# Standard Operating Procedure for

# Regimen Design (endTB)

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# Standard Operating Procedure for

# Regimen Design (endTB)

## PURPOSE

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| This standard operating procedure (SOP) describes the design of a regimen for the control arm of the endTB clinical trial (NCT02754765). |

## SCOPE

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| --- |
| This SOP applies to design of a regimen for the participants in the control arm of the endTB clinical trial. The regimen design is based on the “WHO consolidated guidelines on drug-resistant tuberculosis treatment, 2019” and incorporates information contained in the “Rapid communication: key changes to treatment of drug-resistant tuberculosis” published by WHO in December 2019. |

## RESPONSIBLE FUNCTIONS

|  |  |
| --- | --- |
| **Function** | **Activities** |
| **Site Principal Investigator (PI)** | * Advice the Site Co Investigator on the design of a regimen for participants in the control arm in compliance with 2019 WHO guidance (”Consolidated guidelines on drug-resistant tuberculosis treatment” and “Rapid communication” - December 2019).
 |
| **Site Co Investigator**  | * Prescribe a regimen to participants in the control arm in compliance with 2019 WHO guidance (”Consolidated guidelines on drug-resistant tuberculosis treatment” and “Rapid communication” - December 2019).
 |
| **Clinical Advisory Committee (CAC)** | * Support the Site Co Investigator and Site Principal Investigator in designing a regimen for participants in the control arm.
 |

## DEFINITIONS and ABBREVIATIONS

**Conventional (or longer) multidrug-resistant (MDR)/rifampicin-resistant tuberculosis (RR-TB) regimen:** This is a regimen of at least 18 months duration that has been the WHO standard of care for MDR-TB treatment since 2006. The conventional MDR/RR-TB regimen should be designed according to 2019 WHO recommendations.

**Shorter all-oral bedaquiline-containing** **MDR/RR-TB regimen:** The 9- to 12-month standardized shorter MDR/RR-TB regimen that was approved by WHO in 2016 has now been replaced by a shorter all-oral bedaquiline-containing regimen. In the “Rapid communication” issued in December 2019, the WHO recommended to modify the composition of the shorter MDR/RR-TB regimen (switching to an all-oral regimen where the injectable agent is replaced with bedaquiline) and its eligibility criteria (adding extensive TB disease and severe extrapulmonary TB as exclusion criteria). The shorter all-oral bedaquiline-containing MDR/RR-TB regimen may be used in the endTB clinical trial. The shorter MDR/RR-TB regimen should be designed as recommended by WHO in the “Rapid communication” of December 2019 and used in participants who meet the WHO eligibility criteria (see Section 5.3 below for more information).

**Local standard of care consistent with WHO guidelines:** Participants in the control arm will receive either the conventional or shorter all-oral bedaquiline-containing MDR/RR-TB regimen as recommended by the national programs in the respective countries and by 2019 WHO recommendations. If there is any conflict between national norms and WHO guidelines, then the WHO guidelines will prevail.

## PROCEDURE

### Choice of the regimen between shorter and conventional (longer) regimens

Both the shorter and conventional MDR/RR-TB regimens may be used in the endTB clinical trial as the regimen for participants randomized to the control arm. However, the shorter MDR/RR-TB regimen is only offered as the control in countries where it is being used as a choice in the National TB Program for MDR/RR-TB. In countries that are not offering the shorter regimen programmatically, the shorter regimen is not allowed as a choice for the control arm. If a country is using the older shorter regimen with the injectable programmatically, and has not yet made the switch to replacing the injectable with bedaquiline, the shorter all-oral bedaquiline-containing MDR/RR-TB regimen can be used as the control.

The shorter MDR/RR-TB regimen may be used in participants who do not have the following conditions:

1. Resistance confirmed by validated phenotypic DST or by first- or second-line molecular line probe assay, or suspected ineffectiveness, to a medicine in the shorter MDR/RR-TB regimen (excluding resistance to isoniazid);
2. Previous exposure for ≥ 1 month to a second-line medicine included in the shorter MDR/RR-TB regimen;
3. Intolerance to one or more medicines in the shorter MDR/RR-TB regimen or increased risk of toxicity (e.g. drug-drug interactions, cardiotoxicity);
4. Extensive TB disease is present. While not clearly defined by the WHO, we propose to interpret lung TB disease as described in the SOP SP-009-ET Chest X-Ray Reading and SP-021-CT Chest X-ray Reporting[[1]](#footnote-2);\*
5. Severe forms of extrapulmonary TB (i.e. disseminated, meningeal or TB of the central nervous system).\*

Participants not eligible for the shorter regimen should receive the conventional MDR/RR-TB regimen. In addition to these criteria, the clinician may choose to use the conventional treatment for any participant based on individual circumstances.

In the “Rapid communication” issued in December 2019, the WHO recommended to modify the composition of the shorter MDR-TB regimen by replacing the injectable (amikacin) with bedaquiline. The composition of this regimen is defined in section 5.3. Further modifications of this shorter, all-oral, bedaquiline-containing regimen are not recommended by WHO for routine use and should NOT be used in the control arm of the endTB clinical trial.

### Design of the conventional regimen

The standard of care regimen will be designed according to the national recommendations and in accordance to the 2019 WHO recommendations.

#### Drugs included in the conventional regimen

**Table 1. Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB [adapted from WHO consolidated guidelines on drug-resistant tuberculosis treatment, 2019].**

|  |  |  |
| --- | --- | --- |
| **GROUP**  | **DRUG**  | **Abr.**  |
| **Group A:**  | Fluoroquinolones | LevofloxacinMoxifloxacin | LfxMfx |
| Diarylquinolines | Bedaquiline | Bdq |
| Oxazolidinone | Linezolid | Lzd |
| **Group B** | Clofazimine | Cfz |
| CycloserineTerizidone | CsTrd |
| **Group C** | Ethambutol | E |
| Delamanid | Dlm |
| Pyrazinamide | Z |
| Amikacin | Am |
| Imipenem-cilastatinMeropenem | Ipm/ClnMpm |
| EthionamideProthionamide | EtoPto |
| Para-aminosalicylic acid | PAS |
| IsoniazidHigh dose isoniazid | HHh |

Kanamycin, capreomycin, and amoxicillin/clavulanic acid (given without a carbapenem [imipenem-cilastatin, meropenem]) are no longer recommended. Amoxicillin/clavulanic acid is systematically given with carbapenems.

#### Principles of regimen design

Conventional regimens are designed by the Site Co Investigator, with the support of the Site PI, and CAC as needed, according to the following principles:

* In general, the regimen is designed with at least four effective TB medicines, including 3 from Group A and 1 from Group B.
* If this combination cannot be used, a minimum of 5 effective drugs is preferred and drugs from Group C have to be added to bring the total to at least five likely effective drugs. Regimens may contain more than five drugs if there is uncertainty of effectiveness in some of the drugs being used.
* In general, the choice of drugs is based on the hierarchy of drugs in Table 1. Use all Group A and B drugs that are likely effective and then add Group C drugs that are likely effective with a preference for drugs that are higher up on the list.
* In case one or more drugs have to be stopped (e.g. for toxicity reasons), the regimen should contain not less than 4 effective drugs, and preferably 5 effective drugs if less than 2 Group A drugs are included.

The definition of an "effective TB medicine" includes both laboratory DST results and the participant's TB treatment history. Clinical judgement is often necessary to decide whether a specific drug counts as an effective TB medicine. An anti-TB drug is considered likely to be effective if:

* The drug has not been used in a regimen that failed to cure the individual patent.
* DST performed on the participant’s strain indicates that it is susceptible to the drug (WHO endorsed rapid molecular test as well as phenotypic DST is only available for FQ, H, Eto/Pto, and Am). Routine phenotypic DST is often not available yet for Bdq, Lzd, Cfz, and it is not reliable for Cs, PAS, and E. No molecular tests are commercially available for Bdq, Lzd, Cfz, Cs, PAS, and Z.
* No known resistance to drugs with cross-resistance (i.e., among drugs of the same class,[[2]](#footnote-3) or between Bdq and Cfz).
* No known close contacts with known resistance to the drug or contact with a patient that had treatment failure of an MDR-TB regimen that contained the drug.
* Drug resistance surveys demonstrate that resistance to the drug is rare in participants with a similar TB history. For example, E and Z are effective TB drugs, but most circulating MDR/RR-TB strains are likely resistant to them; they should not, therefore, be considered likely to be effective.

In addition to the likelihood of effectiveness as defined above, other characteristics are to be taken into consideration, such as:

* The side effects of individual drugs and the overlapping toxicities they may have with other drugs in the regimen;
* Whether the participant has any comorbidity that might make an individual drug or a certain combination more likely to result in toxicity;
* Whether the participant is taking any drug which may interact with anti-TB drugs.

Table 2 describes the steps to design a conventional regimen for MDR/RR-TB treatment. Dosing of anti-TB drugs included in the conventional regimen should be defined as according to Table 3.

**Table 2. Steps to design a conventional regimen for the treatment of rifampicin-resistant and multidrug-resistant TB.**

|  |  |
| --- | --- |
| **STEP 1**  | **Use as many Group A drugs as possible**  |
| **1.1. Use a later-generation FQ** * Consider using Lfx rather than Mfx when associated with two or more other strong QT-prolonging drugs. Bdq and Cfz are considered strong QT-prolonging drugs. Dlm is considered a mild QT-prolonging drug.
* Of note, oral Lfx does not significantly affect the QT interval and is not normally counted as a QT-prolonging drug.

**1.2. Use bedaquiline** * Bdq is one of the most potent anti-TB drugs and is always employed in regimens for MDR/RR-TB, unless there is documented intolerance or resistance.
* Programs can choose to continue Bdq for the entire treatment duration under the “WHO best-practice statement on the off-label use of bedaquiline and delamanid”.
* DST to Bdq is not commonly available. Resistance to Bdq is still highly unlikely in most settings. There may be cross-resistance between Bdq and Cfz, although there is limited evidence to characterize the degree of cross-resistance.

 **1.3. Use linezolid** * Lzd is commonly employed in regimens for MDR/RR-TB, unless there is documented intolerance or resistance.
* The optimal duration of use of Lzd is unknown, however due to toxicity it is likely that many participants won’t receive it for the full treatment. As for any Group A or B drug, it is not recommended to stop Lzd if well tolerated.
* Lzd may cause myelosuppression, optic neuritis and peripheral neuropathy (that can be irreversible).
* DST to Lzd is not commonly available. Resistance to Lzd is still highly unlikely in most settings.
 | Lfx, MfxBdqLzd |
| **STEP 2**  | **If all three Group A drugs are being used, add at least one Group B; if less than three Group A drugs are being used, use as many Group B drugs as possible.**  |
| **2.1. Clofazimine** * Resistance to Cfz is still unlikely in most parts of the world, although that may change in some areas with the wider use of the shorter MDR/RR-TB regimen.
* Cfz will be commonly included in the design of the control arm as participants infected with strains that have documented or suspected resistance are not eligible for enrollment in endTB (i.e., participants in whom a Cfz-containing shorter MDR/RR-TB regimen has failed, or are close contacts of such patients, are not to be included in the endTB trial).
* There may be cross-resistance between Bdq and Cfz, although there is limited evidence to characterize the degree of cross-resistance.

**2.2. Cycloserine / Terizidone** * Trd is cleaved into two Cs molecules quickly after it enters the body; these drugs are considered equivalent.
* DST to Cs/Trd is not reliable. This drug has been largely used in some regions in MDR/RR-TB treatment and may therefore not always be counted as an effective drug.
* Cs/Trd is associated with CNS toxicity and peripheral neuropathy, and may not be tolerated in some participants.
 | CfzCs/Trd |
| **STEP 3**  | **Add necessary number of Group C drugs to bring the regimen to five likely effective drugs if needed (more than five may be needed if certainty of effectiveness in any of the five is in doubt: see above for the definition of an "effective TB medicine")**  |
| **3.1. Consider adding first-line drugs.** * First-line TB drugs are generally of limited utility due to high prevalence of resistance in MDR/RR-TB, but they can be considered when susceptibility is proven (DST to E is not reliable; DST to Z is reliable but difficult to perform, no commercially available molecular test).
* The prevalence of Z and E resistance among MDR/RR-TB strains is significant in almost all countries and DST is generally not done. Therefore, if these drugs are used and DST is unknown or pending, they are not counted as effective drugs in the regimen.
* If DST from a reliable lab demonstrates susceptibility to Z, this drug may be counted as an effective drug.
* H is usually of limited utility due to high prevalence of resistance in MDR/RR-TB, but its use can be considered when susceptibility is proven.
* If no *katG* or *inhA* mutation is detected by the first-line line-probe assay (Hain MTBDRplus), consider adding H at standard dose to the regimen.
* If susceptibility is proven by phenotypic DST, H at standard dose should be included in the regimen.

 **3.2. Consider adding delamanid** * Dlm has an excellent safety profile.
* Because of the high prevalence of Z and E resistance in MDR/RR-TB strains, Dlm is often the first choice of a Group C drugs in case of resistance or intolerance to a Group A or B drug.
* Dlm is a mild QT-prolonging drug. It is acceptable to combine the strong QT-prolonging drugs Bdq and Cfz with Dlm in the control arm regimen of endTB.
* DST to Dlm is not commonly available. Resistance to Dlm is still highly unlikely in most settings.
* Programs may choose to continue delamanid for the entire treatment duration under the “WHO best-practice statement on the off-label use of bedaquiline and delamanid”.

 **3.3 Consider adding an injectable:** **Amikacin (or streptomycin in rare circumstances)** * Am is only used when drug susceptibility has been documented.
* The endTB trial will not allow the use of kanamycin or capreomycin because the WHO no longer recommends these agents in the treatment of MDR/RR-TB.
* The endTB trial will not employ the use of streptomycin (S) in the control regimen for the following reasons: there is low experience of its use in MDR/RR-TB strains, the DST for S is not routinely done in most countries, there is a high likelihood of resistance in such strains, and there is high toxicity associated with prolonged use.
* Because of the high toxicity of Am, it should only be given when other effective options do not exist.
* The second-line line-probe assay (Hain MTBDRsl) can provide an indication on susceptibility to Am but not to S.
* It is suggested that Am be used for 6-7 months duration for most participants; the duration may be modified according to the participant's response to therapy.

**3.4. Consider adding ethionamide or prothionamide** * Eto and Pto are considered weak bacteriostatic TB drugs.
* They should not be included in the regimen if an *inhA*mutation is detected by first-line line-probe assay (Hain MTBDRplus) or if phenotypic resistance is detected or suspected.

 **3.5 Consider PAS** * PAS is considered a weak bacteriostatic and poorly tolerated TB drug.
* If a regimen with five likely effective drugs is not possible otherwise, consider using PAS (manage nausea and vomiting aggressively).

 **3.6 Consider high-dose H** * If only an *inhA* mutation is detected by first-line line-probe assay (Hain MTBDRplus), consider adding HH.
* HHshould never be counted as a likely effective drug.
* If possible, avoid using HH with Lzd because of potential additive toxicity of peripheral neuropathy.
* If a *katG* mutation is detected by first-line line-probe assay (Hain MTBDRplus), do not use H or HH.
 | E, ZHDlmAmEto/PtoPASHH |

#### Duration of the conventional regimen

The total duration of treatment for MDR/RR-TB is 18 to 20 months, depending on the individual treatment response and on country national recommendations.

In all-oral regimens the concept of intensive phase does not apply. The duration of use of different drugs will depend upon their tolerability and individual treatment response, up until the expected total duration of treatment or time after culture conversion are completed. The duration and composition of an intensive phase will henceforth only apply to participants receiving amikacin and is likely to apply rarely to participants in the control arm, as most FQ-susceptible MDR/RR-TB cases can be treated with all-oral longer regimens according to the new 2019 WHO recommendations.

#### Transition from old to new WHO-recommended conventional regimens

Participants in the control arm receiving a conventional treatment regimen designed according to WHO recommendations predating the 2018 WHO Rapid Communication should be re-assessed on a case-by-case basis, according to the following principles:

1. Patients on treatment for **less than one month**: initiate a new regimen constructed according to current recommendations, regardless of culture status. This will neither constitute nor count toward an unfavorable outcome (i.e. the change will have to be reported as treatment change, indicating that it is done to conform to 2018 WHO guidance, but this change will not be counted as treatment change leading to patient withdrawal).
2. Patients on treatment for **more than one month who have signs of good treatment response** (i.e. negative culture, clinical improvement): if still taking an injectable (Am, Cm or Km), consider replacing the injectable with a Group A drug whenever possible. If Group A and B drugs are not appropriate, Km or Cm should be replaced by Am. This will neither constitute nor count toward an unfavorable outcome (i.e. the change will have to be reported as treatment change, indicating that it is done to conform to 2018 WHO guidance, but this change will not be counted as treatment change leading to patient withdrawal).
3. Patients on treatment for **more than one month who have signs of slow or no treatment response** (i.e. positive sputum culture after 12 weeks of treatment or more, clinical worsening): consider restarting a new treatment according to current recommendations. Care should be taken to design the regimen with a case-by-case approach recognizing that resistance may have been developed to some of the drugs used in the regimen.  If two or more drugs are changed, this will constitute an unfavorable outcome (i.e. the change will have to be reported as related to absence of treatment response and this change will be counted as treatment change possibly leading to patient withdrawal).

The CAC should be involved in all such cases to support the decisions by the Site Co Investigator and the Site PI.

### Design of the shorter bedaquiline-containing regimen

The shorter bedaquiline-containing regimen is permissible in countries in which a shorter regimen is in routine use when participants meet all the study-specified inclusion criteria for its use. It may be prescribed by the Site Co Investigator, with the support of the Site PI, and of the CAC if needed.

A shorter all-oral bedaquiline containing MDR TB regimen refers to a regimen lasting 9-12 months consisting of:

**4-6 Bdq\*-Lfx/Mfx-Eto-E-Z-HH-Cfz / 5 Lfx/Mfx-Cfz-Z-E (\*Bdq is given for 6 months)**

In summary, the regimen contains bedaquiline, levofloxacin (or moxifloxacin), ethionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol, given together in an initial phase of 4 months (with the possibility to extend to 6 months if participant remains sputum smear positive at the end of month 4), and followed by 5 months of treatment with four of the medicines (levofloxacin, clofazimine, pyrazinamide, and ethambutol).

Acceptable alternatives: replacing ethionamide with prothionamide, replacing levofloxacin with moxifloxacin at either standard or high-dose.

For patients starting the shorter regimen in the control arm of the study, the injectables are no longer allowed as an option. Bedaquiline must be used in place of the injectable (unless there is an intolerance or suspected or documented resistance to it). How to handle patients already on the injectable and the shorter regimen is described below in section 5.3.1.

Dosing of anti-TB drugs included in the shorter regimen should be defined according to Table 4.

#### Transition from old to new WHO-recommended shorter regimen

Participants in the control arm receiving an “old” version of the MDR/RR-TB shorter treatment regimen including an injectable should be re-assessed on a case-by-case basis, according to the following principles:

1. Participants at any point of treatment **who have signs of good treatment response** (i.e. negative culture, clinical improvement): if still taking an injectable (Am, Cm or Km), consider replacing the injectable with bedaquiline whenever possible. This will neither constitute nor count toward an unfavorable outcome (i.e. the change will have to be reported as treatment change, indicating that it is done to conform to 2018 WHO guidance, but this change will not be counted as treatment change leading to participant withdrawal).
2. Participants at any point of treatment **who have signs of slow or no treatment response** (i.e. positive sputum culture after 12 weeks of treatment or more, clinical worsening): rather than simply replacing the injectable with bedaquiline, consider restarting a new conventional treatment according to 2019 WHO recommendations. Care should be taken to design the regimen with a case-by-case approach recognizing that resistance may have been developed to some of the drugs used in the regimen.  If two or more drugs are changed, this will constitute an unfavorable outcome (i.e. the change will have to be reported as related to absence of treatment response and this change will be counted as treatment change possibly leading to participant withdrawal).

The CAC should be involved in all such cases to support the decisions by the Site Co Investigator and the Site PI.

### Dosing of drugs in the conventional and shorter regimens

Dosing of anti-TB drugs should be defined as according to Tables 3 and 4.

**Table 3. Dosing of anti-TB drugs for the conventional regimen in adolescents and adults.** **Dosing is daily unless otherwise specified.**

| **Medication (abbreviation, common presentation)** | **Weight class** |
| --- | --- |
| **>24-30 kg** | **>30-35 kg** | **>35-45 kg** | **>45-55 kg** | **>55-70 kg** | **> 70 kg** |
| ***GROUP A***  |
| Levofloxacin (Lfx) (250, 500 mg)  | 500 mg | 750 mg | 1,000 mg |
| Moxifloxacin (Mfx) (400 mg) | 400 mg |
| Bedaquiline (Bdq) (100 mg) | 200 mg daily for 2 weeks,followed by 100 mg 3 times/week | 400 mg daily for 2 weeks,followed by 200 mg 3 times/week |
| Linezolid (Lzd)(600 mg) | 300 mg | 600 mgMay need to stop or reduce dosage after a few months of therapy due to adverse effects (see ***SOP SP-018-CT Management of Specific Adverse Events*** for detailed instructions). |
| ***GROUP B***  |
| Clofazimine (Cfz)(100 mg) | 100 mg |
| Cycloserine (Cs) (250 mg)  | 500 mg | 750 mg |
| Terizidone (Tzd) (250mg) | 500 mg | 750 mg |
| ***GROUP C*** |
| Ethambutol (E) (400 mg)  | 400 or 600 mg | 800 mg | 1,200 mg |
| Delamanid (Dlm)(50 mg) | 50 mg twice daily | 100 mg twice daily (total daily dose = 200 mg) |
| Pyrazinamide (Z) (400 mg)  | 1,000 mg | 1,200 mg | 1,600 mg | 2,000 mg |
| Amikacin (Am) (500-mg/2ml amp)1  | 500 mg | 625 mg | 750 mg | 750 or 1000 mg | 1,000 mg |
| Ethionamide (Eto) (250 mg)  | 500 mg | 750 mg | 1,000 mg |
| Prothionamide (Pto) (250 mg)  | 500 mg | 750mg | 1,000 mg |
| P-aminosalicylic acid (PASER®) (4-g sachets) | 3 to 3,5 g twice daily | 4 g twice daily | 4 or 6 g twice daily |
| ***OTHERS*** |
| Isoniazid (H)(100, 300 mg) | 150 mg | 200 mg | 300 mg |
| High-dose isoniazid (HH)(100, 300 mg)  | 400 mg | 450 mg | 600 mg |

1 For adults over 59 years of age, the dose will be reduced to 10 mg/kg (max dose: 750 mg). For example a 65 year-old with normal creatinine function and a weight of 50Kg would get 500 mg of amikacin daily, instead of the normal dosing of 750 mg daily.

Adapted from WHO consolidated guidelines on drug-resistant tuberculosis treatment, 2019.

**Table 4. Dosing of anti-TB drugs in shorter regimen. Dosing is daily unless otherwise specified.**

| **Medication (abbreviation, common presentation)** | **Weight class** |
| --- | --- |
| **>24-30 kg** | **>30-35 kg** | **>35-45 kg** | **>45-55 kg** | **>55-70 kg** | **> 70 kg** |
| Levofloxacin (Lfx) (250, 500 mg)  | 500 mg | 750 mg | 1,000 mg |
| Moxifloxacin (Mfx)  (400 mg) | 400 mg |
| High-dose Mfx (MfxH)(400 mg) | 400 mg | 400 or 600 mg | 600 mg | 600 or 800 mg | 800 mg |
| Bedaquiline (Bdq) (100 mg) | 200 mg daily for 2 weeks,followed by 100 mg 3 times/week | 400 mg daily for 2 weeks,followed by 200 mg 3 times/week |
| Clofazimine (Cfz)(100 mg) | 100 mg |
| Ethambutol (E) (400 mg)  | 400 or 600 mg | 800 mg | 1,200 mg |
| Pyrazinamide (Z) (400 mg)  | 1,000 mg | 1,200 mg | 1,600 mg | 2,000 mg |
| Ethionamide (Eto) / Prothionamide (Pto) (250 mg)  | 500 mg | 750 mg | 1,000 mg |
| High-dose isoniazid (HH)(100, 300 mg)  | 400 mg | 450 mg | 600 mg |

*Adapted from* WHO consolidated guidelines on drug-resistant tuberculosis treatment, 2019*.*

Notes

* Dosing of anti-TB drugs is based on the weight of the participant.
* Monthly monitoring of participant body weight is important. During trial participation, the dosage of drugs should be adapted to changes in participant’s body weight, as feasible. Please refer to **SOP SP-017-CT Treatment and Study Adherence Counseling and Support, including Directly Observed Therapy and Handling of Missed Doses** for detailed instructions to perform the dose adaptation.

### Prescription and recording

Each time a regimen (or drug or dose) is initiated or changed, the Site Co Investigator should record in the source document the regimen, the dose, the changes, and the date they occurred.

## REFERENCES

* Rapid communication: key changes to treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.26). Licence: CC BY-NC-SA 3.0 IGO.
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* World Health Organization. (‎2017)‎. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. World Health Organization. <http://www.who.int/iris/handle/10665/258941>. License: CC BY-NC-SA 3.0 IGO.

## SUPPORTING DOCUMENTS

* SOP SP-017-CT Treatment and Study Adherence Counseling and Support, including Directly Observed Therapy and Handling of Missed Doses (endTB Site Study Documents)
* SOP SP-018-CT Management of Specific Adverse Events (endTB Site Study Documents)
* SOP SP-009-ET Chest X-Ray Reading (endTB Site Study Documents)
* SOP SP-021-CT Chest X-ray Reporting (endTB Site Study Documents)

## APPENDIX

## None

1. “Limited”: presence of lesions with slight to moderate density, but no cavitations. Lesions may be present in a small portion of one or both lungs but the total extent of the lesions should not exceed the size of the apex of the lung (area above the first chondrosternal junction) ; “Moderate”: lesions present in one or both lungs, with a total extent which does not exceed the following: a) scattered lesions of slight to moderate density that may extend throughout the total volume of one lung or may partially involve both lungs; b) dense, confluent lesions that extend up to 1/3 of the volume of one lung; c) cavitation with a diameter of < 4 cm in any single cavity; “Extensive”: lesions that are more extended than those defined as moderate.

\* The latter two exclusion criteria were added for the bedaquiline-containing all-oral shorter MDR/RR-TB regimen in the WHO “Rapid communication” of December 2019. [↑](#footnote-ref-2)
2. The following drugs belong to the same class: Mfx and Lfx; Cs and Trd; Ipm/Cln and Mpm; Am and S; Eto and Pto. [↑](#footnote-ref-3)