks 39 and 73 5](#_Toc176189589)

[5.4.4 Participant Withdraws Consent 6](#_Toc176189590)

5.4.5 Participant terminates treatment as planned at Week 24 and starts new DR-TB treatment (endTB-Q participants) 6

5.4.6 Participant discontinues treatment before Week 39 (not planned) 6

[6. REFERENCES 7](#_Toc176189592)

[7. SUPPORTING DOCUMENTS 7](#_Toc176189594)

[8. APPENDIX 7](#_Toc176189595)

# Standard Operating Procedure for

# Reporting of Treatment Outcomes

## PURPOSE

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| This standard operating procedure (SOP) describes the assignment of treatment outcomes in the endTB Clinical Trials. |

## SCOPE

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| This SOP describes the assignment of outcomes at Weeks 39, 73, and 104 for experimental and control treatment regimens in the endTB Clinical Trials. |

## RESPONSIBLE FUNCTIONS

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| **Function** | **Activities** |
| **Site Principal Investigator (Site PI)** | * Support the delegated site co-investigator and the event validation group (EVG) in validating the treatment outcomes. |
| **Site Principal Investigator (Site PI) and/or delegated Site Co investigator (Site CI)** | * Assign treatment outcome for each enrolled participant and report treatment outcome in the source documentation (the Treatment Outcome Worksheet). |
| **Site Study Coordinator** | * Ensure that each enrolled participant has a treatment outcome reported. |
| **Event Validation Group (EVG)** | * Review the outcome assignment. |
| **Delegated data entry personnel** | * Enter the treatment outcomes from the source documentation (the Treatment Outcome Worksheet) in the electronic Case Report Form (eCRF). |

## DEFINITIONS and ABBREVIATIONS

In the endTB Clinical Trials, treatment outcomes are defined at Weeks 39, 73, and 104 post randomization. Outcomes at Week 73 are used as primary endpoints and outcomes at Weeks 39 and 104 as secondary endpoints. Participants in the control arm are still on treatment at Week 39 and some of them may still be on treatment at Week 73. Definitions of treatment outcomes in the endTB Clinical Trials differ from the MDR-TB treatment outcomes definition from the national drug resistance TB guidelines, the WHO guidelines, and MSF/PIH guidelines. See Appendix 1 for the endTB Clinical Trials’ endpoint definitions.

Clarification of some of the definitions:

**Addition** of a drug is defined as introduction of a new drug that was not part of the regimen at initiation.

**Replacement** of a drug is defined as removal of a drug that was included at initiation and introduction of a new drug that was not part of the regimen at initiation. These definitions apply regardless of the reason for addition or replacement. Changing the dose of drugs already contained in the regimen and removal of drugs without replacing them *do not* constitute “addition” or “replacement”. Replacement applies to all drugs (including pyrazinamide) except for that occurring *within a drug class*. Replacing one member of the fluoroquinolone, thioamide, or aminoglycoside/polypeptide class with another member of the same class does not constitute replacement.

***Re-infection*** is defined as the confirmation, using genotyping results, that a positive culture occurring after completion of the treatment is due to a different *Mycobacterium tuberculosis* strain than that isolated in the baseline positive culture result (at screening or inclusion). This determination should be made by the microbiology laboratory (in consultation with ITM).

***Laboratory cross-contamination*** is defined as “the transfer of MTB complex bacilli from one specimen to another specimen that does not contain viable bacilli during laboratory processing, causing a false-positive result” ([APHL Training Module](https://www.aphl.org/programs/infectious_disease/tuberculosis/TBCore/Specimen_Collection-Handling-Transport_and_Processing-WithNotes.pdf)). This can be due to technician error, reagent contamination, or equipment failure. Laboratory cross-contamination should be considered if a high number of MTB–positive cultures are observed, relative to previous time periods, or when the laboratory result is discordant with the clinical evolution of the participant. Confirmation is very difficult. Genotyping can help to identify if the strain is identical from other strains identified in samples processed during the same time period, but such methods are not available in most of the endTB Clinical Trials site laboratories. Therefore, it is the responsibility of the mycobacteriology laboratory (in consultation with ITM) to conclude if the positive result is likely the result of laboratory cross-contamination.

***Loss to follow-up*:** Participants who a) do not complete their scheduled final study visit and b) for whom study staff have no information and whom they have been unable to contact, in-person or by phone for more than 14 weeks before the last study visit per study schedule will be considered lost to follow-up. The “loss to follow-up” designation is made only after the scheduled final study visit.

## PROCEDURE

### Material

1. Participant file (source documents);
2. Treatment Outcome Worksheet (Form 15) (source documents);
3. Clinical Trial Protocols.

### Definition of overall culture results at each visit for outcome assignment

### Not assessable culture result

Individual culture results will be defined as not assessable if they are: 1) missing, 2) contaminated, or 3) AFB/contaminated.

### Overall culture result at any visit

In the specific context of outcome assignment, the overall culture result at any study visit where more than one culture result is available, will be defined as follows:

* If MGIT culture result on sample A is positive or negative, consider this as the overall culture result.
* If MGIT culture result on sample A is not assessable, assess the culture result on sample B (LJ or MGIT, depending on the country). Then, if the culture result on sample B is positive or negative consider this as the overall culture result.
* If culture results from all samples are not assessable, the overall culture result is not assessable.

### Special considerations for Week 73 and 104 outcomes

For assignment of treatment outcomes at Weeks 73 and 104: if relevant results are not available between 65 to 73 Weeks (Week 73 outcome) or between 97 to 104 Weeks (Week 104 outcome), data collected up to 30 days after the close of the window period around the Week 73 and Week 104 study visits may be used to inform outcome classification. This applies to culture and evolution (microbiological, clinical, and radiological) data.

### Post-termination follow-up visits

Data collected during post-termination follow-up visits at Week 39 and/or Week 73 should be used for outcome assignment, unless the participant has already been assigned an outcome among those listed in 5.4.1 (outcomes that may be assigned as soon as they occur).

### Treatment Outcome Assignment Procedures

1. Planned Outcome assignment should occur around 8 weeks after the relevant study visit (Weeks 39, 73, and 104), or sooner if all information is available.
2. Most outcomes (see exceptions below in *Special Circumstances)* can only be assigned once the participant has completed the study visit for that endpoint (Weeks 39, 73, and 104) and results become available from a culture collected during the window period.
3. **All outcomes should be assigned, if possible, by 2 delegated investigators together.**
4. Before the assignment of outcomes, the **site PI** or **site CI** should ensure that:
   * Culture results are available from specimens collected up to the study visit at which outcome is assessed.
   * Clinical and radiological evolution is documented in the participant’s file and X-rays are available.
   * Treatment prescription information is complete and updated to be able to assess any addition or replacement of drugs.
   * Participant follow-up information is documented as much as possible; extra effort may be required in case of death or if a participant has missed visits.
5. In some cases, assigning an outcome will require assessing the bacteriological, radiological, and clinical evolution. Specific instructions are provided in ***SOP SP-032-CT for evaluating bacteriological, radiographic and clinical evolution for outcome classification.*** All outcomes should be recorded as soon as possible by the **site PI** or **site CI** in the ***Treatment Outcome Worksheet*** and other source document, if applicable.
6. The **site PI** or **site CI** should date, initial, and sign the ***Treatment Outcome Worksheet***.
7. As soon as one or more ***Treatment Outcome Worksheet*** is completed and signed, the **delegated data entry personnel** should enter all assigned outcomes into the eCRF in the study database.
8. Some outcomes will be validated by the EVG (See ***SOP SP-031-CT Event Validation***).

### Special Circumstances

### Outcomes that should be assigned as soon as they occur (and should apply to all subsequent endpoints)

The outcome should be assigned immediately when one of the following unfavorable outcomes occurs (the **number** between brackets represents the number of the corresponding outcome as listed in endTB/Q Case Report Form 15):

* + Death (see also section 5.4.2) (**4** at W39, **7** at W73 and W104);
  + Replacement or addition of one or more investigational drugs in the experimental arm for endTB and endTB-Q or in the control arm if using the shortened regimen for endTB (**3** at W39, **4** at W73 and W104);
  + Replacement or addition of two or more investigational drugs in the control arm for endTB-Q and endTB (**2** at W39, **5** at W73 and W104);
  + Initiation of a new MDR-TB treatment regimen after the end of the allocated study regimen; and before Week 73 (applies to 73-Week and 104-Week endpoints) or Week 104 (applies to 104-Week endpoint) (**6** at W73 and W104).

If any of these occur, the outcome should not be re-assessed at later endpoints (see also section 5.4.3).

The **site PI** or **site CI** should complete the ***Treatment Outcome Worksheet*** for all subsequent endpoint assessments (e.g.***, if death occurs at or before Week 39, forms for Weeks 39, 73, and 104 should be completed; if a new regimen is started after Week 39 and before Week 73, forms for Weeks 73 and 104 should be completed***).

### Special Requirements in case of Death

For death, additional requirements apply:

* + The **site PI** or **site CI** should record the following in the source document: date and location of death; whether the death was an outcome of a notified Serious Adverse Event and in such case the SAE number; the cause of death according to the **site CI** and **site PI** judgement; whether an autopsy was requested; and the treatment received at the time of death.
  + The **site PI** or **site CI** should complete and send to PV unit the SAE report within 24 hours (see ***SOP PV-001-CT Safety data collection and reporting at trial sites***).

### Unfavorable due to Unassessable at Weeks 39 and 73

If a participant is assigned an unfavorable outcome prior to Week 104, subsequent outcomes are automatically unfavorable. Similarly, for participants 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 (**10** at W73, **11** at W104); b) if the most recent post-baseline culture result is negative, the evolution is unassessable (**11** at W73 and W104).

**In all other situations, if:**

* + The participant’s outcome is not assessable at Week 39, it should be reassessed at Week 73;
  + The participant’s outcome is not assessable at Week 73, it should be reassessed at Week 104.

**Delegated site personnel** should follow the procedures detailed in ***SOP SP-022-CT Subject Tracing***, if there is inadequate information to evaluate a participant’s outcome at Week 39 or 73. If the information remains inadequate, the outcome should be assigned as “non-assessable.” Loss to follow-up can only be assigned after the scheduled final study visit.

### Participant Withdraws Consent

If a participant expresses an intent to **withdraw consent**, an early termination visit should be performed to allow as much as possible the classification of the outcome (see ***SOP SP-028-CT Management of Early Termination*** for detailed instructions).

### Participant terminates treatment as planned at Week 24 and starts new DR-TB treatment (endTB-Q participants)

If a participant terminates study treatment as planned at Week 24 **AND** starts a new drug-resistant (DR-TB) treatment before Week 39:

Select **3-6-6** for the Week 39 outcome (addition or replacement of one or two drugs). The **new DR-TB** should be completed in the End of Study and Treatment form (OpenClinica).

#### **5.4.6 Participant discontinues treatment before Week 39 (not planned)**

If the participant discontinues treatment before Week 39 (not planned) and starts either:

* **DR-TB treatment** before Week 39:

Select the **DR-TB treatment** as the reason in End of Study and Treatment form.

Select **2-5-5** or **3-4-4** for the Treatment Outcome for control or experimental arm, respectively.

* **Drug-Sensitive (DS)** **TB treatment** before Week 39:

**Site PI or CI** should not complete “Started TB treatment” in the End of Study and Treatment form.

Select **DS-TB treatment** as the “Reason” in End of Study and Treatment form.

Select **2-5-5** or **3-4-4** for the Treatment Outcome for control or experimental arm, respectively.

***Note:*** *The Treatment Outcome will be discordant since the algorithm cannot know that participant has started new DS-TB treatment, but the CAC shall assess with the End of Treatment reason.*

## REFERENCES

## [www.aphl.org](http://www.aphl.org)

## SUPPORTING DOCUMENTS

* Clinical Trial Protocols (specifically section 3.2).
* Treatment Outcome Worksheet (Form 15) (endTB Site Study Document).
* SOP PV-001-CT Safety data collection and reporting at trial sites (endTB Site Study Document).
* SOP SP-022-CT Subject Tracing (endTB Site Study Document).
* SOP SP-028-CT Management of Early Termination (endTB Site Study Document).
* SOP SP-031-CT Event Validation (endTB Site Study Document).
* SOP SP-032-CT Evaluating Bacteriological, Radiographic and Clinical Evolution for Outcome Classification (endTB Site Study Document).

## APPENDIX

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| **Number** | **Title** |
| A1 | SP-026-CT\_A1- Algorithm Trees for Treatment Outcomes Assignment |