# Standard Operating Procedure for

# Treatment and Study Adherence Counseling and Support, including Directly Observed Therapy and Handling of Missed Doses

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| **SOP Number**: SP-017-CT | **Effective Date**:  |
| **Version Number and Authorization Date**: 3.0, 19-Dec-2019 |

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## PURPOSE

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| Strong compliance requires an appreciation of the importance of completing treatment (and study visits) according to the study schedule. This can be best achieved through a foundation of mutual respect, trust, and support between the study participant and study staff. All interactions between study staff and participants should reflect the understanding that participants with MDR-TB often suffer from many social, economic, and other medical issues that further complicate an already difficult treatment (and study participation). This foundation should inform all other study procedures, particularly those related to recruitment and retention (SM-003-CT) and (the need for) subject tracing (SP-022-CT).This standard operating procedure (SOP) describes the procedure for anti-tuberculosis treatment compliance in the endTB clinical trials. This SOP also describes the steps for establishing the structures that provide respectful support for study participants to ensure successful treatment and study completion according to the protocol. It also describes the practicalities of observing, supporting, and counseling around treatment and study adherence. |

## SCOPE

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| This SOP applies to the activities involved in the administration of treatment, counseling for treatment compliance, and adherence to study schedule for subjects in the endTB Clinical Trials. |

## RESPONSIBLE FUNCTIONS

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| **Function** | **Activities** |
| **Site Principal Investigator (Site PI) and Site Study Coordinator (Site SC)** | * Ensure the study protocol is respected in the respective Site, including the use of directly observed therapy for the treatment of tuberculosis.
* Ensure that this SOP is implemented in the Site.
* Ensure that deviations to the study protocol concerning treatment administration and treatment adherence are recorded.
* Foster a climate conducive to trust and open communication with study participants (and their families/friends), which permits an understanding of potential or actual barriers to study and treatment adherence.
* Schedule treatment and study visits at times (and locations) that facilitate adherence.
* Ensure that consistent messages about treatment and study adherence are delivered by all members of study staff.
* Develop tool(s) (e.g. calendar, reminder cards) for study participants to facilitate study and treatment adherence.
 |
| **Site Clinical Investigator**  | * Prescribe anti-tuberculosis treatment at each trial visit and assess treatment response, tolerance and adherence during the study visits.
 |
| **Delegated study site personnel** | * Monitor treatment compliance and supervise the DOT nurses or treatment supporters.
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| **DOT nurse or treatment supporter** | * Observe the participant during drug intake.
* Through treatment support visits, further develop the relationship with participants (and their families/friends) that supports participants’ adherence to study and treatment.
* Ensure documentation of each study dose administration is accurate and complete.
* Document occurrence of incomplete dose administration and reasons.
* Develop plans to improve participant compliance.
 |
| **DOT nurse or designee (e.g. adherence counsellor or social worker)** | * Perform counselling on study and treatment adherence in a respectful manner that takes into consideration each study participant’s unique situation and challenges.
 |
| **Pharmacy Staff** | * Produce simple guidance (accompanying study drugs) that permits DOT nurses/treatment supporters to easily monitor treatment administration and for participants to adhere to treatment.
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## DEFINITIONS and ABBREVIATIONS

**Directly Observed Therapy (DOT)** means that a trained health care worker or other designated individual watches the participant swallow every dose of the prescribed TB drugs.

In the endTB clinical trials, DOT may be ***clinic based or home-based. Clinic based*** DOT will be performed in inpatient or outpatient departments of hospitals or other healthcare facilities. ***Home-based DOT*** will be performed by a nurse or a community health worker or the participant’s relative/friend (called treatment supporter) trained under the supervision of a trial investigator or other delegated trial staff member. DOT is organized differently in each study site but follows principles listed above. For the trial purpose, it is important to precisely record adherence to treatment for each drug to be able to assess the level of drug exposure and to interpret the treatment efficacy results in regards to the treatment exposure.

**Daily dose**: The compilation of all anti-tuberculosis medications prescribed for a given day, including morning and evening doses. Anti-tuberculosis medications considered in the daily dose include: amikacin, bedaquiline, capreomycin, clofazimine, cycloserine, delamanid, ethambutol, ethionamide, isoniazid, kanamycin, levofloxacin, linezolid, moxifloxacin, PAS, prothionamide, pyrazinamide and terizidone.

**Institutional Review Board (IRB):** An independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

**IP Dispensation Log**: a document used to track each unit of IP dispensed to a participant; one IP Dispensation Log is maintained for each unique type of IP. The IP Dispensation Log will be completed at the dispensing pharmacy (in case of home-based DOT), designated wards and/or DOT corners where IPs are dispensed to participants.

**Investigational product (IP):** All the TB drugs listed in the endTB clinical trial protocols are considered IPs: amikacin, bedaquiline, capreomycin, clofazimine, cycloserine, delamanid, ethambutol, ethionamide, isoniazid, kanamycin, levofloxacin, linezolid, moxifloxacin, PAS, prothionamide, pyrazinamide and terizidone. In addition, for the endTB-Q protocol, amoxicillin/clavulanate and imipenem/cilastatin.

**Protocol:** A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline, the term protocol refers to protocol and protocol amendments.

**Site Principal Investigator (Site PI):** A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the Investigator is the responsible leader of the team and may be called the Principal Investigator.

**Sponsor:** An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

**Study Treatment and Adherence:** Completion of all study visits and doses of study treatment in the time and manner specified in the study protocol and according to prescription of study regimen. Receiving anti-tuberculosis drugs inconsistently, or in an inappropriate way or stopping treatment too soon, can lead to treatment failure or relapse. Second-line treatment requires complicated regimens, may not be well tolerated, and thus requires ***DOT*** as part of a package of treatment support.

**Treatment Adherence Source Document**: Log book or worksheet for each individual participant in which the DOT nurse or other delegated study personnel records treatment delivery, deviations from the prescribed treatment or from DOT (i.e., self-administered treatment), and their cause (if known), any reactions reported by the participant, any reaction (e.g., vomiting) observed during administration.

## PROCEDURE:

### Materials

* Participant’s prescription documentation from the medical chart (i.e. local prescription notes).
* Treatment initiation form and, if applicable, treatment change form and subsequent prescription forms.
* Trial Treatment card (DOT card, DOT treatment card, or log): can be adapted from the program’s existing tools, should allow identification of the intake of individual drugs (and not only “treatment”) by day and dose intake (for example in case of 2 intakes per day), including Sundays.
* Treatment Adherence Source Document.

### DOT and treatment adherence

The DOT nurse or “treatment supporter” should:

1. Verify that the participant’s name or the subject identification number matches the treatment card.
2. Ask if the participant has taken any study medicine or other medicine or herbal product on his/her own since the last DOT. The DOT nurse or treatment supporter should record such participant reported use of other medicines to delegated site personnel. Delegated site personnel should document this information on the concomitant medication log and the site clinical investigator should be informed.
3. Ask participant about any particular difficulty, complaint, or adverse event in relation to his/her participation in the trial. If the participant has any medical complaint, assess its potential dangerousness according to the table (below).

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| **Not Dangerous** | **Dangerous** |
| NauseaNo appetiteStomach acheGasPain in the joints | Skin rash and itchingVomiting repeatedlyDeafnessDizzinessVisual impairmentBurning sensation in the feet |

*Adapted from “A guide for TB Treatment Supporters”*[*http://apps.who.int/iris/bitstream/10665/67356/1/WHO\_CDS\_TB\_2002.300.pdf*](http://apps.who.int/iris/bitstream/10665/67356/1/WHO_CDS_TB_2002.300.pdf)

* + If dangerous, do not administer the drugs, inform the study investigator immediately and refer the participant to the clinical trial site.
	+ If not dangerous, reassure the participant and administer the drugs.
	+ The DOT nurse or treatment supporter should relay participant reported adverse events and/or other complaints to delegated site personnel. Delegated site personnel should document these events in the adverse event log and the study investigator should be informed immediately if the event has worsened compared to previous days or prevents the participant from taking the treatment properly.
1. Clinic-based DOT: the DOT nurse prepares the treatment dose according to the prescription indicated on the prescription documentation (i.e., local prescription notes and/or treatment initiation form and, if applicable, treatment change form or subsequent prescriptions).
2. Home-based DOT with treatment supporter: the prescribed dose of TB medications is prepared by the DOT nurse or site pharmacist in prefilled bottles or blister pack(s) (in such case the treatment supporter should check that the participant’s name [or subject identification number] matches the name or subject identification number on the prefilled bottles/blister packs).
3. Hand-over the treatment dose to the participant.
4. Watch the participant swallow the drugs.
5. Indicate the intake of the drugs on the participant’s DOT treatment card.
6. In case of immediate vomiting of the drugs (within 30 minutes from the intake of the last drug administered):
	* Reattempt administration with a new dose (only for the drugs which were administered before vomiting);
	* Record vomiting event in the treatment card (specifying which drugs were vomited and which ones were re-administered);
	* If the participant vomits again, record the vomiting episode, inform the site clinical investigator immediately, do not try to give the drugs again.

In case DOT is performed by a DOT nurse or other study personnel, the name and function of each person in charge of the DOT for the participants of the trial should be recorded in the trial site delegation log. Should this not be possible (e.g., a high number of DOT nurses per participant due to shifts and turnover), documentation of DOT nurses’ training on DOT specific processes should be filed in the Investigator Site File in the appropriate section, at a minimum. Treatment supporters do not have to be included in the delegation of responsibility log. DOT nurses and/or treatment supporters should be adequately trained on DOT. Only trained personnel with similar qualifications should replace the regular person during an absence or breaks.

Information about the absence of DOT and reason for any drug delivery without DOT should be documented in the treatment card and then subsequently reported in the Treatment Adherence Source Document.

#### Monitoring of treatment adherence

At each trial visit, the investigator or delegate should:

* Review the treatment related source documents, including the treatment card, the treatment initiation form and the follow up prescriptions and verify the consistency between the treatment delivered and the prescription(s).
* Count the number of doses taken in total, and the number taken under DOT for each individual drug as recorded on the treatment card since the last visit and record the findings in the Treatment Adherence Source Document.
* Ask the participant whether he/she has any difficulty with the treatment and if he/she received any concomitant drugs/herbal medicine since the last visit.
* Organize regular meetings (weekly or biweekly) with the DOT nurses or treatment supporters to review IP dispensation log, treatment card, Treatment Adherence Source Documents and any issues around treatment. Establish trust and good communication to be able to handle any difficulty with treatment.

### Adherence Counseling

For participants followed by a treatment supporter, s/he should accompany the participant to the (portion of each) study visit at which adherence counseling is scheduled. At that visit, the procedure nurse, adherence counsellor or designee should:

1. Inquire about the participant’s (and family’s) overall well-being.
2. Discuss with study participant and supporter any challenges to adherence to the study and treatment; ask about any expected life changes (home, work, travel, etc.) that may compromise adherence, including changes in degree of privacy. Work with the participant to develop solutions to these challenges or changes. These may include:
	1. changes in support system (i.e., removing family members/friends from or adding family members/friends to the Subject identification and contact log, updating contact info in the Subject identification and contact log [see Supporting documents]);
	2. referral to mental-health provider;
	3. referral to specialist for adverse event or comorbidity evaluation and/or management;
	4. meetings with the coordinator of treatment support if arrangements for support need to be changed (personnel, location, timing, etc.);
	5. reinforcement of medical/scientific reasons for importance of adherence by clinical investigator;
	6. discussion with family members/friends how adherence can be supported;
	7. discussion with health facility to reinforce study and treatment compliance.
3. Confirm that the participant has current and complete contact information for investigator, study coordinator, treatment supporter.
4. Solicit and answer questions from the participant (and supporter) about study participation and treatment.
5. Review prescribed dosing (using visual guide provided by pharmacy) and study schedule, composition of regimen, remaining duration of treatment and study participation.
6. Review the treatment card and the Treatment Adherence Source Documents with the participant and supporter. Provide positive feedback on successes and discuss constructively any missed doses or deviations from the study schedule since the last visit.
7. Review the timing of the subsequent study visit and any planned changes in study regimen.
8. Solicit and answer any remaining questions from the participant (and supporter) about study participation and treatment.
9. Provide and document any enabler.

### Handling missed treatment days

For each full day of treatment missed (i.e., all prescribed doses of all prescribed drugs are missed, or all the treatment is temporarily discontinued by the Site Clinical Investigator/Principal Investigator for toxicity or other reasons) during treatment, that day will need to be made up.

In experimental arms, treatment should be continued until all missed days have been made up or until 47 weeks (corresponding to 8 weeks after the end of the planned treatment duration) have elapsed, whichever comes first.

In the control arm, no make-up days will be administered when using the conventional regimen.

When using a shorter regimen in the control arm, make-up days can be administered as needed up to 8 weeks after the end of the planned treatment duration.

#### Determining days that require make-up

* A ‘full day of treatment’ or ‘daily dose’ includes all doses of all study-regimen drugs prescribed for that day, including morning and evening doses. This applies also if all the treatment is temporarily discontinued by the Site Clinical Investigator/Principal Investigator.
* If a participant receives even 1 single pill out of a given day’s daily dose, it is considered that treatment has been administered on that day. This day will not be made up at the end of the regimen.
* Make-up days are required for the days on which a participant does not intake any of the intended anti-tuberculosis drugs for that day, and for the days when all the treatment was temporarily discontinued by the Site Clinical Investigator/Principal Investigator.

#### Administering make-up days

* In the experimental arms, track the days on which no anti-TB treatment has been administered throughout the participant’s treatment. Sum the total number of missed days and add this number of treatment days to the end of the 39-week period, starting on the first day of week 40.
* In the control arm, when using the conventional regimen, continue treatment until the number of daily doses administered matches the intended duration of treatment. Make up days are not required.
* In the control arm, when using a shorter regimen, track the days on which no anti-TB treatment has been administered throughout the participant’s treatment. Sum the total number of missed days and add this number of treatment days to the end of the treatment period.
* If the regimen has changed during the course of the trial, the regimen of make-up days will be the one prescribed at the end of the planned treatment duration (week 39 for the investigational arms). This may be different from the regimen at the time of the missed day(s).
* Each make-up day should contain the entire daily dose of the regimen, in a manner consistent with the existing schedule (i.e., injectables in the control arm are not always given on Sundays).

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| Please note that administering make-up days in this manner may potentially require exceeding the allowable number of doses for some drugs. This will be the case if participants consistently miss treatment on certain days of the week. For example, consider a participant with the following regimen: |
| **Sunday** | **Monday** | **Tuesday** | **Wednesday** | **Thursday** | **Friday** | **Saturday** |
| Dlm, Le, Z | Dlm, Le, Bdq, Lzd, Z | Dlm, Le, Z | Dlm, Le, Bdq, Lzd, Z | Dlm, Le, Z | Dlm, Le, Bdq, Lzd, Z | Dlm, Le, Z |
| If this participant were to miss 10 Saturday doses (and did not miss doses on any other day), he would have only missed doses of delamanid and levofloxacin and pyrazinamide; he would have successfully completed his bedaquiline and linezolid doses. Even still, though, his make-up days would have to follow this same regimen and, therefore, would include additional doses of bedaquiline and linezolid.The main principle of anti-tuberculosis treatment is to always administer an effective treatment combination. Stopping the bedaquiline and linezolid for the make-up period would weaken the regimen and could cause resistance. Thus, even if a participant only misses doses not containing all the drugs composing the regimen, all drugs that were included in the regimen prescribed at the end of 39-weeks should be included in the make-up days.In these cases, the study team should report exceeding the allowable number of doses as a minor deviation for the applicable drugs. |

#### Missed days during initial bedaquiline intensive dose

Bedaquiline-containing regimens start with an intensive 2-week posology of bedaquiline, meant to be a loading dose to quickly reach effective drug concentrations in the blood. Therefore, if doses are missed during this period, it is important to address these missed doses. Handling of these missed doses of bedaquiline will follow a protocol different from the one outlined above.

**Figure 1. Correct administration of intensive 2-week posology of bedaquiline**



During the initial 2-weeks, study participants receive four 100 mg tabs daily (400 mg/day) of bedaquiline. If a subject misses any bedaquiline dose (i.e., all the 4 daily tablets) during the intensive 2-week phase, this dose of bedaquiline will need to be made up at a 400mg/day dose (*see* Figure 2 and 3 below). All participants should receive at least 14 administrations of bedaquiline at 400 mg/day.

**Figure 2. Administration of intensive 2-week posology of bedaquiline with two consecutive missed doses.**



**Figure 3. Administration of intensive 2-week posology of bedaquiline with four “sparse” missed doses.**



If only bedaquiline is missed during these days, then there is no need to add additional treatment days beyond 39 weeks of treatment but 400mg/day of bedaquiline should be extended until 14 total days are administered.

* If all drugs are missed during the intensive bedaquiline phase, 400mg/day dose of bedaquiline should be extended until 14 total days are administered. Additionally, these missed days should be made up at the end of the 39 weeks and contain a lower dose of bedaquiline (200mg/day, three times/week).

For example, if all drugs are missed on days 5 and 6, 400mg of bedaquiline should be administered on days 15 and 16 of treatment. Further, two additional full days of treatment (following 200mg bedaquiline, 3 times weekly) should be added after the 39-week treatment period.

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| NOTE: While linezolid-containing regimens also start with a higher dose of linezolid, missed doses of linezolid are NOT considered exceptions and should be handled as outlined above, in sections 5.4.1 and 5.4.2. |

#### Treatment interruptions during initial bedaquiline intensive dose

If 7 or more days are missed during the intensive bedaquiline phase, then this phase should be re-started to ensure that the participant receives 14 consecutive days of bedaquiline dosed at 400mg/day.

#### Participant already on treatment with bedaquiline at study treatment initiation

If the participant is already on treatment with bedaquiline at the moment of starting study treatment, the dose of bedaquiline should be adapted to the previous treatment. For instance, if a participant already received 6 days of treatment with bedaquiline at 400 mg/day, s/he should receive only 8 days of bedaquiline at 400 mg/day after switching to study treatment. If the participant has already received all the 14 days of bedaquiline treatment at 400 mg/day, the study treatment should start with bedaquiline given at 200 mg thrice weekly.

### Discontinuation

There is no standard threshold of missed doses triggering permanent discontinuation of a drug or treatment. Any permanent discontinuation of a drug or treatment must be discussed with the Clinical Advisory Committee (CAC). No classification of permanent discontinuation can be made without the CAC’s input from that discussion. Regardless of the total number of missed days, if a participant continues the trial, treatment in the experimental arms will only be continued up to 47 weeks. Total treatment period in the experimental arms, including make-up days, should not exceed 47 weeks.

### Adaptation of drug posology according to weight bands

The initial dosage of levofloxacin and pyrazinamide in experimental arms, and of most drugs in the control arm of the endTB clinical trials, is determined by weight. During trial participation, the dosage of these drugs should be adapted to changes in participant’s weight, as feasible. It is advised to adapt the dosage of these drugs when a participant’s weight changes enough that it is within a different weight band (compared to the previous one) at two consecutive study visits. The adapted dose may be started immediately or at the next preparation of drugs for administration.

### Food and administration of Investigational Products

Investigational Products in experimental and control arms of the endTB trial should be administered respecting the recommendations below:

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| Drug | Intake with/without food | Notes |
| Amikacin, capreomycin, kanamycin | Not applicable | Increase fluid intake to avoid toxicity |
| Amoxicillin/clavulanate (endTB-Q) | With food |  |
| Bedaquiline | With food | High-fat, high-calorie meal |
| Clofazimine | With food | Avoid orange juice and antacids |
| Cycloserine, terizidone | With or without food | Prophylaxis with 50 mg of pyridoxine daily for every 250 mg of cycloserine/terizidone |
| Delamanid | With food | High-fat, high-calorie meal |
| Ethambutol | With or without food |  |
| Ethionamide, prothionamide | With food | Prophylaxis with 50 mg of pyridoxine daily |
| Imipenem/cilastatin (endTB-Q) | Not applicable | Administer after amoxicillin/clavulanate |
| Isoniazid | Without food (1 hour before or 2 hours after meals) | Prophylaxis with 50 mg of pyridoxine daily |
| Levofloxacin, moxifloxacin | With or without food | Milk-based products, iron and zinc salts, magnesium- or aluminum-containing antacids, sucralfate, and multivitamins should be avoided or taken at least two hours before or after |
| Linezolid | With or without food | Prophylaxis with 50 mg of pyridoxine daily |
| PAS | Administer with acidic juices (i.e., orange, apple) | Increase fluid intake to avoid toxicity |
| Pyrazinamide | With or without food |  |

During the course of treatment, it is recommended to:

* Avoid drinking alcohol (i.e., vodka, beer, wine);
* Avoid smoking or chewing tobacco, betel, gutka, khat/coca leaves, and other preparations;
* Strictly abstain from illegal drugs (heroin, cocaine) – ask participants to please talk to their doctor and counsellor about any prior or current use to get proper care.

If participants regularly use herbal tea blends or traditional preparations, ask them to please discuss with their doctor whether it is safe to use the herbs while on treatment (e.g., unsafe=St John’s wort, possibly bad for your heart=valerian).

## REFERENCES

None

## SUPPORTING DOCUMENTS

## Treatment Adherence Worksheet (Form 04) (endTB Site Study Document).

## IP dispensation log (Appendix to SOP IP-004-CT) (endTB Site Study Document).

## Subject identification and contact log (endTB Site Study Document).

## APPENDIX

None