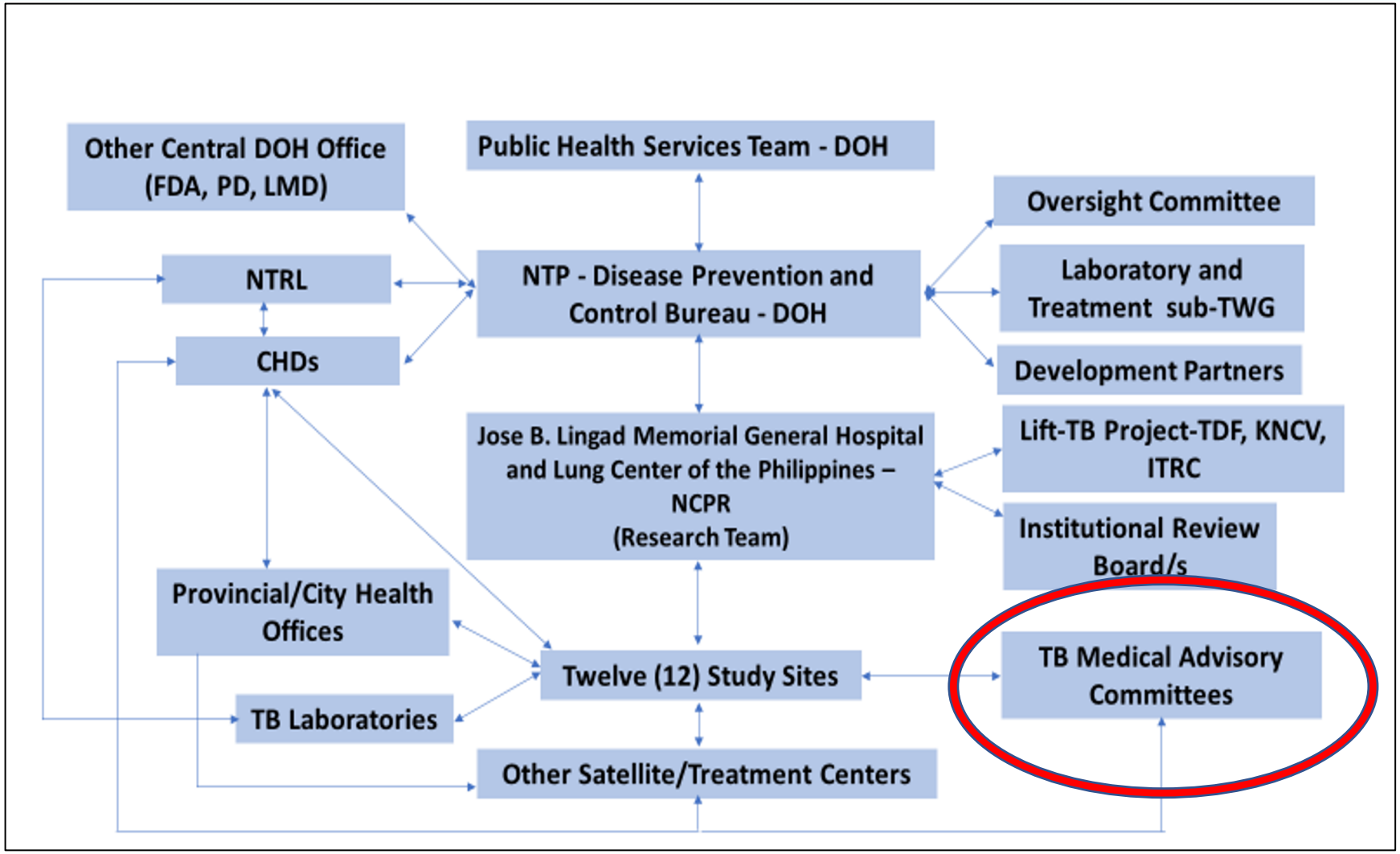
ROLE OF TBMAC IN THE BPAL RESEARCH

Implementing structure and roles/responsibilities of stakeholders



Screening /Enrollment

1. **Inclusion in BPaL of MDR-TB patients with non-response to the MDR-TB treatment**

1. **Inclusion in BPaL of MDR-TB patients with intolerance to the MDR-TB treatment**

1. **Exclusion from enrolment in the BPaL OR of patients thought to benefit more from an individualized MDR-TB**

Inclusion criteria

c. has been treated for MDR-/RR-TB and has documented non-response21 to treatment, has bacteriologically active TB ** within the last three months* of the screening date, and a decision has been made by the TB Medical Advisory Committee (TB MAC) to shift the patient to the BPaL regimen; or

d. has been treated for MDR-/RR-TB, has documented intolerance, 22 to treatment, has bacteriologically confirmed active TB** within the last three months* of the screening date, and a decision has been made by the TB MAC to shift the patient to the BPaL regimen

Exclusion Criteria

The TB MAC decides that it is not in the best interest of the patient to be enrolled on the BPaL OR due to the necessity of an individualized treatment regimen.

4. **Inclusion or exclusion of patients in the BPaL regimen with relative contraindications (as long 1 and 2 of the inclusion criteria are fulfilled)**

- is 15-17 years old at the time of enrolment with recommendation for inclusion in BPaL by the TB MAC
- has mild form of extrapulmonary TB with or without pulmonary TB with recommendation for inclusion in BPaL by the TB MAC

5. Other relative contraindications - advice of the TB MAC should be sought

Table 3. Selected relative contraindications to the use of the BPaL treatment regimen for patients with MDR-/RR-TB

Relative contraindication	Notes
Concurrent use of medications that have known interactions or overlapping toxicities with BPaL component drugs	Inducers of CYP450 enzymes: • Efavirenz • Rifamycin • Antiepileptics Inhibitors of CYP450 enzymes: • Fluconazole/itraconazole • Clarithromycin/erythromycin First-line TB drugs (HRZE) Drugs that prolong the QT interval (see list in clinical guide) Drugs that increase serotonin levels (see list in clinical guide)
High risk of cardiac arrhythmia	Baseline QTcF > 500ms History of syncopal episodes, ventricular arrhythmias, heart failure or severe coronary artery disease Family history of long-QT syndrome
Severe anaemia Moderate thrombocytopaenia Moderate neutropaenia	Haemoglobin level < 8.0 g/dL Platelet count <75,000/mm^3 Absolute neutrophil count < 1000/ mm^3
Severe peripheral neuropathy	Grade 3 or Grade 4, according to the Division of Microbiology and Infectious Diseases (DMID) [23]
Evidence of hepatic impairment	AST/ALT > 3.0 x upper limit of normal (ULN) Total bilirubin > 2.0 x ULN Albumin < 32 g/L
Significant renal insufficiency	Serum creatinine > 3.0 x ULN No dose adjustment, other than an interruption for an AE, should be made for Bdq or Pa. Lzd dose reductions, interruptions or discontinuations are allowed (see section 8.1). Primary metabolites of Lzd accumulate in renal impairment and the clinical significance of this is unknown. Due to limited experience, caution should be exercised in patients with significant renal impairment.

6. Special circumstances

Circumstance	Notes
Adolescents	Adolescents 15 years -17 years may be included for treatment with the BPaL regimen on the decision of the TB MAC (as noted in the inclusion criteria). Note: Bdq is recommended for use in patients aged 6 and over by the WHO, and Lzd for all ages. There is no recommendation for Pa (Dlm is recommended in those aged 3 and over).
Extrapulmonary TB	Patients with "minor" forms of extrapulmonary TB can be included for treatment with BPaL on the decision of the TB MAC (as noted in the inclusion criteria). Consideration should be given to the planned duration of treatment, and any planned strategies for monitoring treatment response in the absence of sputum testing. Note: The BPaL regimen should not be used for the treatment of CNS TB and osteomyelitis. Meningitis / central nervous system (CNS TB) • There is limited experience of use of the BPaL regimen. • CNS infections usually require a longer course of treatment than pulmonary TB Osteomyelitis • There is limited experience of use of the BPaL regimen. • These infections often warrant extended treatment durations.
HIV infection	People living with HIV may be included for treatment with the BPaL regimen. In the Nix-TB study, 50% of participants were HIV-positive and treatment outcomes were similar between groups. There are two important drug-drug interactions between antiretroviral drugs and Bdq, also mentioned above: • Efavirenz: induces metabolism of Bdq, reducing drug levels • Ritonavir: inhibits metabolism of Bdq, increasing drug

Treatment Follow-ups

1. Missed treatments

- In case the full BPaL regimen is interrupted for more than 35 consecutive days, the patient will be referred to the TB MAC to decide on further management including the need for change to a new individualized regimen, based on clinical assessment and reason for interruption.

- Any treatment interruptions should be discussed within preferably 1-2 days with the TB MAC (including external experts whenever necessary), and optimally prior to the interruption of treatment.

1. Discontinuation of treatment due to toxicity or treatment failure

- **Intolerable toxicity**

  In case Bdq and/or Pa need to be suspended permanently owing to intolerable toxicity, the patient will be shifted to another regimen as advised by the TB MAC.

- **Treatment failure**

  - If a patient is failing treatment, he should be referred to the TB MAC for review and design of a new individualized regimen.

3. Modification and discontinuation of the BPaL regimen

- Permanent discontinuation of Lzd with a total exposure of less than 4 months should be discussed with the TB MAC.
- If there are toxicities due to Lzd requiring interruption/dose reduction, then the TB MAC (including external experts if needed) should balance the risk of inadequate treatment and relapse with the burden of additional/prolonged treatment. The regimen may need to be strengthened (and the patient withdrawn from the study).
- Continuing or discontinuing patients on the BPaL OR Lzd depending on the duration and dose taken
- Recommencing the BPaL regimen after an interruption of $\leq$14 days within the first four weeks of treatment, and < 35 days after the first four weeks of treatment
- Pregnancy during treatment
- Resistance to drugs in the BPaL regimen

4. Designing an individualized MDR-TB regimen in patients with intolerable toxicity.

a. had > *14 consecutive days* interruption of the BPaL regimen within the first four weeks of treatment

b. *>35 consecutive days* interruption of the BPaL regimen after the four weeks of treatment

c. dose modification or discontinuation of Lzd even before a total of 4 weeks on 1200 mg daily dose

d. discontinuation of Bdq and/or Pa at any time

e. women who become pregnant while on BPaL treatment

f. patients who failed the BPaL regimen including those with poor clinical and/or radiologic response to the BPaL regimen

6. Treatment outcome decisions

Reviewing the status of patients on a quarterly basis particularly those with intolerance and non-response to the BPaL regimen and those with favorable treatment outcomes.

Advice for treatment outcome of failure

- poor clinical or radiological response or adverse drug reactions as decided by the TB MAC; or

- Permanent discontinuation of either Bdq or Pa at anytime,or Lzd if having less than 4 weeks of full dosage, or having a total of four weeks full dosage but without smear conversion and clinical improvement.

PROGRAM OF ACTIVITIES

The referral of patients at the OR sites needing TB MAC guidance and decision-making will be through emails addressed to the regional TB MAC with copy furnished to the National TB MAC in one thread. The regional TB MAC will have the liberty to decided in the cases without necessarily seeking the approval of the national TB MAC if the issues are simple and straightforward. Response is expected within 48 hours.

Cases that cannot be decided on by the NTBMAC will be elevated to International Expert Committee for decision.

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