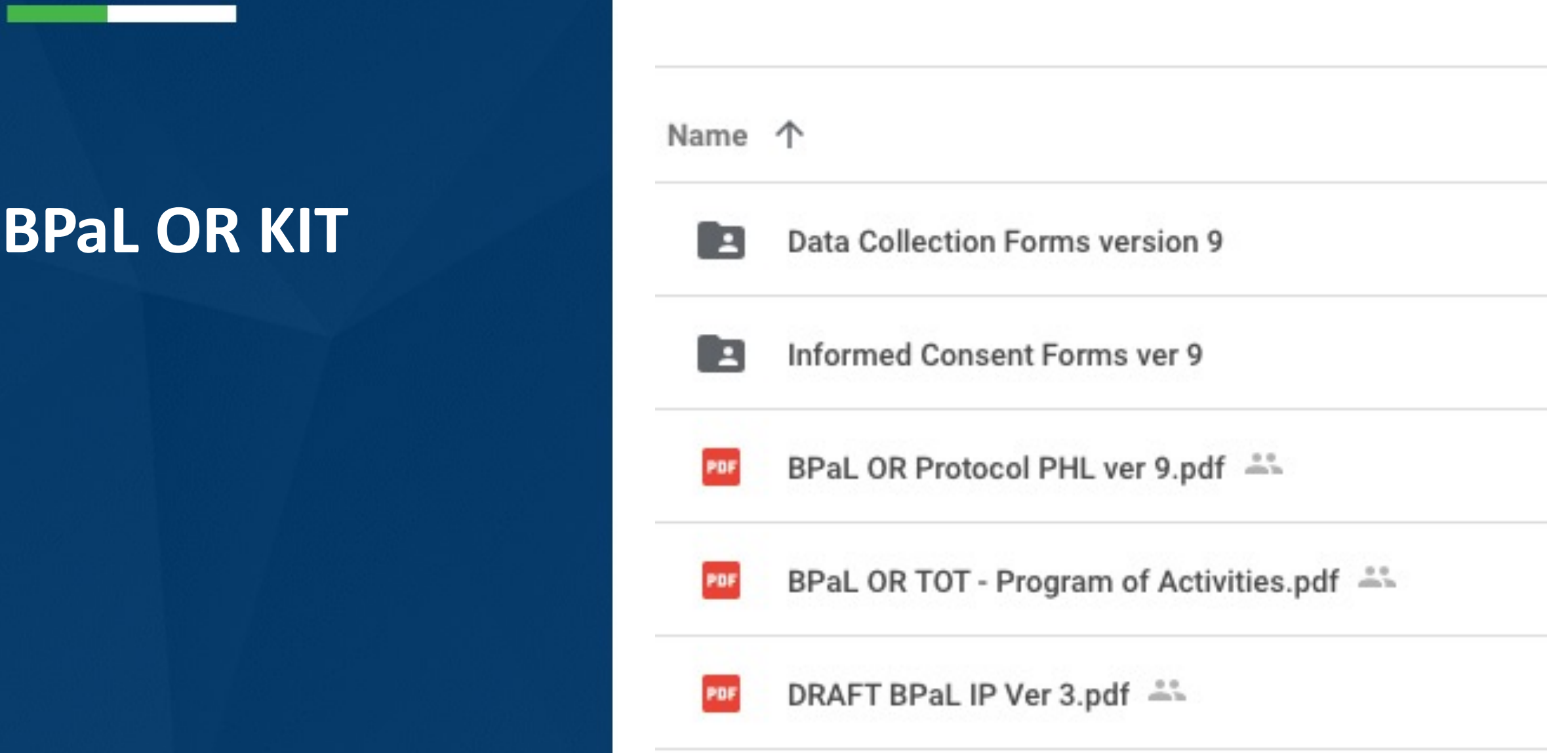
PBSP
Philippine Business for Social Progress
Business United. Lives Uplifted.

50 ANNIVERSARY
FOUNDED 1970

Pilot study to estimate the effectiveness and safety of the BPaL treatment regimen in Philippines

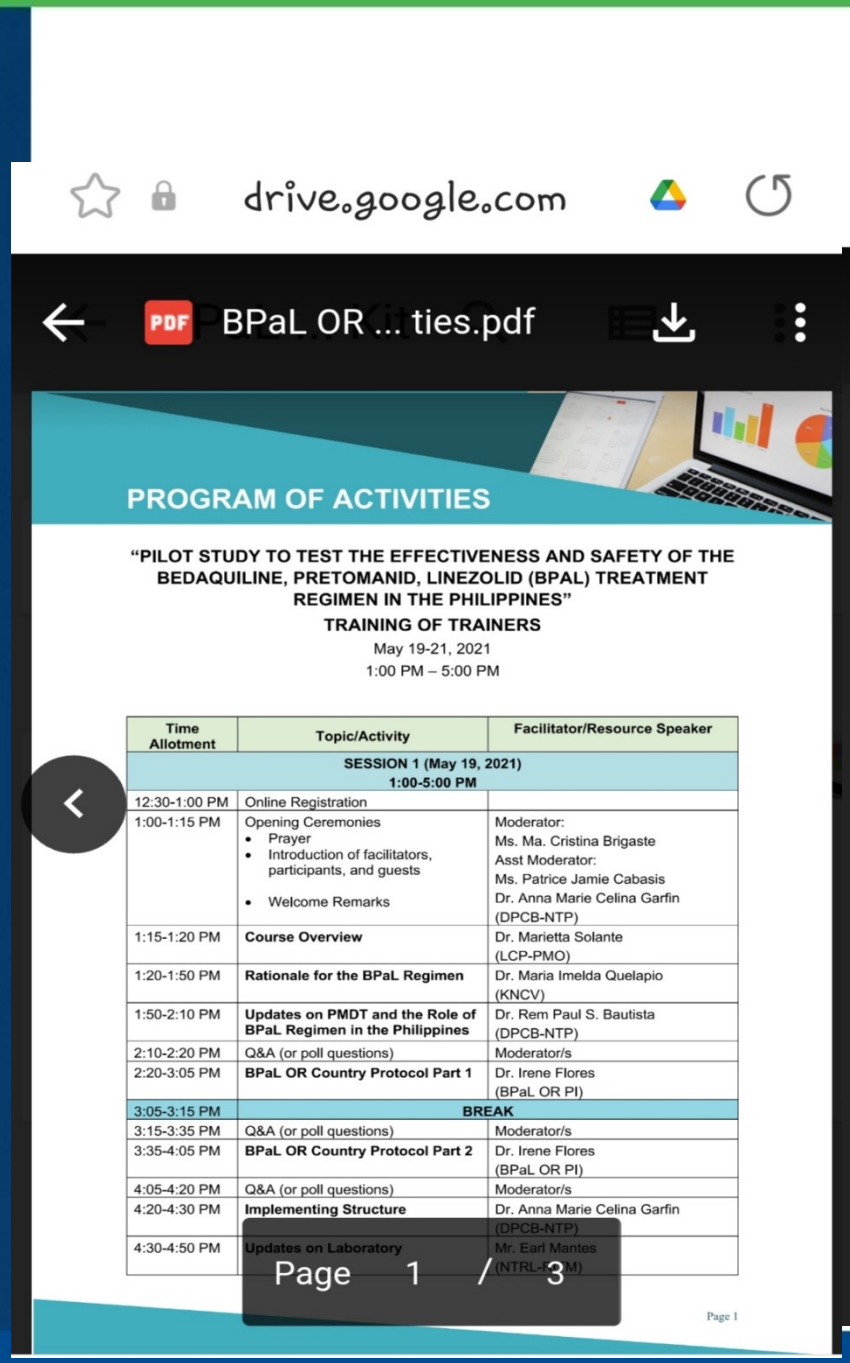
Irene A. Flores, MD

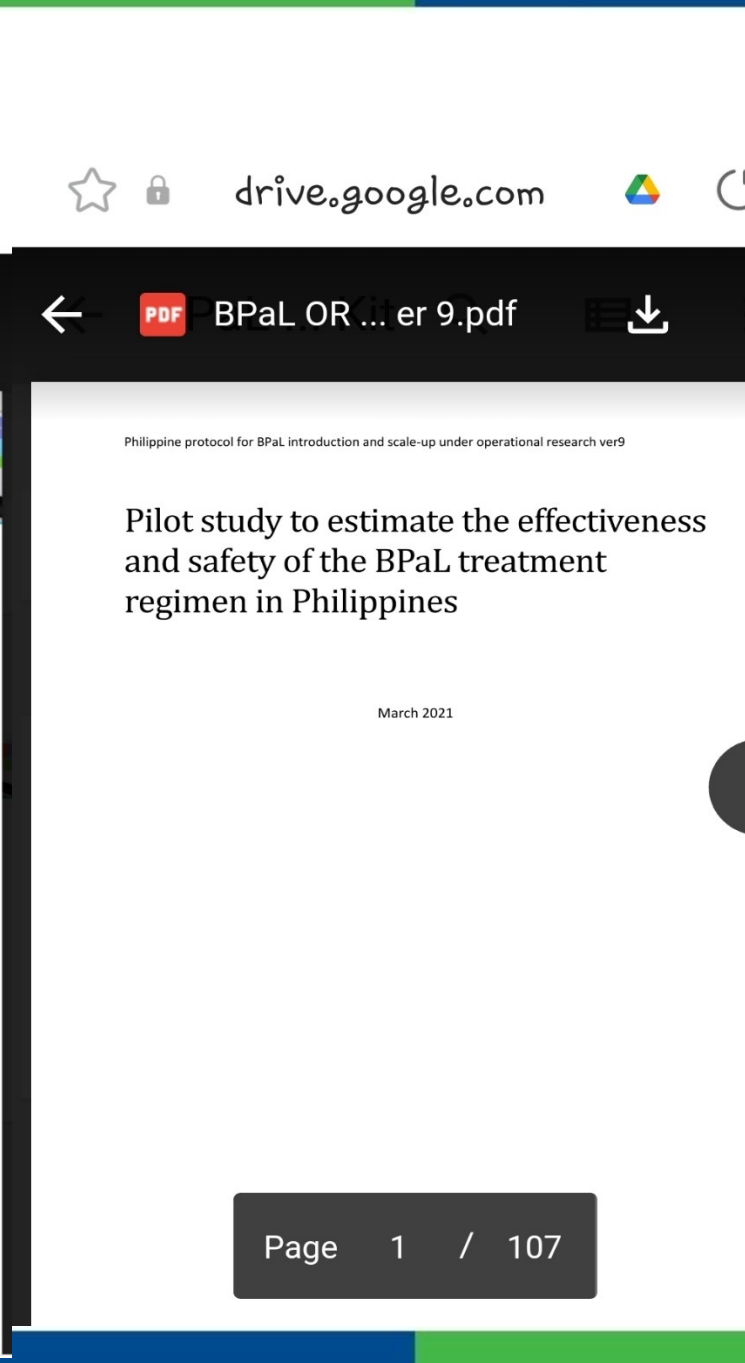
BPaL OR KIT


Name
Data Collection Forms version 9
Informed Consent Forms ver 9
PDF
BPaL OR Protocol PHL ver 9.pdf
PDF
BPaL OR TOT - Program of Activities.pdf
PDF
DRAFT BPaL IP Ver 3.pdf

BPaL OR KIT

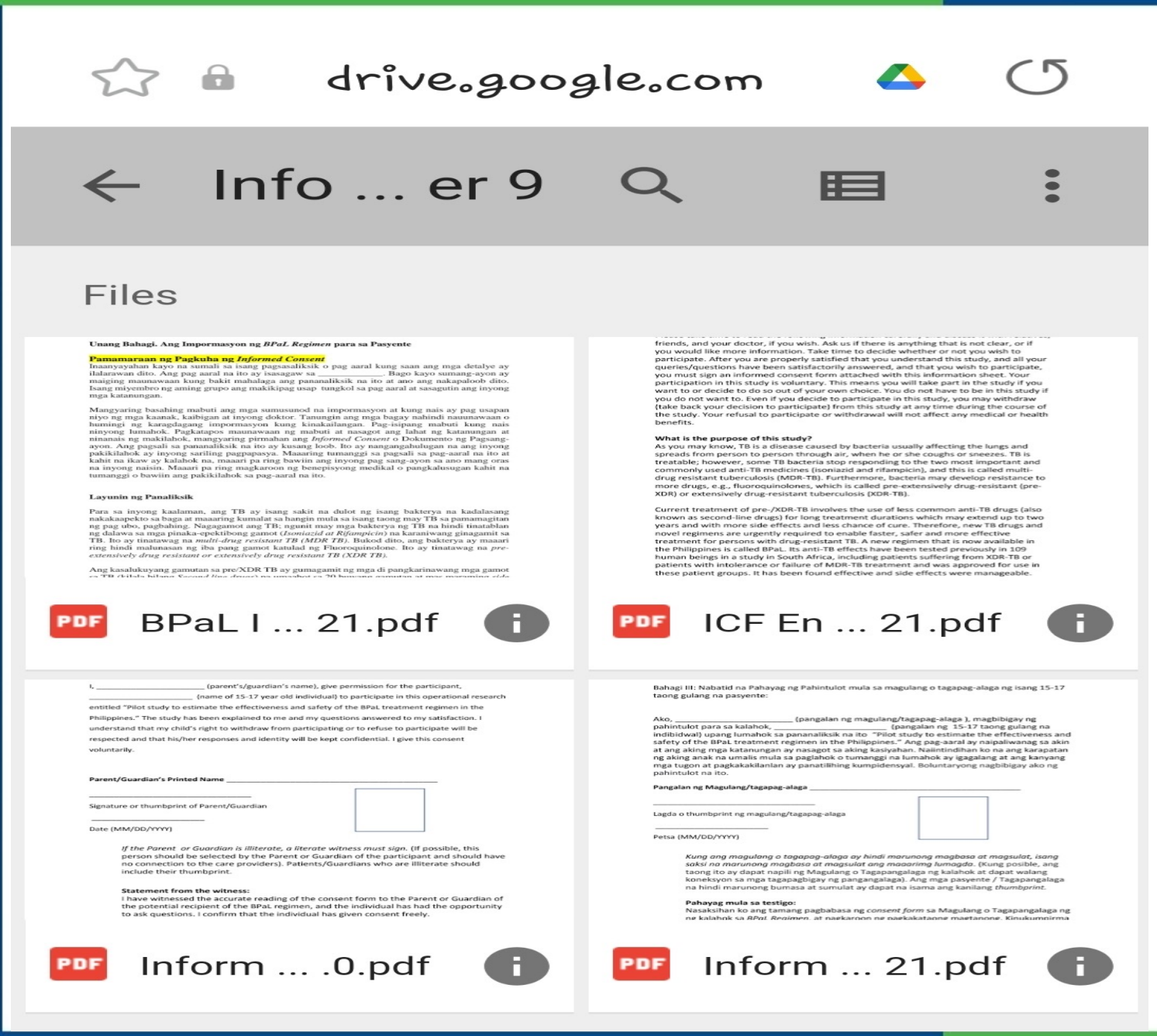
- TOT Program Of Activities
- BPaL Protocol





BPaL OR KIT

- Informed Concent Forms (ICF)



BPaL OR KIT

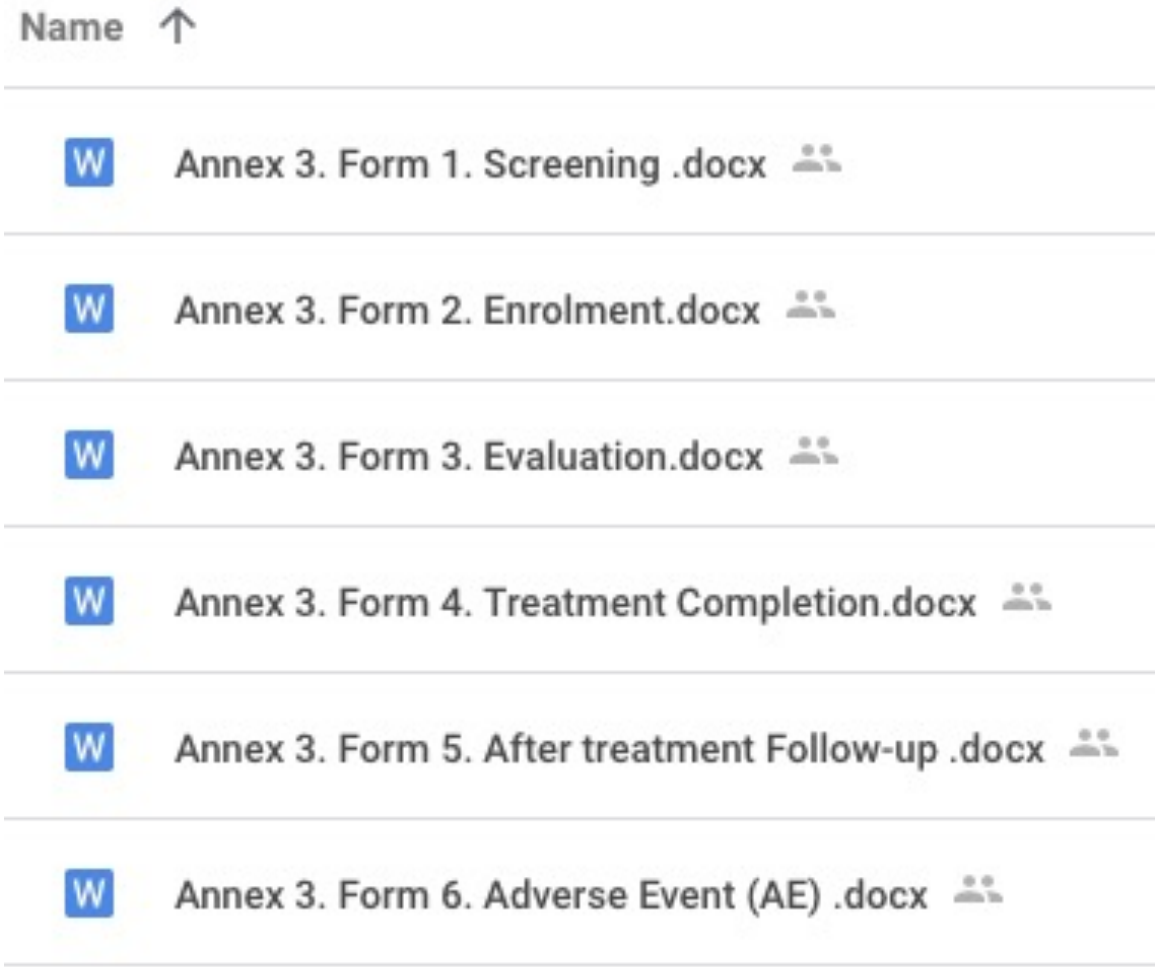
Implementation Plan (IP)

IMPLEMENTATION PLAN FOR THE BEDAQUILINE-PRETOMANID-LINEZOLID OPERATIONAL RESEARCH (BPAL OR), PHILIPPINES

TABLE OF CONTENTS

BPaL OR KIT

- REDCap Data Collection Forms



Objectives of the Study

- **Primary objectives:**
  - To estimate the effectiveness of the BPaL regimen by assessing the end of treatment outcome
  - To estimate the safety of the BPaL regimen by determining the rates of serious adverse events (SAE)

- **Secondary objectives:**
  - To determine the time to sputum culture conversion
  - To determine the rate of recurrence at 6 and 12mo after the successful treatment with the BPaL regimen.
  - To determine the rate of occurrence of AESIs (QT-prolongation, peripheral neuropathy, myelosuppression, optic neuritis and hepatotoxicity)

Objectives of the Study

- The goal is to enrol 100 patients over a period of 2 years in 12 sites in the Philippines based on the inclusion and exclusion criteria after informed consent.

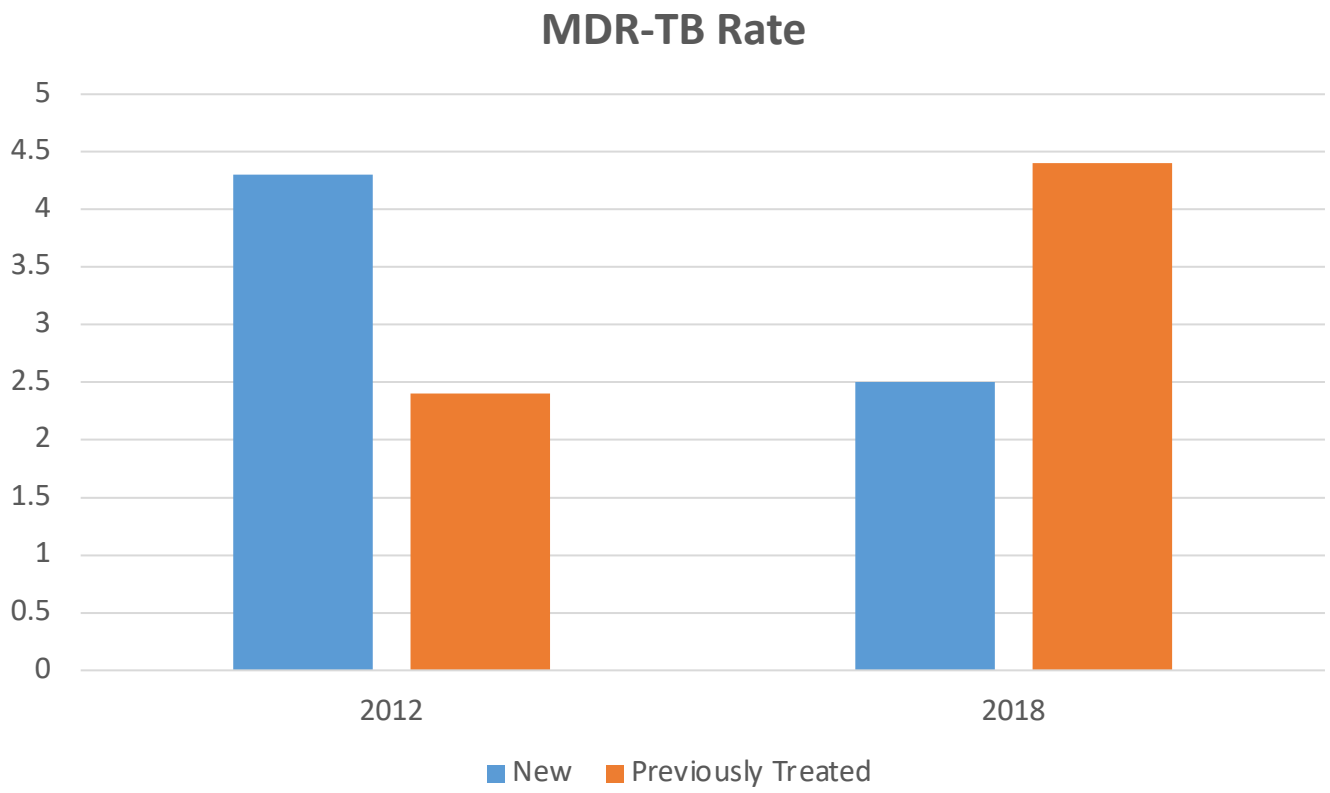
- The OR study, will strengthen the NTP to implement the BPaL regimen, and the results of the OR will be used to support national scale-up of the regimen.

DRTB in the Philippines

- The Philippines is among the world's high burden countries for TB and MDR-TB with an MDR-/RR-TB incidence of 21,000 (10,000-34,000) and 19/100,000 (9.6-32).

DRS in the Philippines, 2012 and 2018

- The Philippines has had two drug resistance surveys (DRS) of nationwide scale:



DRS in the Philippines

- The Global TB Report, 2020, showed that MDR-/RR-TB was 1.8% (1.3–2.6) among new, and 28% (27–29) among previously treated TB cases.

- Only 1 patient had XDR among 2,107 with MDR-TB; pre-XDR was 2%

Patient recruitment and selection

- The study site staff or the focal point persons, either the PMDT doctor or nurse, will recruit BPaL patients from the DR-TB patients who are assessed using a triage approach.

- All detected TB patients are tested for both FL and SL resistance, using rapid molecular methods (including Xpert MTB/XDR cartridge, once available).

Patient recruitment and selection

- If this is not feasible, FL and SL DST could be limited to only those TB patients who have detected R resistance.

- They can also recruit patients who are on programmatic treatment regimens who need to be shifted to another regimen due to intolerance or failure.

DR-TB treatment regimens in the country

Regimen	Composition	Duration
A. UNDER PROGRAMMATIC CONDITIONS		
Shorter Regimen		
Standard short all-oral regímen (SSOR)	4-6 Lfx-Bdq (6)-Cfz-Pto-E-Z-Hhd/ 5 Lfx-Cfz-Z-E	9-11 months
Longer Regimen **		
1. Standard long all-oral regimen (SLOR) for FQ- susceptible (FQ-S) 2. Standard long all-oral regimen (SLOR) for FQ-resistant (FQ-R)	6 Lfx-Bdq-Lzd-Cfz/12-14 Lfx-Lzd-Cfz 6 Bdq-Lzd-Cs-Cfz-Dlm/12-14 Lzd-Cs-Cfz	18-20 months - 18-20 months
Individualized Regimen		
Individualized Treatment Regimen (ITR)	Composed of at least 4 likely effective drugs as approved by the Medical Advisory Committee (MAC)	20.months
B. UNDER OPERATIONAL RESEARCH CONDITIONS***		
BPaL regimen	Bdq–Pa-Lzd	6-9 months

Component Drugs in the Study

Bedaquiline

Pretomanid

Linezolid

Evidence on the drugs proposed in this study: BDQ

Study is limited for Bedaquiline

- regarding the safest and most effective dose,
- the dose response relative to TB outcomes,
- the singular contribution of Bdq when added to other active drugs in a regimen, and
- the use of Bdq together with other new anti-TB drugs

Evidence on the drugs proposed in this study: BDQ

Safety and Tolerability

- *QTC Prolongation*
- Transaminitis or elevated liver enzymes
- Drug to Drug Interaction with EFAVIRENZ
- No adequate and well-controlled studies in pregnant women.

Evidence on the drugs proposed in this study: Linezolid

Dosing

- **600 mg daily and given for the entire course of therapy**
  - Current recommendation in PMDT
  - Can either be decreased to 300 mg daily or stopped if limiting toxicity develops.

- **1200 mg daily was used for Lzd (NIX trial)**
  - with the option to reduce or stop after **one month of treatment** in case of toxicity

Evidence on the drugs proposed in this study: Linezolid

Efficacy

- **increase culture conversion and treatment success in DR-TB patients.**
  - demonstrated in two *randomized controlled trials* and in *observational studies*
- **It is an effective agent, but its use is limited by safety concerns.**

Evidence on the drugs proposed in this study: Linezolid

Safety and Tolerability

- **myelosuppression, optic neuritis, neuropathy, and lactic acidosis,**
  - **discontinuation of Lzd use can occur in as many as 18% of persons who receive treatment with Lzd.**
- **Adverse events (AE) more frequent at more than 600 mg a day**
  - can be identified early with routine monitoring
  - often reversible upon discontinuation of the drug or lowering of the dose.
- **Effect on pregnancy and breastfeeding**
  - **limited; Caution is advised**

Evidence on the drugs proposed in this study: Pretomanid

Safety and Effectiveness

- has *M.tb* bactericidal activity as a single drug based on Phase 2 Early Bactericidal Activity studies
- Its safety and effectiveness for its use is established ONLY in combination with Bdq and Lzd as part of the recommended dosing regimen.
- Tested for use among DR-TB patients co-infected with HIV- including those receiving ARVs.

Evidence on the drugs proposed in this study: Pretomanid

Safety and Effectiveness

- Cause testicular atrophy and impaired fertility in male rats but not in monkeys.

  -potential effects on human male fertility have not yet been adequately evaluated

- There are no data available on the use of Pa in pregnant women.

Inclusion Criteria

1. MTB patient with a laboratory-confirmed (rapid and/or phenotypic DST) resistance to at least rifampicin and fluoroquinolone(s) within the last three months* of the screening date;

2. Patient has strong clinical and radiological evidence of active TB AND has been a close household contact of an index patient with:

   a. active laboratory-confirmed resistant TB to at least rifampicin and FQs within the last 3 months of screening date AND

   b. no documented resistance to any of the BPaL component drugs (Bdq, Pa, Lzd) within the last three months * of the screening date; or

Inclusion Criteria

3. has been treated for MDR-/RR-TB and has documented non-response 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

4.has been treated for MDR-/RR-TB, has documented intolerance, 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; and

Inclusion Criteria

Any of the above AND

- Patient is willing and able to give informed assent or consent (signed or witnessed consent, if illiterate) to be enrolled in the OR and adhere to the OR procedures and the follow-up schedule; and
- Patient is at least 18 years old at the time of enrolment

Inclusion Criteria

****Non-response** is defined as: a) two consecutive positive cultures of sputum samples collected after the end of the 2nd month (separated by at least 30 days) of treatment with lack of clinical improvement or deterioration; or b) treatment outcome of failure according to the WHO definition

*****Intolerance** is defined as: Inability to continue the second-line MDR-/RR-TB regimen due to a documented adverse event to any of the component drugs.

Inclusion Criteria

- Patients for BPaL must have:
- * Documented proof of active TB (LPA or culture) within the last 3 months before deciding that a patient is eligible for the BPaL regimen, regardless of history of previous TB treatment.
- If the patient has not been on treatment during the previous 3 months, a repeat LPA, culture, and pDST are needed.

Inclusion Criteria

- **Patient who developed Intolerance or Non response to Treatment are shifted to BPaL Regimen irrespective of Resistance to Flouroquinolone**

Inclusion Criteria

- Relative indications needing TB MAC recommendation

  - 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

Exclusion Criteria

1. Known severe allergy to any of the BPaL component drugs (Bdq, Pa, Lzd); or

2. DST showing resistance to any of the component drugs; or

3. Previous exposure to any of the component drugs or Delamanid (Dlm) for >4 weeks; or

4. Known severe adverse event associated to any of the BPaL component drugs, or

Exclusion Criteria

5. Extrapulmonary TB that would require treatment longer than would be usual for pulmonary TB (e.g., TB meningitis, other central nervous system TB, or TB osteomyelitis); or

6. Inability to take oral medications; or

7. Body weight of <35 kg

8. Pregnant; or plan to conceive within the next year; or

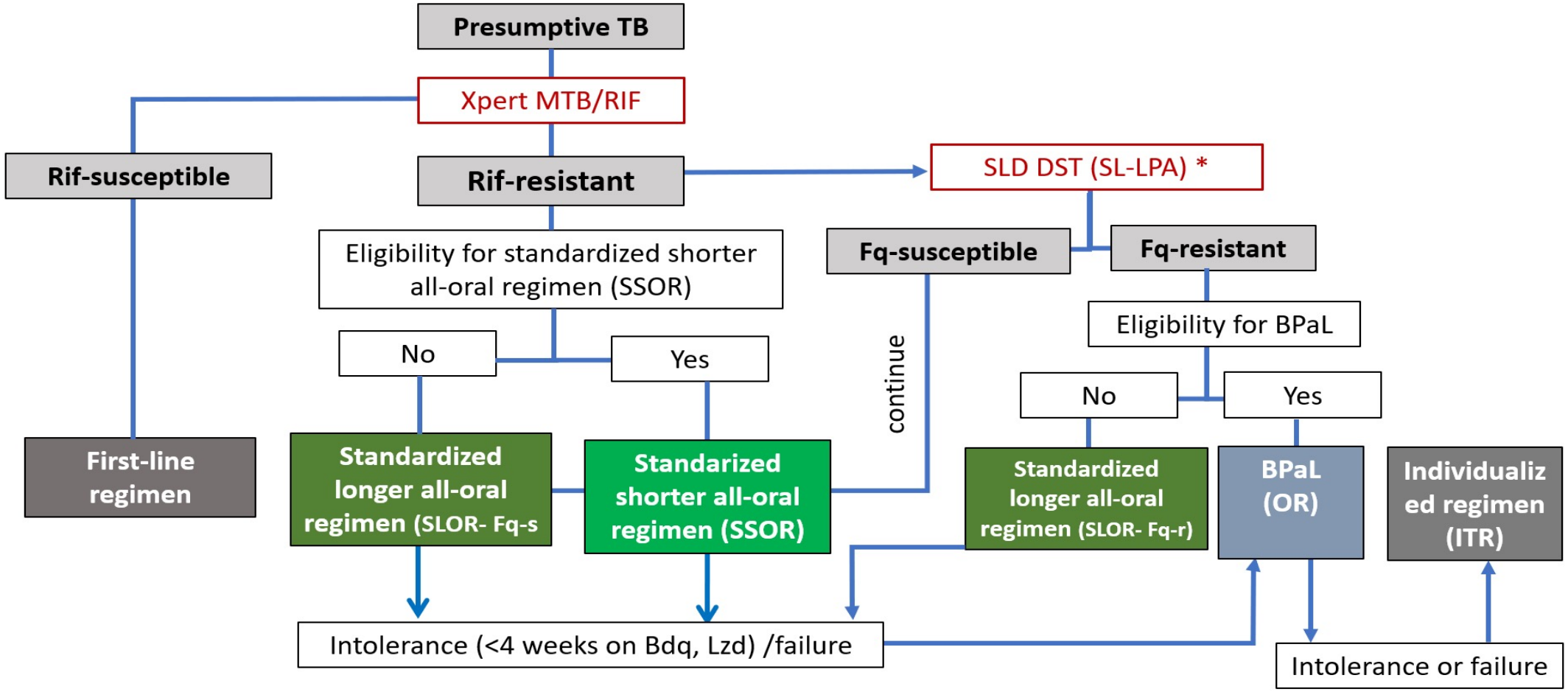
Exclusion Criteria

9. Childbearing ability and is reluctant to use effective contraception while on the BPaL treatment;

10. Breastfeeding; or

11. 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 need of an individualized treatment regimen.

Algorithm showing eligibility to BPaL



Selected relative contraindications to the use of the BPaL patients with MDR-/RR-TB

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

Selected relative contraindications to the use of the BPaL patients with MDR-/RR-TB

Severe peripheral neuropathy	Grade 3 or Grade 4, according to the Division of Microbiology and Infectious Diseases (DMID)

[1] Paresthesia grade 3: severe discomfort; narcotic analgesia required with symptomatic improvement; and /or BPNS subjective sensory neuropathy score 7-10 on any side. Grade 4: incapacitating; or not responsive to narcotic analgesia.

Selected relative contraindications to the use of the BPaL patients with MDR-/RR-TB

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. 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.

Selected relative contraindications to the use of the BPaL patients with MDR-/RR-TB

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)

Selected relative contraindications to the use of the BPaL patients with MDR-/RR-TB

In case of relative contraindications, the clinician judges that the potential benefits outweigh the potential risks (also taking into account alternative treatment options), treatment may proceed with caution as part of the OR study. In these situations, advice needs to be sought from the TB MAC.

Notes on the use of the BPaL regimen in special circumstances

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).

Notes on the use of the BPaL regimen in special circumstances

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.

Notes on the use of the BPaL regimen in special circumstances

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 levels

Notes on the use of the BPaL regimen in special circumstances

HIV Infection	ARV regimens including the above drugs should be modified at least one week before commencing an HIV-positive patient on treatment with BPaL. ARV therapy including zidovudine should be used with special caution as zidovudine and Lzd may both cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity.

Informed Consent

- Patients who are eligible for inclusion in the study will be given information about MDR/XDR-TB and the BPaL treatment regimen. Patients will be provided with information in a language that is understandable to them. Consent for enrolment should be based on the Patient Information Sheet (Annex 1). Patients should have the opportunity to discuss the consent form with the medical officer/treatment supporter. The patients will be assured that their decision to participate in the study or not will not affect the quality of care they will receive.

Informed Consent

- The patient will be given a copy of the Informed Consent Form (ICF) and if needed, the patient is given at least 1-2 days to discuss his or her decision to family and significant others. Once the patient agrees to participate in the study, the patient will be asked to sign the consent form.

- All patients who are not eligible for the study, or refuse to be enrolled, or withdraw after enrolment, will be managed with a DR-TB treatment regimen according to the national guidelines.

Treatment sites and number of patients

The total number of patients to be enrolled on the BPaL regimen during the first 2 years is 100.

The site selection criteria for the BPaL OR include the following characteristics of the site.

Treatment sites and number of patients

- **The site:**
  - has been implementing PMDT for 1 year or more.
  - has a strategic location providing access to other referring facilities.
  - has a strategic location with access to private and public facilities for the identification and management of AEs and comorbidities.
  - has access to diagnostic and monitoring laboratories.
  - has >30 MDR/RR-TB patients enrolled in 2019.
  - has a designated physician trained in PMDT.

Treatment sites and number of patients

- No statistical sampling will be done as all eligible patients will be offered the BPaL regimen.

Treatment sites and number of patients

- The number of patients to be treated under this protocol was estimated based on the following assumptions:

  1) Patients will be recruited from all study sites over the span of 2 years to reach the target of 100 patients. Non-study sites may refer potential patients to the study sites guided by the zoning mechanism.

GION	FACILITY/ADDRESS	PHYSICIAN/NURSE	Current # of ongoing patients	Enrolled cases 2019	Rapid TB Diagnostic Laboratory (Xpert site)	TBC laboratory	DST laboratory	LPA laboratory	Access to lab/dxtics services	ZONING of patients
CR	Lung Center of the Philippines PMDT TC NCPR Bldg, Quezon Ave., Quezon City	Dr. Joan Tuy/09278020796 joantuymd@gmail.com John Alfred Caparos/09178736713 john.alfred.caparros@gmail.com Paula Carmelli Fulgencio/09275345860 paulacarmeli@gmail.com Joanna Kristine Espena/091569332 jespena@gmail.com Ma Jhoanna De Gracia/09329141332 jhoannagascon@gmail.com	108	126	LCP	LCP	NTRL	NTRL	YES	NCR

NCR	**Dr. Jose N. Rodriguez Memorial Hospital (DJNRMH) - PMDT TC** **Administration Site, St. joseph, 187 Tala, Caloocan city**	**Dr. Chiqui Villegas/09175333780** **chiqs126@gmail.com** **Kristine Marie Pulanco/09255458560** **kmtpulanco@gmail.com**	**50**	**93**	**DJNRMH**	**LCP**	**NTRL**	**NTRL**	**YES**	**NCR**
I	Ilocos Training and Regional Medical Center Mc Arthur Hiway San Fernado La Union	Dr. Chester Directo/ 09209481584 chesterdirecto@gmail.com Lovely Ducusin/09399393024 llducusin.pbsp@gmail.com Amor Santiago/09167760011 amorsantiago@gmail.com	20	36	La Union Medical (LUMC)	Dagupan Doctors Villaflor Memorial Hospital (DDVMH)	NTRL	NTRL	YES	Region I CAR Region II (Cagayan Valley)
	Region I Medical Center Arellano St., Dagupan City	Dr. Arthur Sy	48	54	Pangasinan Provincial Hospital (PPH)	DDVMH	NTRL	NTRL	YES	Region I

III	Jose B. Lingad Memorial Regional Hospital (JBLMRH) Mc Arthur Hiway Dolores St., San Fernando, Pampanga	Dr. Sheryll Magayanes / 09176771677 shexy716@yahoo.com Mary Joy Chavez / 09273953871	24	41	JBLMRH	Central Luzon CHD TBC Laboratory (CL CHD TBC Lab)	NTRL	NTRL	YES	Central Luzon
IV A	Batangas Medical Center (BatMC) Kumintang Ibaba, Batangas City	Dr. Luisa Elena L. Ticsay/ 09237358076 ellenlipatticsay@gmail.com Marvin Catilo / 09175617098: mvcatilo@gmail.com	23	61	BatMC	Philippine Tuberculosis Society, Inc. (PTSI QI)	PTSI QI	NTRL	YES	CALABARZON MIMAROPA
V	Sorsogon Medical Mission Group Hospital and Health Services (SMMGHHSC) Pangpang, Sorsogon City, Sorsogon	Dr. Nancy Rose Labarete/09175590422 nflabarete@gmail.com Carlo Ryan Estopace/09175878905 crestopace@gmail.com	39	40	SMMGHHSC (all patients screened in SMMGHHSC only); the rest of the zoned specimens are temporarily routed to Gubat and Pilar	SMMGHHSC	NTRL	NTRL	YES	Bicol Region

VI	Western Visayas Medical Center (WVMC) Q. Abeto St., Mandurriao, Iloilo City	Dr. Leonie Estoce/09228432749 learidel@gmail.com Kristy Corazon Cabanalan/0936-9950195 kgcabanalan.pbsp@gmail.com Elena Belican/09184190667 enbelivano.pbsp@gmail.com Marian Rose Calawigan/09089326161 macalawigan.pbsp@gmail.com	74	77	WVMC	WVMC	WVMC	NTRL	YES	Region VI (Western Visayas)
VII	Eversly Child Sanitarium (ECS) Jagobiao, Mandaue City	Dr. Alimer Nassale/ 09177798804 ainassaie.pbsp@gmail.com	39	98	ECS	PTSI-QI	PTSI-QI	NTRL	YES	Region VII (Central Visayas) Region VIII (Eastern Visayas)
IX	Zamboanga City Medical Center (ZCMC) Dr.Evamgelista St., Sta. Catalina, Zamboanga City	Dr. Marcelino Medina/09279759575 sanmarcelinoclinic@gmail.com Shermain Labrador/09175106300 sheirn23@gmail.com	36	38	ZCMC	ZCMC	Davao TB Reference Laboratory (DTRL)	NTRL	YES	Region IX (Zamboanga Peninsula)

X	**Northern Mindanao Medical Center (NMMC)** **Capitol Road, Cagayan de Oro City**	**Dr. Leslie Christine B. Magsayo-Salon/** **leschristinemagsalon@gmail.com** **Doris F. Apit/09173635761** **dfapit.pbsp@gmail.com** **Marie Fe Chiu/09985512745** **mmchiu.pbsp@gmail.com**	**38**	**49**	**NMMC**	**CDO Poly-medic Plaza (CDOPMP)**	**DTRL**	**NTRL**	**YES**	**Region X (Northern Mindanao)** **BARMM** **CARAGA** **SOCCSKSARGEN**
XI	Southern Philippines Medical Center (SPMC) JP Laurel Ave., Bjada, Davao City	Dr. Virgilio Dave Cania/09228207147 deyvcania@gmail.com deyv_cania_cania@yahoo.com David Glen Olimba/09339476136 olimbadavidglen@gmail.com	86	67	SPMC	DTRL	DTRL	NTRL	YES	Region XI (Davao Region) CARAGA Region XIII (SOCCSKSARGEN)

Treatment sites and number of patients

2) Data on the average enrolment of patients with XDR-TB nationwide from 2017-2019 was 48 patients per year.

3) Trend on final treatment outcome of patients under PMDT from 1999-2018 showed <1% had failed outcome equivalent to an average of 27 patients from 2016-2018.

Treatment sites and number of patients

4) ≥75 patients nationwide may be eligible to receive the BPaL regimen.

5) It is estimated that around 50 patients per year is feasible to be enrolled under the study considering the inclusion and exclusion criteria as well as the access of patients from non-study sites

OR Sites for BPaL OR in the Philippines

- **National Capital Region (NCR):**
  - Lung Center of the Philippines, Quezon City
  - Dr. Jose N. Rodriguez Memorial Hospital, Caloocan City
- **Region 1:**
  - Ilocos Training and Regional Medical Center, La Union
  - Region I Medical Center, Pangasinan
- **Region III:** Jose B. Lingad Regional Memorial Hospital, Pampanga
- **Region IV-A:** Batangas Medical Center, Batangas

OR Sites for BPaL OR in the Philippines

- **Region V:** Sorsogon Medical Mission Group HHSC, Sorsogon
- **Region VI:** Western Visayas Medical Center, Iloilo City
- **Region VII:** Eversley Childs Sanitarium and General Hospital, Cebu
- **Region IX:** Zamboanga City Medical Center, Zamboanga City
- **Region X:** Northern Mindanao Medical Center, Cagayan de Oro City
- **Region XI:** Southern Philippines Medical Center, Davao City

THANK YOU

PBSP

Philippine Business for Social Progress

Business United. Lives Uplifted.