# **Management of baseline resistance to new and re-purposed drugs**

# **in the endTB clinical trials**

**Analysis:**

Exclusion from the mITT population will occur if screening/baseline DST results from the designated study lab indicate resistance (using a test deemed to be reliable by the trial reference lab, ITM) to a drug contained in the regimen.

**Study treatment:**

At the moment of awareness of screening/baseline phenotypic DST results from the designated study lab indicating resistance (using a test deemed to be reliable by the trial reference lab, ITM) to bedaquiline, clofazimine, delamanid, and/or linezolid, the continuation of study treatment should be re-assessed for all participants, both in experimental and control arms, assigned to a regimen that includes any drug(s) with a resistant result.

The main element to consider will be the timing of receipt of screening/baseline phenotypic DST results showing resistance, as follows:

* If the results are received during the first 2 months of study treatment, early termination of the study treatment is strongly recommended;
* If the results are received after 2 months of study treatment, and before the end of study treatment, early termination of the study treatment is recommended but should be assessed according to other elements listed below;
* If the results are received after the participant has already terminated study treatment, no change is required.

Other elements to be considered when assessing the continuation of study treatment:

* Extent of TB disease (number of affected lobes, presence of cavities, baseline smear grade);
* Comorbidities (HIV infection, diabetes, etc);
* BMI at baseline;
* Early treatment response (sputum smear and culture results after study treatment start, clinical and radiological response);
* Alternative treatment options (taking into account the baseline phenotypic DST, reliability of DST result for each drug, availability of drugs at the site, etc).

The final decision on continuation of study treatment will be made by the site PI considering the expected benefits versus the expected risks, after consultation with the CAC. The participant should be informed of the therapeutic options, potential risks and benefits, and agree with the final decision.

**NB:** Patients who stop early study treatment will remain in study and perform early termination and post-termination follow up visits. Patients who continue study treatment will remain on study but will be excluded from mITT population and will probably be included in a sensitivity analysis.