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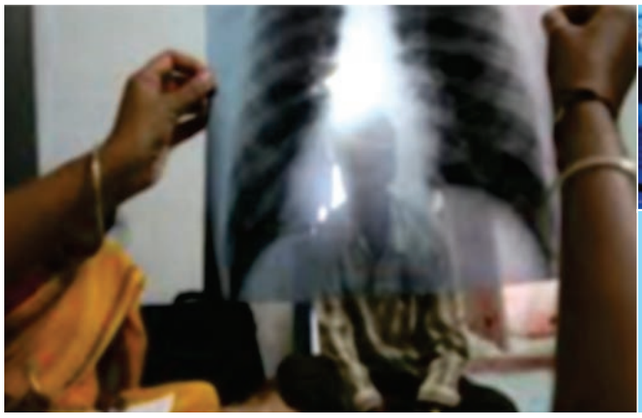

Guidelines for use of Bedaquiline in RNTCP through conditional access under Programmatic Management of Drug Resistant Tuberculosis in India

Revised National Tuberculosis Control Programme
Central TB Division, Directorate General of Health Services
Ministry of Health & Family Welfare
Nirman Bhawan, New Delhi

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This guideline is consistent with the WHO interim guidance on the use of bedaquiline to treat MDR-TB (http://www.who.int/tb/challenges/mdr/bedaquiline/en/) and aligned with use of bedaquiline under RNTCP PMDT Guidelines of India. It complements the existing RNTCP Guidelines for PMDT in India.

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ACKNOWLEDGEMENTS

The Guidelines for use of bedaquiline within the Revised National Tuberculosis Control Programme (RNTCP) through conditional access under the Programmatic Management of Drug Resistant Tuberculosis (PMDT) in India (February 2016) has been developed as the end-product of a series of deliberations and a national workshop. These deliberations and workshop were organized by Central TB Division (CTD), Ministry of Health and Family Welfare (MoHFW), Government of India (GoI) with technical and organizational support from World Health Organization Country Office for India (WCO India) in July 2015 at New Delhi. The deliberations and workshop involved various stakeholders, extensive review of literature including global guidelines and aligning to the approval of its use by the Apex Committee under the MoHFW, GoI for Supervising Clinical Trials on New Chemical Entities in light of the directions of the Honourable Supreme Court of India. Based on this apex committee approval, the permission to import finished formulation of the new drugs was issued by Drugs Controller General of India (DCGI), Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services (DGHS), GoI.

We express our gratitude to Shri Bhanu Pratap Sharma – Secretary, MoHFW, GoI; Dr Soumya Swaminathan – Secretary, Dept. of Health Research, GoI & Director General (DG), Indian Council for Medical Research; Dr Jagdish Prasad – DGHS, MoHFW, GoI; Shri Anshu Prakash – Joint Secretary Public Health, MoHFW, GoI; Dr BD Athani – Special DG, DGHS; Dr GN Singh – DCGI, DGHS; Dr Henk Bekedam – WHO Representative to India; Dr Prakin Suchaxaya – Coordinator Health Programmes (WHO India) and Dr Sunil D Khaparde – Deputy Director General (DDG)-TB, CTD, GoI for providing leadership, encouragement and support to the core team in this endeavour of introducing bedaquiline under RNTCP PMDT for augmenting management of drug-resistant TB (DR-TB) in India.

The core team from Central TB Division, National Institute for Research in Tuberculosis Chennai and WCO India took the lead in this process. Premier institutions in India, namely National Institute of TB and Respiratory Diseases New Delhi, National TB Institute Bangalore, BJ Medical College Ahmedabad, Rajan Babu Institute for Pulmonary Medicine & Tuberculosis New Delhi, KEM Hospital Mumbai, Guwahati Medical College Assam and Pharmacovigilance Programme of India contributed significantly to the process. Eminent experts from the Global TB Programme, WHO Headquarters Geneva – Dr Christian Leinhardt, Dr Ernesto Jaramillo, Dr Fraser Wares and Dr Dennis Falzon provided technical inputs in facilitating the process and developing this document. International experts: from South Africa – Dr Norbert Ndjeka, Dr F Conradie; from USA – Dr J Furin, Dr Y Mukadi and from France – Dr D Marigot-Outtandy shared their valuable programmatic and clinical experience of introducing bedaquiline (BDQ) in their practice areas respectively, during the national workshop at New Delhi. WCO India provided funding support to this initiative through their developmental partners USAID and the Lilly MDR-TB Partnership supported by Eli Lilly and Company. Johnsons and Johnsons Co. India (Janssen & Janssen Co.) and USAID have agreed to extend initial patient courses of BDQ drug to RNTCP India through their donation programme.

We acknowledge the valuable contribution of eminent experts and officials from the above institutes and organizations, all participants of the workshop and also those experts who reviewed this guideline and provided inputs for its finalization. Special appreciation is due for the medical consultants of WHO–RNTCP technical assistance network for their contribution, particularly in updating the PMDT records and reports including NIKSHAY, to incorporate the technical and operational changes with integration of BDQ within the existing PMDT guidelines. These changes have been incorporated in this guideline. The communications team at WCO India has provided crucial support in editing, formatting and designing this document and we thank them for their efficient efforts.

Overall coordination for developing this document was done by Dr Malik Parmar, National Professional Officer–DR-TB (WHO India) and Dr Ranjani Ramachandran, National Professional Officer – Labs (WHO India).

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The guidelines were reviewed, edited and further enriched by (in alphabetical order): Dr A Bhatnagar, Dr A Khanna, Dr A Sreenivas, Dr B Thomas, Dr B Vadera, Dr C Lienhardt, Dr D Behera, Dr E Jaramillo, Mr E Thanaraj, Dr F Wares, Dr I Syed, Dr J Jaju, Dr K Rade, Dr M Ghedia, Dr M Gupta, Dr N Kshirsagar, Dr P Kumar, Dr R Sarin, Dr R Singla, Dr R Solanki, Dr S Chadha, Dr S Chandra, Dr S Sharma, Dr S Swaminathan and Mr V Kalaiselvan. These contributions are appreciatively acknowledged.

This guideline are consistent with the WHO interim policy guidance on the use of bedaquiline in the treatment of MDR-TB, WHO document on Implementation Plan for Introduction of bedaquiline for the treatment of MDR-TB at country level, Companion Handbook to WHO Guidelines on PMDT and aligned with RNTCP PMDT Guidelines of India. The technical and operational aspects in this guideline are intended to complement the existing RNTCP Guidelines for PMDT in India for smooth introduction of BDQ under conditional access for management of DR-TB under RNTCP PMDT in India.

This guideline would be implemented by the initial identified sites to gain and document experience on feasibility, safety monitoring and enhancement in interim treatment outcomes of DR-TB patients under RNTCP PMDT to further guide the country on its refinement and extension to other sites in India.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
Am	amikacin
Amx/Clv	amoxicillin/clavulanate
ARV	antiretroviral
AST	aspartate aminotransferase
BDQ	bedaquiline
Cfz	clofazimine
Clr	clarithromycin
Cm	capreomycin
CP	continuation phase
Cs	cycloserine
CTD	Central TB Division
DAIDS	Division of AIDS
DCGI	Drugs Controller General of India
DDG	Deputy Director General
DG	Director General
DGHS	Directorate General of Health Services
DOTS	Directly Observed Treatment Short-course
DR-TB	drug-resistant tuberculosis
DSMC	data safety monitoring committee
DST	drug susceptibility testing
E	ethambutol
Eto	ethionamide
FDA	Food and Drug Administration
FQ	fluoroquinolone
Gfx	gatifloxacin
GoI	Government of India
H	isoniazid
hINH	high dose isoniazid
ICH	International Conference on Harmonization

IP	intensive phase
Ipm	imipenem
IRL	intermediate reference laboratory
Km	kanamycin
LFT	liver function test
Lfx	levofloxacin
LPA	line probe assay
Lzd	linezolid
MDR-TB	multi-drug resistant TB
Mfx	moxifloxacin
MGIT	mycobacteria growth indicator tube
MoHFW	Ministry of Health and Family Welfare
NIRT	National Institute for Research in Tuberculosis
NRL	national reference laboratory
OBR	Optimized Background Regimen
Ofx	ofloxacin
PAS	p-aminosalicylic acid
PK/PD	pharmacokinetic/pharmacodynamic
PMDT	programmatic management of drug-resistant tuberculosis
PQC	product quality compliance
PSM	procurement and supply management
Pto	protionamide
R	rifampicin
RNTCP	Revised National Tuberculosis Control Programme
RR-TB	rifampicin-resistant tuberculosis
SAE	serious adverse event
SLDST	second-line drug susceptibility testing
SLI	second-line injectables
STR	standardized treatment regimen
TB	tuberculosis
Thz	thioacetazone
Trd	terizidone
ULN	upper limit of normal
WCO	World Health Organization Country Office for India
WHO	World Health Organization
XDR-TB	extensively-drug resistant TB
Z	pyrazinamide

1. INTRODUCTION

The emergence of drug resistance is a major threat to global tuberculosis (TB) care and control. Multi-drug resistant TB (MDR-TB) is defined as resistance to isoniazid (H) and rifampicin (R) with or without resistance to other first-line drugs. Additional resistance to fluoroquinolones (FQs) and second-line injectables (SLIs), either alone or together, are considered to be advanced forms of MDR-TB.

About 3% of new TB patients and about 20% of previously treated patients in the world have multi-drug resistant strains, i.e. resistant to both H and R (1). The World Health Organization (WHO) estimates that 480 000 new cases of MDR-TB emerged worldwide in 2014. Among patients with pulmonary TB who were notified in 2014, an estimated 300 000 had MDR-TB. More than half of these estimated patients were from India, China and the Russian Federation. Extensively drug-resistant TB (XDR-TB) i.e. MDR-TB patient with additional resistance to any FQ and any SLI, has been reported by 105 countries. On average, an estimated 9.7% of people with MDR-TB have XDR-TB. Only 50% of patients with MDR-TB were successfully treated, largely as a result of high mortality and loss to follow up. Of 2685 XDR-TB patients reported in 41 countries in the 2012 cohort, overall only 682 (26%) completed their treatment successfully and 809 (30%) patients died (1). Studies conducted in India by Tuberculosis Research Centre and National Tuberculosis Institute have found MDR-TB levels of 2–3% in new cases and around 12–17% in previously treated cases (2–4). Although the proportion is small, the number of persons with MDR-TB is sizeable in numbers. WHO has estimated that in 2014, 71 000 cases of MDR-TB emerged from among the notified TB cases in India (1).

The national Guidelines for Programmatic Management of Drug-resistant Tuberculosis (PMDT) in India offers an integrated drug-resistant tuberculosis (DR-TB) treatment algorithm with standard treatment regimen for MDR-TB and XDR-TB designed in accordance with WHO Guidelines for PMDT (2011 updates). Further, rifampicin-resistant tuberculosis (RR-TB) patients detected using WHO-endorsed rapid molecular tests are treated with the standard regimen for MDR-TB. The algorithm also offers scope for modifying the standard regimen for MDR-TB in cases with additional resistance to FQ or SLI based on second-line drug susceptibility testing (SLDST) at baselines, wherever available (5). The current treatment success rates for MDR-TB with FQ or SLI resistance and XDR-TB are around 27–35% with a mortality of nearly 50%. Adding bedaquiline (BDQ) to the optimized background regimen (OBR) has shown significant benefit in improving survival and treatment outcomes in such patients under clinical and programmatic settings (6–9).

Bedaquiline (BDQ): This is a new class of drug, diarylquinoline that specifically targets mycobacterial ATP synthase, an enzyme essential for the supply of energy to Mycobacterium tuberculosis and most other mycobacteria. Strong bactericidal and sterilizing activities against M. tuberculosis have been shown in pre-clinical, laboratory and animal experiments. The drug has a high volume of distribution, with extensive tissue distribution, highly bound to plasma proteins and hepatically metabolized. The drug has an

extended half-life, which means that it is still present in the plasma up to 5.5 months post stopping BDQ. The dosing schedule has been established after extensive pharmacokinetic / pharmacodynamic (PK/PD) studies in animals and humans and hence needs to be administered as per the manufacturer's advice (Appendix 1).

BDQ has been granted accelerated approval by the United States Food and Drug Administration (US FDA), based on Phase IIB data, in December 2012 (10). BDQ demonstrates no cross-resistance with existing first- and second-line anti-TB drugs and has shown significant benefits in improving the time to culture conversion in MDR-TB patients (11–13). In June 2013, WHO published interim policy guidance for the use of BDQ in conjunction with the WHO-recommended MDR-TB treatments (14). The guidance recommends that BDQ may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB under the following conditions:

- When an effective treatment regimen containing four second-line drugs in addition to pyrazinamide (Z) according to WHO recommendations cannot be designed;
- When there is documented evidence of resistance to any FQ in addition to multidrug resistance (14, 15).

The drug has been available to individual patients under “compassionate use” with pre-approval of Drugs Controller General of India (DCGI) upon request from the treating physician, who submits patient details fulfilling the US FDA criteria for accessing the drug from Jansen as donation.

2. APPROVAL FOR USE OF BEDAQUILINE UNDER CONDITIONAL ACCESS THROUGH RNTCP PMDT IN INDIA

BDQ has been given approval for use along with the background regimen under conditional access through the Revised National Tuberculosis Control Programme (RNTCP) PMDT services in India. BDQ will continue to be available for "compassionate use" in the country till such time that the expanded access programme is rolled out under RNTCP.

2.1 Apex Committee approval in light of directions of the Honorable Supreme Court of India

The Apex Committee under the Ministry of Health and Family Welfare for supervising clinical trials on new chemical entities in the light of directions of the Honorable Supreme Court of India has approved the use of BDQ under RNTCP PMDT through conditional access.

The approval dated 24 December 2014 reads as follows:

"Drug name: Bedaquiline (100 mg);
Indication: Indicated in adults aged 18 or over 18 years as part of combination therapy of pulmonary tuberculosis (TB) due to multi-drug tuberculosis (MDR) Mycobacterium tuberculosis;

Technical Committee recommendations: The committee observed that BDQ is approved in US, EU and other major countries. BDQ is indicated for the treatment of pulmonary tuberculosis due to multi-drug resistant tuberculosis (MDR-TB), for which presently no effective therapy is available in India. MDRTB is a serious condition with high mortality and it is disease of special relevance in the Indian health scenario. Therefore, the Committee recommended waiver of local clinical trials at this stage and approval of the drug BDQ with restriction that it shall be approved for use under RNTCP framework for conditional access through the PMDT programme for treatment of MDR-TB patients only" (16).

The Apex committee deliberated upon the proposal and concurred with the recommendations of the Technical Committee.

2.2 Permission to import finished formulation of the new drug

Following the Apex committee approval, the DCGI granted an import license to Janssen (M/s. Johnson & Johnson Limited, India) dated 04 January 2015, F.No. 12-73/2013-DC (Pt-A), that reads "Bedaquiline Fumarate uncoated tablets 100 mg to be used in adults >18 years as part of combination therapy of pulmonary tuberculosis due to multi-drug resistant Mycobacterium tuberculosis when an effective treatment regimen cannot be otherwise provided. The label on the immediate container of the drug as well as the packing in which the container is kept should have the following warning;

WARNING: For use in the Revised National Tuberculosis Control Programme (RNCTP).

The drug has been approved for conditional access, i.e. it shall be used under RNTCP framework for conditional access through the PMDT programme for treatment of MDR-TB patients only. Janssen has been directed to do post-marketing surveillance for periodic safety review every 6 months for the first 2 years and thereafter annually for the next 2 years. All adverse reactions shall be reported to DCGI and any regulatory action shall be complied with. Janssen would supply the drugs to RNTCP only after submission of a testing/analysis report from Indian Pharmacopoeia Commission, Ghaziabad to DCGI. Janssen would also develop a study protocol for post-marketing surveillance and submit within 3 months of supply of drugs to RNTCP (17).

3. BEDAQUILINE INTRODUCTION UNDER RNTCP

Six RNTCP DR-TB centres have been identified as initial sites for the introduction of BDQ under the RNTCP PMDT through conditional access. All identified DR-TB centres have the capacity to manage complicated DR-TB patients and laboratory support for first- and second-line drug susceptibility testing (DST) as per WHO standards through the attached intermediate or national reference culture-drug susceptibility testing (C-DST) laboratory.

These centres are as follows:

Location	**DR-TB Centre & Laboratory**
Ahmedabad	B.J. Medical College & Hospital & IRL, Ahmedabad
Chennai	Govt. Hospital for Thoracic Medicine & NRL National Institute for Research in Tuberculosis (NIRT), Chennai
Guwahati	Guwahati Medical College (GMC), Guwahati & IRL, Guwahati
Mumbai	KEM Hospital & C-DST Lab JJ Hospital, Mumbai
New Delhi	National Institute of Tuberculosis and Respiratory Diseases (NITRD) & NRL NITRD, New Delhi
New Delhi	Rajan Babu Institute of Pulmonary Tuberculosis (RBIPMT) & IRL New Delhi Tuberculosis Center (NDTB), Delhi

IRL – intermediate reference laboratory; NRL – national reference laboratory

The physicians at these DR-TB centres are responsible for the management of patients who would be treated using BDQ, as well as for safety monitoring. As a special requirement, DR-TB centres should make available or have referral linkages with a consultant cardiologist for stringent ECG/cardiac monitoring as a safety monitoring requirement for BDQ-containing regimen, and a general laboratory for close monitoring of haematological and biochemical parameters for management of adverse events.

4. CRITERIA FOR PATIENTS TO RECEIVE BEDAQUILINE

Basic criteria

The criteria for patients to receive BDQ as approved by the Apex Committee is: adults aged > 18 years having pulmonary MDR-TB.

Additional requirements

- Females should neither be pregnant nor be using effective non-hormone-based birth control methods. They should be willing to continue practicing birth control methods throughout the treatment period, or have been post-menopausal for the past 2 years.
- Patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation.

Reasons for exclusion

Patients may not be administered BDQ if he or she:

- can be treated with a regimen designed in adherence to principles of designing a WHO-recommended MDR-TB regimen typically composed of at least pyrazinamide and four second-line drugs that are considered to be effective based on drug susceptibility test and/or previous use and/or drug resistance surveillance data
- is currently having uncontrolled cardiac arrhythmia that requires medication;
- has any of the following QT/QTc interval (Appendix 2) characteristics at screening:
  a. a marked prolongation of QT/QTc interval, e.g. repeated demonstration of QTcF (Fredericia correction) interval > 450 ms (14, 15);
     - a history of additional risk factors for Torsade de Pointes, e.g. heart failure, hypokalaemia, family history of long QT syndrome (14, 15);
- has evidence of chorioretinitis, optic neuritis, or uveitis at screening which precludes long term linezolid (Lzd) therapy;
- Patients with following laboratory abnormalities (DAIDS Grading of Adverse Events) (18):
  - Creatinine grade 2 or greater, i.e. >1.5 times the upper limit of normal (ULN);
  - Hemoglobin grade 4 (<6.5 gm/dL);
  - Platelet count grade 3 or greater (≤ 49 999/mm3);
  - Absolute neutrophils count grade 3 or greater (≤ 749/mm3);
  - Aspartate aminotransferase (AST) grade 2 or greater (>2.5 times ULN);
  - Alanine aminotransferase (ALT) grade 2 or greater (>2.5 times ULN);
  - Total bilirubin grade 2 or greater (>1.6 times ULN);
  - Lipase grade 2 (with no signs or symptoms of pancreatitis) or greater (>1.5 time ULN).

Note: If the results of the serum chemistry panel, haematology or urinalysis are outside the normal reference ranges (including the above listed parameters), the patient may still be considered if the physician judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable. Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to a patient receiving BDQ.

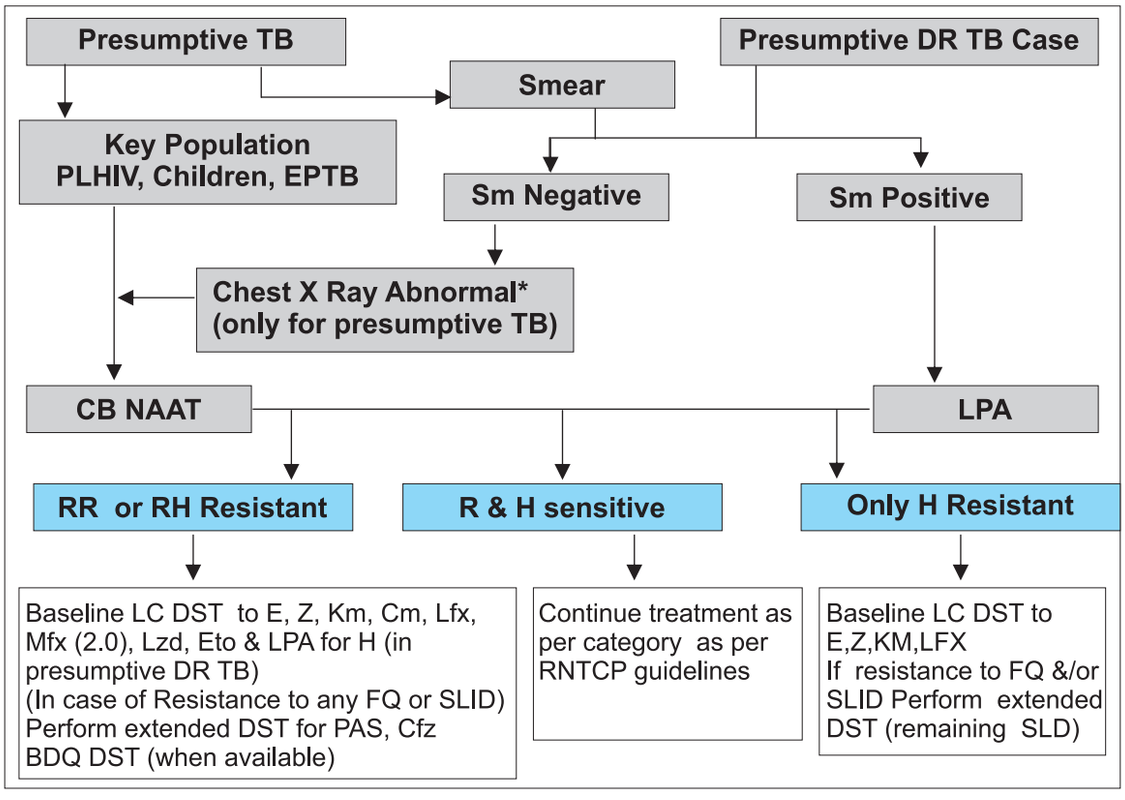
Patients who could not be initiated on a BDQ containing regimen would have the DST results for all first line and most of the second line drugs. Hence, it would be rational to respect the DST results and offer them the treatment regimen tailored as per the RNTCP PMDT DST guided treatment guidelines. These regimens adhere to the principles of designing a WHO-recommended MDR-TB regimen. The DST guided treatment guidelines were evolved through a national consultative process in August 2014, with eminent experts from all sectors. This approach would be applicable to these selected six sites as the laboratory support is available for first and second-line drug susceptibility testing (DST) through the attached intermediate or national reference laboratories. This group of patients would serve as an opportunity for CTD to generate evidence on feasibility and effectiveness of the DST guided approach in various forms of DR-TB, as recommended by national expert committee. This will also enable RNTCP to address this long standing challenge in improving treatment outcomes in variants of DR-TB cases in India.

5. DIAGNOSIS OF MDR-TB/RR-TB CASES WITH ADDITIONAL RESISTANCE TO FQ AND / OR SLI

All patients diagnosed as MDR-TB/RR-TB using various technologies as per RNTCP PMDT Guidelines would be offered baseline SLDST using liquid culture for Lfx (1.5), Mfx (2.0), Km, Cm, E, Eto, Lzd and Z along with LPA for H on sample/culture isolate (reported as KatG or inhA mutation to decide on use of hINH). Extended SLDST panel will be performed on PAS, Cfz and BDQ as soon as introduced within the programme. The SLDST results will be used for decisions on patient selection for BDQ and on use of appropriate FQ or SLI in the OBR. All culture isolates will be stored for all patients put on BDQ containing regimen and DST for BDQ (phenotypic or molecular) will be performed on all culture positive isolates at baseline and follow up once it becomes available to the programme.

This is reflected in the diagnostic algorithm below:

Diagnostic Algorithm



- **If RR by CBNAAT, in addition to other drugs, H resistance (by LPA) to be done and treatment modified accordingly.**
- **For samples reported by LPA- report must mention- H resistance by Kat G or INH A mutation.**
- **For new* patients diagnosed as TB with RR by CBNAAT– a second CBNAAT test will be offered along with Liquid culture DST**

* Those who do not fit in the definition of presumptive DRTB case

6. PRE-TREATMENT EVALUATION OF PATIENTS

All eligible patients would be subjected to a thorough pre-treatment evaluation at the DR-TB centres as per the RNTCP PMDT Guidelines. In addition, the following specific pre-treatment evaluations would be added for patients eligible for BDQ containing regimen:

- Baseline (0 months) culture isolate will be stored for subsequent DST for BDQ when it is standardized;
- Serum electrolytes
- Serum magnesium, calcium, lipase;
- Urine gravindex (for all women in the child-bearing age group);
- ECG in 12 leads with long lead;
- Ophthalmologist opinion – rule out chorioretinitis/uveitis;
- Surgical evaluation.

Each of the DR-TB centres must ensure that the necessary laboratory capacity and consultancy services from various specialists are available in the sites, either in-house or through an outsourced mechanism supported under institutional/state govt. mechanisms.

7. TREATMENT INITIATION

While waiting for the results of baseline SLDST as detailed above, all patients diagnosed as MDR-TB/RR-TB using various technologies will be initiated on standard regimen for MDR-TB as per RNTCP PMDT Guidelines. Once the results of baseline SLDST are available, the patients eligible and consented to be treated with BDQ containing regimen will be identified and an appropriate regimen will be designed by the DR TB center committee as described in the next chapter.

All eligible patients need to be offered counseling along with a patient education booklet (Appendix 18) which will give details of the nature and duration of treatment including information on the new drug BDQ; need for regular treatment; possible side-effects of these drugs; drugs to be avoided with BDQ and the consequences of irregular treatment or premature termination of treatment. Female patients will receive special counseling on family planning. After this, a written informed consent (Appendix 19) will be obtained from patients before administration of BDQ containing regimen.

The RNTCP PMDT treatment register (Appendix 10) has been updated. Once the BDQ CAP is initiated, this new format of the register will be used for all DR-TB patients by the concerned DR-TB centers. The patient would be registered in this updated register and all necessary records would be maintained as detailed in the relevant section and appendices in this document.

All patients would be counseled and managed indoor for a mandatory period of 2 weeks (15 days) to complete the initial 2 weeks of BDQ doses. The final decision of further duration of indoor management of the patients rests with the DR-TB Centre committee and must be well-documented for every patient. After discharge the treatment will be continued on ambulatory basis as per RNTCP PMDT guidelines with strict adherence of treatment and the follow up schedule.

All measures for airborne infection control must be implemented as per the national AIC guidelines while managing all TB patients.

8. REGIMEN, DOSAGE AND ADMINISTRATION

The principles of designing a WHO-recommended MDR-TB regimen will be adhered to. Such a regimen is typically composed of at least pyrazinamide and four second-line drugs that are considered to be effective based on drug susceptibility test and/or previous use and/or drug resistance surveillance data.

BDQ is indicated if such a regimen is not feasible because of:

(i) in vitro resistance to fluoroquinolones and/or second-line injectable drugs;
(ii) known adverse reaction, poor tolerance or contraindication to any component of the combination regimen; or
(iii) unavailability or lack of a guaranteed supply of a drug(s).

Accordingly, the following subgroups of patients will be eligible for BDQ:-

1. MDR/RR-TB with resistance to all FQ
2. MDR/RR-TB with resistance to all SLI
3. XDR-TB
    a. XDR-TB (All FQ & All SLI resistant)
    b. XDR-TB (All FQ and any SLI resistant)
    c. XDR-TB (All SLI & any FQ resistant)
    d. XDR-TB (Any FQ & any SLI resistant)
4. Treatment failures of MDR-TB + FQ/SLI resistance
5. Treatment failures of XDR-TB

The BDQ containing regimen in context of MDR-TB with additional resistance to all FQ or all SLI as well as XDR-TB (all sub-groups) would contain BDQ + at least four second-line drugs considered to be effective (choice of drugs should be based on DST pattern in descending order)

1. SLI (Group 2): Km / Cm
2. FQ (Group 3): Lfx / Mfx
3. Two bacteriostatic drugs (Group 4): Eto, Cs, PAS*
4. Group 5: Lzd / Cfz / hINH / Clr
5. Z if sensitive

*because of GI side effects of PAS, as far as possible, it will be avoided in BDQ containing regimen

All patients will receive Tab. BDQ 400 mg once daily for the first 2 weeks and 200 mg three times a week (with at least 48 hours between doses) for the following 22 weeks, in combination with an optimized background regimen (OBR) of selected second-line drugs used to treat MDR-TB/RR-TB with additional FQ and/or SLI resistance in RNTCP. The OBR will be continued beyond the 24 weeks of BDQ administration for the RNTCP recommended duration of treatment. As mentioned above, the OBR will be designed as per RNTCP PMDT guidelines and WHO recommendations for designing an OBR for concomitant use with BDQ for avoiding drugs that are likely to cause increased toxicity when administered in combination with BDQ.

- Week 0–2: BDQ 400 mg (4 tablets of 100 mg) daily (7 days per week) + OBR
- Week 3–24: BDQ 200 mg (2 tablets of 100 mg) 3 times per week (with at least 48 hours between doses) for a total dose of 600 mg per week + OBR.
- Week 25 (start of month 7) to end of treatment: Continue other second-line anti-TB drugs only as per RNTCP recommendations.

If taking a light meal with BDQ and other anti-TB drugs, patients should not consume milk-containing products at the same time, as the calcium in these can decrease the absorption of FQs. Also, large fatty meals should be avoided as these can impair absorption of some of the other anti-TB drugs (Cs, H, etc).

BDQ will be provided through RNTCP once the patient has been confirmed as eligible by the DR-TB centre committee and has consented. The dosage of BDQ would apply to all weight bands while the dosage of other drugs in the OBR would be as per the weight bands in accordance to the RNTCP PMDT guidelines.

The decision on drugs to be included in OBR would be based on the following conditions:

Resistance pattern	**Subgroup**	**Intensive phase**	**Continuation phase**
Regimen with Bedaquiline for MDR-TB + FQ/SLI resistance			
MDR/RR + resistance to all FQ		(6) BDQ + (6-12) Km Eto Cs E* Z* Lzd	(18) Eto Cs E* Lzd
MDR/RR+ resistance to all SLI		(6) BDQ + (6-12) Lfx Eto Cs E* Z* Lzd	(18) Lfx Eto Cs E* Lzd
Regimen with Bedaquiline for XDR-TB			
XDR TB	Resistance to all FQ and all SLI	(6) BDQ + (6-12) E* Z* Eto Cs Lzd Cfz Amx-clv hINH**	(18) E* Eto Cs Lzd Cfz Amx-clv hINH**
	Resistance to any FQ and all SLI	(6) BDQ + (6-12) Lfx*/Mfx* E* Z* Eto Cs Lzd Cfz	(18) Lfx*/Mfx* E* Eto Cs Lzd Cfz
	Resistance to all FQ and any SLI	(6) BDQ + (6-12) Km*/Cm*E* Z* Eto Cs Lzd Cfz	(18) E*Eto Cs Lzd Cfz
	Resistance to any FQ & any SLI	(6) BDQ + (6-12) Km*/Cm* Lfx*/Mfx* E* Z* Eto Cs Lzd Cfz	(18 m) Lfx*/Mfx* E* Eto Cs Lzd Cfz

Regimen with Bedaquiline for failures of regimen for MDR-TB ± FQ/SLI resistance			
Failures of second line regimen for MDR TB ± FQ/SLI resistance [§] (BDQ not administered previously)	Persistent culture positive or reversion but no resistance amplification (FQ and/or SLI sensitive)	(6) BDQ + (6-12) design treatment regimen for XDR TB	Stop BDQ after 6m and SLI after 6-12m (18m) continue rest of the oral drugs from IP
	Persistent Culture positive or reversion with resistance amplification	(6) BDQ + (6-12) design treatment regimen for XDR TB (Omit SLI and/or FQ to which patient is resistant).	Stop BDQ after 6m and SLI after 6-12m (18m) continue rest of the oral drugs from IP
Regimen with Bedaquiline for failure of regimen for XDR-TB			
Failures of second line regimen for XDR TB[§] (BDQ not administered previously)	Persistent Culture positive: with/without Resistance amplification	BDQ containing regimen may be designed if composed of at least Z and four second-line drugs considered to be effective based on drug susceptibility test and/or previous use and/or drug resistance surveillance data minimum 5 drug and maximum 8-9 drug regimen	Stop BDQ after 6m and SLI after IP 18(m) continue rest of the oral drugs from IP

*If sensitive; ** hINH based on LC/LPA report; §If patient is given Mfx Cfz and BDQ, monitor ECG more frequently

BDQ administration:

It is important that BDQ be taken with food. The management of missed doses are described later. After their last dose of BDQ, all patients will continue to take their OBR under the supervision of their treating physician in accordance with RNTCP PMDT guidelines. Sputum culture should continue throughout treatment and DST results used to guide necessary changes in the OBR.

Management of patients found to be ineligible or who did not consent for BDQ:

Patients who could not be initiated on a BDQ containing regimen (either found ineligible or who did not consent for BDQ) would be treated with treatment regimen tailored as per the RNTCP PMDT DST guided treatment guidelines. These regimens are as follows:

Resistance pattern	Intensive phase	Continuation phase
Regimen for H mono/poly resistant TB*		
R sensitive H resistant[1] TB & DST of SEZ not known	(3-6) Km Lfx R E Z *(modify treatment based on baseline DST report to E, Z, Km, Cm, Lfx, Mfx)*	(6) Lfx R E Z
Regimen for MDR/RR-TB		
RR-TB + H sensitive or unknown[2]	(6-9) Km Lfx Eto Cs Z E H	(18) Lfx Eto Cs E H
MDR TB[1]	(6-9) Km Lfx Eto Cs Z E *(Modify treatment based on the level of H resistance as per the footnote)*	(18) Lfx Eto Cs E
MDR or RR-TB + E resistance[1,2]	(6-9) Km Lfx Eto Cs Z	(18) Lfx Eto Cs
MDR or RR-TB + Z resistance[1,2]	(6-9) Km Lfx Eto Cs E	(18) Lfx Eto Cs E
MDR or RR-TB + E + Z resistance[1,2]	(6-9) Km Lfx Eto Cs PAS	(18) Lfx Eto Cs PAS
Regimen for MDR/RR-TB + FQ/SLI resistance		
MDR or RR-TB + Lfx resistance	(6-9) Km Mfx Eto Cs Z E PAS Cfz	(18) Mfx Eto Cs E PAS Cfz
MDR or RR-TB + Mfx resistance	(6-9) Km Lfx Eto Cs Z E PAS Cfz	(18) Lfx Eto Cs E PAS Cfz
MDR or RR-TB + resistance to all FQ	(6-12) Km Eto Cs Z E PAS Cfz Lzd	(18) Eto Cs E PAS Cfz Lzd
MDR or RR-TB + Km resistance	(6-9) Cm Lfx Eto Cs Z E	(18) Lfx Eto Cs E
MDR or RR-TB + resistance to all SLI	(6-12) Lfx Eto Cs Z E PAS Cfz Lzd	(18) Lfx Eto Cs E PAS Cfz Lzd
Regimen for XDR-TB		
XDR	(6-12) Cm PAS Mfx hINH Cfz Lzd Amx/Clv	(18) PAS Mfx hINH Cfz Lzd Amx/Clv
Regimen for mixed pattern resistance		
Mixed pattern resistance	(6-9) Km Lfx Eto Cs Z E	18 Lfx Eto Cs E

(any FLD/SLI/FQ, Eto, PAS, Lzd, Cfz)[3]	**Modify based on resistance pattern:** Use any SLI and FQ as per recommendation above. Consider other oral drugs as per DST pattern and **Duration:** *If SLI & FQ are included:* Minimum 6 Drugs in IP. *If SLI and /or FQ are not included:* Minimum 8-9 drugs are to be given in IP. *In pre-XDR/XDR patients, duration of IP will be 6-12 months*	**Duration:** If SLI & FQ are included: Minimum 4 Drugs in CP If SLI and /or FQ are not included: Minimum 7-8 drugs in CP

*This regimen will be scaled up when DST guided treatment guidelines will be implemented for the entire country

1. For H resistance, decision on use of H in the regimen depends on following:
   - If High level resistance detected by Liquid culture - omit H.
   - If low level resistance detected by Liquid culture - add hINH.
   - If LPA reports H resistance by Kat G mutation- Omit H
   - If LPA reports H resistance by inhA mutation- Use hINH. Eto in the treatment regimen will be replaced with PAS

2. If RR by CBNAAT, add H in the standard doses to the treatment regimen till results of LPA or Liquid culture DST are known.
   - For new patients diagnosed as TB and RR by CBNAAT, put up both a repeat CBNAAT & send sample for liquid culture. Till then - following will be the treatment:
     - If second CBNAAT also shows RR - start standard MDR-TB regimen with H till the results from culture DST are known. Await DST results to H & SLDST on the liquid culture.
     - If second CBNAAT shows R sensitive - start regimen for new TB cases and wait for report of Liquid culture DST.
       - o If Liquid culture shows R sensitive - continue regimen for new TB cases.
       - o If Liquid culture shows R resistance-refer the patient to DR TB center committee for clinical, radiological & microbiological assessment and decision regarding starting standard MDR-TB regimen with baseline SLDST or continuing regimen for new TB cases depending upon the response to treatment given so far.

3. For mixed resistance pattern, oral drugs in following sequence of preference :-
   - Z (if sensitive), E, Eto, Cs, PAS, Cfz, Lzd, Amx/clv, hINH & Clr

The regimen designing/modification will be the prerogative of the DR TB center committee only.

9. FOLLOW-UP MONITORING OF PATIENTS

Once the BDQ-containing regimen is started, the patient will be monitored for QTc prolongation which will prompt a regular ECG and other safety monitoring as shown in the table below. A cardiologist must be available for expert interpretation of ECG. All patients enrolled on BDQ-containing regimen would be closely monitored by the DR-TB Centre or district hospital physician as per the schedule below.

	2 wk	1 m	2 m	3 m	4 m	5 m	6 m	7 m	9 m	12 m	15 m	18 m	21 m	24 m	30 m	36 m
Clinical evaluation	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Weight		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Sputum culture by MGIT	Wkly		√	√	√	√	√	√	√	√	√	√	√	√	√	√
DST by MGIT				√			√									
CBC /platelets	Wkly		√	√	√	√	√	√	√	√	√	√	√	√	√	√
CXR							√			√		√		√		√
LFT		√	√	√	√	√	√		√	√	√	√	√	√	√	√
S.Creatinine		√	√	√	√	√	√		√	√	√	√	√	√	√	√
S.Electrolyte		√	√	√	√	√	√									
S. Lipase	√															
Thyroid Function							√									
ECG*	√*	√*	√*	√*	√	√	√	√	√	√	√	√	√	√		√
K, Mg, Ca		√	√	√	√	√	√									
Urine Gravindex		√	√	√	√	√	√									

*ECG to be done daily (first 2 weeks), weekly (for 3 months) then monthly

Sociological/psychological evaluation for treatment adherence, reasons for non-adherence, depression status, quality of life, motivation and counselling will be done. Referral services for care and rehabilitation will be provided if required.

10. DRUG PROCUREMENT, SUPPLY AND QUALITY ASSURANCE

10.1 Drug procurement

RNTCP will obtain patient courses of BDQ through Janssen and supply to the selected sites. Rest of the drugs in the background regimen will be from RNTCP. The procurement and supply management (PSM) will be through the regular mechanism of RNTCP like other second-line drugs.

10.2 Product quality compliance

Product quality compliance (PQC) is defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or drug delivery system. Timely, accurate and complete reporting and analysis of PQC information are crucial for the protection of patients, investigators and the company, and are mandated by regulatory agencies worldwide. Janssen has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. All initial PQCs must be reported to RNTCP and Janssen as soon as possible after being made aware of the event. If the defect is combined with an adverse event (AE), the physician must report the PQC according to the AE reporting timelines in the relevant section on AEs given as an annexure to this document. A sample of the suspected product should be maintained for further investigation.

10.3 Supply chain management

BDQ will be supplied to the state drug stores from Janssen in cartons containing white high-density polyethylene (HDPE) containers comprising of 188 tablets of 100 mg each for oral administration. This is enough to treat one patient for the 6-month period indicated. It will have a shelf-life of 24 months and will need to be stored at 25 ºC (15–30 ºC). Tablets dispensed outside the original container should be stored in a tight light-resistant container with an expiration date that should not exceed 3 months (19). BDQ bottles will be issued by the state drug stores along with the other second-line drugs through the DR-TB centres. The BDQ bottle will be opened at the DR-TB centre where the patient is given the first dose. On discharge, the patient will carry the bottle and hand it over to the treatment supporter under supervision of the DR-TB/TB-HIV supervisor, to be included in the first monthly Type B box for the intensive phase containing SLI and Z that is issued to the treatment supporter. The bottle will remain under custody of the treatment supervisor up to 24 weeks, while the Type B box will be issued on a monthly basis. In the event of lost to follow up or death or discontinuation of BDQ for any reason, the leftover tablets will be returned back to the State Drug Stores for reconstitution. The existing records and reporting formats for second-line drug supply chain management will be used to enter details about BDQ storage, issue and reconstitution in conjunction with other second-line drugs.

11 ADVERSE EVENTS OF BEDAQUILINE

Specific toxicities

Monitoring for specific toxicities is based upon target organs defined in preclinical toxicity studies. For monitoring the specific toxicities related to second-line TB drugs, the RNTCP guidelines should be followed, e.g. eye care, audiometry.

Management of patients with AST and/or ALT elevations, amylase and/or lipase elevations, musculoskeletal system and cardiac muscle abnormalities, cardiac rhythm disturbances, gastrointestinal system disorders or other toxicities is enumerated below.

11.1 AST and/or ALT elevations

Management will be at the discretion of the physician, according to generally accepted medical practice standards.

- Grade 1 (>1.0 to <2.0 x ULN) or Grade 2 (>2.0 to <3.0 x ULN) AST or ALT elevation: Patients may continue BDQ. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.
- Grade 3 (>3.0 to <8.0 x ULN) or Grade 4 (>8.0 x ULN) AST or ALT elevation: Patients are allowed to temporarily discontinue treatment of the suspected causative agent (usually Eto, Z or PAS). AST, ALT and serum bilirubin should be monitored as frequently as necessary to manage the patient's condition.

If ALT and AST do not return to baseline, BDQ may be temporarily withheld for up to 2 weeks. Additional tests should be performed to evaluate the cause of hepatitis (e.g. hepatitis A, B, C). Liver enzymes, including serum bilirubin should be monitored as frequently as necessary to manage the patient's condition. If LFT improves, then the rest of the dosages of BDQ can be given. For patients who fail to show improvement in the clinical course and to return to baseline values of AST and ALT, it is recommended that the patient discontinue BDQ.

11.2 Amylase and/or lipase elevation

Management will be at the discretion of the physician, according to generally accepted medical practice standards.

- Grade 1 (>1.0 to <1.5 x ULN) or Grade 2 (>1.5 to <2.0 x ULN): Patients may continue BDQ and should be carefully evaluated and followed closely.
- Grade 3 (2.0 to <5.0 x ULN) or Grade 4 (> 5.0 x ULN): For asymptomatic grade 3 amylase elevations with no history or concomitant disease of pancreatitis, patients may continue BDQ but should be carefully evaluated and followed closely.

For confirmed grade 4 elevations of amylase and confirmed grade 3 or 4 elevations of lipase, it is recommended that the patient discontinue BDQ.

11.3 Musculoskeletal system and cardiac muscle abnormalities – myalgia

- Grade 1 (mild with no limitation of activity): Patients may continue BDQ and should be carefully evaluated and followed closely.
- Grade 2 (muscle tenderness at site other than injection site or with moderate impairment of activity), Grade 3 (severe muscle tenderness with marked impairment of activity) or Grade 4 (frank myonecrosis): It is recommended that the patient discontinue BDQ.

11.4 Cardiac rhythm disturbances

QT interval monitoring: An ECG should be obtained before initiation of treatment and daily for the first 2 weeks, then every 2 weeks for 3 months and then monthly. ECGs should be done at least weekly throughout the BDQ course if other QT prolonging drugs like FQ (Mfx, gatifloxacin [Gfx]), Cfz or macrolide antibacterial drugs (erythromycin, clarithromycin, azithromycin) are included in the regimen. Other drugs with additive or synergistic QT prolongation observed when BDQ is co-administered are those with serotonin 5-HT3 receptor antagonist (ondansteron), azole agents (ketoconazole, itraconazole, fluconazole), common ART drugs, antimalarials (quinine sulfate, chloroquine), some drugs used for psychiatric disorders (chlorpromazine, haloperidol, thioridazine) and drugs known to lower serum electrolytes. If possible, avoid the use of QT prolonging drugs with BDQ. If it is absolutely necessary to include a QT prolonging drug, increase ECG monitoring as described earlier.

QT prolongation can result in ventricular arrhythmias (Torsades de Pointes) and sudden death. It is therefore imperative that ECGs be used to monitor the QT interval regularly during BDQ use.

- Grade 1 (asymptomatic) or Grade 2 (asymptomatic, transient rhythm abnormality not requiring any treatment) cardiac rhythm disturbances: Patients may continue BDQ and should be carefully evaluated and followed closely.
- Grade 3 (recurrent, persistent, symptomatic arrhythmia requiring treatment) or Grade 4 (unstable dysrhythmia requiring hospitalization and treatment) cardiac rhythm disturbances: It is recommended that the patient discontinue BDQ.

A normal value for the corrected QTcF interval is less than 0.44 seconds (440 ms). Whenever an abnormal QTc value is found, the ECG and calculations should be repeated.

- A value greater than 440 ms is considered prolonged but does not need action until >450 ms.
- A value between 450 – 480 ms: Rule out other causes of prolonged QTc, before deciding to withhold BDQ.
- A value greater than 480 ms (or an increase of greater than 60 ms from baseline) should trigger the following actions:
    - Repeat ECG to confirm prolongation.
    - Check for serum K, Mg and Ca and correct the levels if found to be abnormal. Withhold BDQ until the electrolytes have normalized.
    - If the QTc interval is between 480 and 500 ms, the patient is stable and electrolytes are within normal values, repeat weekly ECGs to confirm that the QTc interval is stable.
    - If the QTc interval is > 500ms (confirmed by repeat ECG), DISCONTINUE BDQ and all other QTc-prolonging drugs in the regimen.

BDQ and all other QTc-prolonging drugs are to be discontinued if the patient develops a clinically significant ventricular arrhythmia. If BDQ is stopped for QTc prolongation, monitor ECGs at least weekly to confirm that the QTcF interval has returned to baseline. If syncope occurs, obtain an ECG to detect QT prolongation. Because of the long half-life of BDQ, if the ECG has QTc prolongation at week 24, ongoing weekly monitoring should take place until the QTc interval normalizes (even though the drug is no longer being given).

If a QTcF of greater than 500 ms is recorded and is confirmed by a repeat ECG, it is recommended that BDQ and all other QTc-prolonging drugs must be discontinued. Such patients must be closely monitored until the resolution of the prolonged QTcF. The physician should rule out other causes of QTc prolongation such as electrolyte imbalances and steps should be taken to remedy any underlying causes of such prolongation.

11.5 Gastrointestinal system disorders

Patients with grade 4 elevation of gastrointestinal parameters should be hospitalized and monitored closely. In case of grade 4 nausea (hospitalization required) or grade 4 vomiting (physiologic consequences requiring hospitalization or requiring parenteral nutrition), the patient's BDQ treatment should be discussed with the DR-TB centre committee.

11.6 Other toxicities

- Grade 1 or 2: Patients who develop grade 1 or 2 AE or laboratory toxicity may continue intake of BDQ.
- Grade 3 or 4: Patients who develop grade 3 or 4 AE or laboratory toxicity should be carefully evaluated by the physician. Patients may discontinue intake of BDQ if, in the opinion of the physician, the AE or laboratory toxicity poses a significant risk for the patient in case of continued treatment. Patients should be followed as appropriate until resolution of the AE or toxicity.

Refer DAIDS criteria for grades [18].

Patients should be monitored for the common side-effects of concomitant TB therapy, including decreased hearing, tinnitus, vision changes, dizziness, psychosis, depression, tremors, nausea, vomiting, diarrhoea, joint pain and renal function.

12 ADVERSE EVENT MONITORING AND REPORTING

Timely, accurate, and complete reporting and analysis of BDQ-related adverse events are required to be reported under the programme. This is crucial for the protection of the patients.

12.1 Adverse event definitions and classifications

Adverse event: An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Conference on Harmonization [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures including laboratory test abnormalities.

Serious adverse event: A serious adverse event (SAE) based on ICH is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening. (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is a suspected transmission of any infectious agent via a medicinal product;
- is medically important.*

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Non-serious adverse drug reaction (ADR) (associated with the use of the drug): Any untoward medical occurrence that does not meet the above criteria to be serious and also is considered associated with the use of the drug.

Life threatening: Any event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

Associated with the use of the drug: An AE is considered associated with the use of the drug if the attribution is possible, probable or very likely.

12.2 Attribution definitions

Causality assessment will be done by the physician at DR-TB centre. There are five categories as mentioned below. The drug safety monitoring committee (DSMC) for BDQ conditional access will review and confirm the causality of all serious events/reactions in relation to the therapy [20].

i. **Not related:** An AE that is not related to the use of the drug.

ii. **Doubtful:** An AE for which an alternative explanation is more likely, e.g. concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

iii. **Possible:** An AE that might be due to the use of the drug. An alternative explanation, e.g. concomitant drug(s) or concomitant disease(s) is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

iv. **Probable:** An AE that might be due to the use of the drug. The relationship in time is suggestive, e.g. confirmed by dechallenge. An alternative explanation is less likely, e.g. concomitant drug(s), concomitant disease(s).

v. **Very likely**: An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive, e.g. it is confirmed by dechallenge and rechallenge.

12.3 Severity criteria

An assessment of severity grade will be made using the following general categorical descriptors:

- Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- Moderate: Sufficient discomfort is present to cause interference with normal activity.
- Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject, e.g. laboratory abnormalities.

12.4 Reporting of Adverse Events, Serious Adverse Events And Pregnancy

A brief summary table of the most common AEs and SAEs are listed with the management for ready reference at Appendix 3.

All SAEs and AE's, (i.e. non-serious adverse events which are possibly, probably or very likely related to the administration of BDQ) that fit the definition as detailed later related to detailed formats for AE reporting and pregnancy occurring during the programme must be reported by the physician to RNTCP as they occur.

If pregnancy occurs during BDQ treatment, BDQ must be stopped and OBR must be modified as per the RNTCP PMDT guidelines.

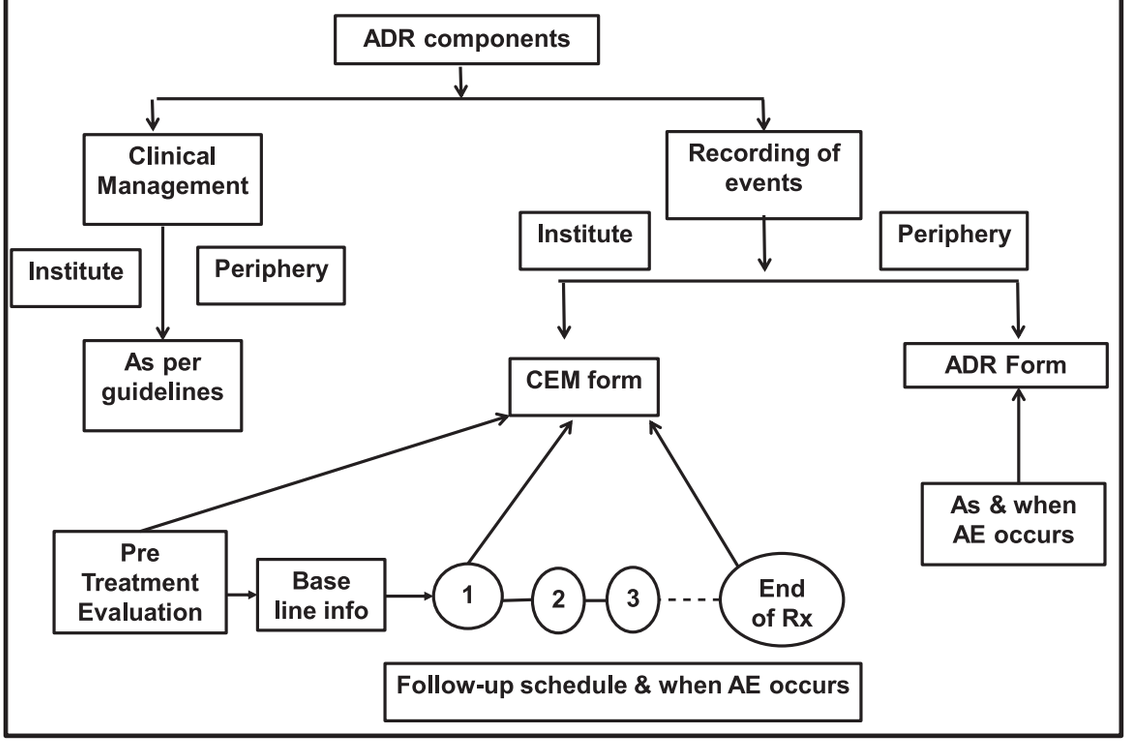
Any death of a patient occurring during treatment in a BDQ-containing regimen, regardless of causality, must be reported as SAE and a verbal autopsy (Appendix 4) should be undertaken.

It is recommended that the patient be questioned before the commencement of treatment and at each subsequent consultation in order to obtain a detailed description of any sign of toxicity or adverse drug reaction, which they might have experienced. The standard WHO formats for cohort event monitoring in the prescribed formats need to be maintained for every patient.

RNTCP will ensure that strict active pharmacovigilance is implemented by all the DR-TB centres and district physicians for ambulatory patients.

The flowchart 1 on ADR management and data capturing format related to Pharmacovigilance is shown below.

Flowchart 1: ADR management and data capturing related to pharmacovigilance for BDQ



The treating physician at DR-TB centre and medical practitioners at periphery will observe patients for any adverse events (spontaneous reporting by patient and active screening) and will manage as per laid down criteria in document. The SAE will be reported to ADR monitoring center (AMC) and CTD within 24 hours. The recording of events has been divided in to two components.

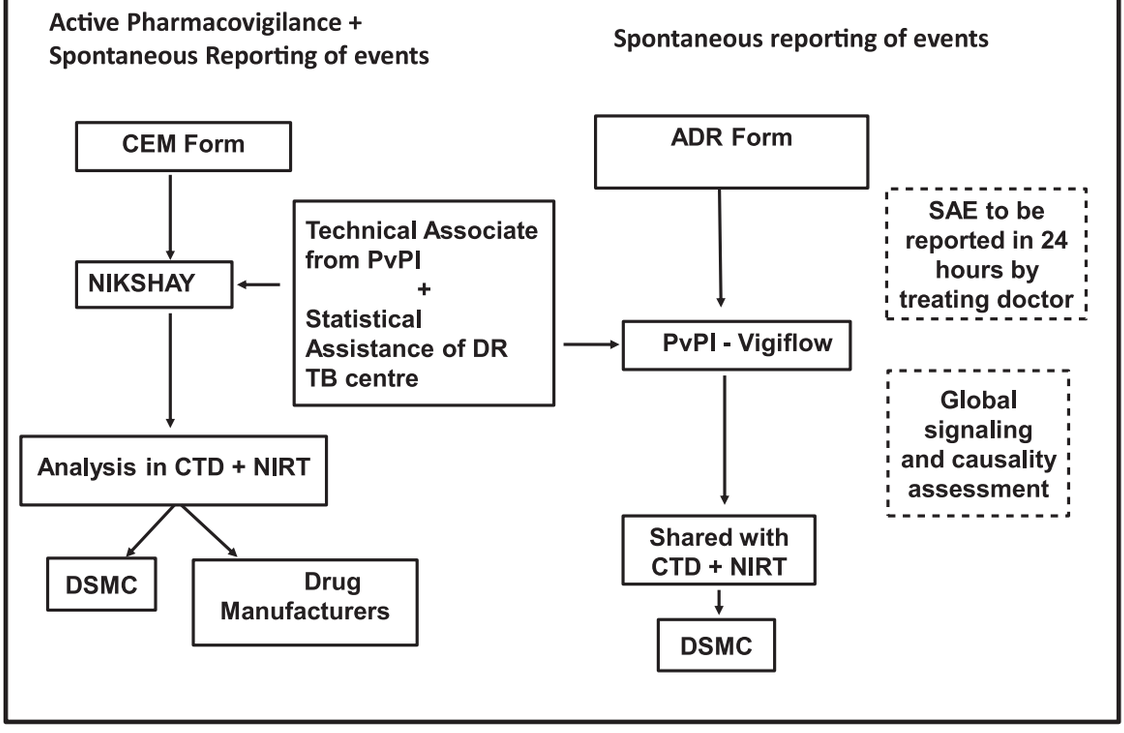
1. Cohort Event Monitoring (CEM) will follow the patient pathway from registration to the treatment outcome. The patient details will be captured as baseline (before starting treatment) and will get updated at regular monthly interval till completion of treatment.

2. Any AE/SAE will be captured additionally using Suspected ADR form of PvPI.

The primary responsibility of filling up of above forms will be with treating physician.

Protocol on BDQ drug safety, data entry, sharing of data and analysis has been shown in the flowchart 2 below.

Flowchart 2: Protocol on BDQ drug safety, data entry, sharing of data and analysis



Once the relevant forms CEM, Suspected ADR forms are filled in NIKSHAY and Vigiflow by Technical Associate from PvPI in coordination with statistical assistance of DR TB centre. The sites need to ensure reporting of SAE within 24 hours to Central TB Division using NIKSHAY followed by email to ddgtb@rntcp.org and bdq@rntcp.org. Records need to be maintained in hard copies at respective sites.

The CEM data will be analyzed at CTD and NIRT. The relevant information will be shared with DSMC on monthly basis as a routine. The data on action required on immediate basis will be shared with DSMC by CTD and NIRT.

The data related to suspected ADR format will be analyzed by PvPI using Vigiflow and shared with CTD, on monthly basis. The data with action required on immediate basis will be shared with CTD by PvPI.

The primary role of DSMC would be to evaluate periodically (quarterly and whenever required) accumulated data for patient safety, progress and continuation of CAP and make recommendation to CTD concerning use of BDQ.

13 OUTCOME AND CEM INDICATORS

Interim outcome definitions will conform to the RNTCP PMDT guidelines. The final treatment outcomes of the patients would be reported after the end of continuation phase with OBR as per the RNTCP PMDT guidelines with definitions particularly that of 'Treatment Failure' will be adapted from the recent WHO Companion Handbook on PMDT [15]. Accordingly, Treatment Failure would be defined as follows: “Treatment terminated or need for permanent regimen change of atleast two anti-TB drugs because of:

- Lack of conversion by the end of the intensive phase; or
- Bacteriological reversion in the continuation phase after conversion to negative; or
- Evidence of additional acquired* resistance to fluoroquinolones or second-line injectable drugs; or
- Adverse drug reactions.”

(* This would not include patients with evidence of resistance to fluoroquinolones or second-line injectable drugs detected with SLDST at baseline)

Apart from these, monitoring indicators specific for cohort event monitoring of patients initiated on BDQ containing regimen with OBR or DST guided treatment will be applied. These indicators cover measures of CEM coverage, sputum culture conversion, case fatality while on treatment, SAEs, AEs and discontinuation of BDQ. The following table details these indicators, their definitions and data source:

Indicator	Numerator	Denominator	Data source
Indicators on CEM coverage			
1. *Proportion of DR-TB patients on BDQ included in CEM*	Number of DR-TB patients registered on BDQ containing regimen included in CEM	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM format
Indicators on sputum culture conversion			
2. *Time to sputum culture conversion*	Number of days/weeks from the date of treatment initiation to the date of sample collection of the first culture among the two consecutive negative cultures		PMDT TB register/ Nikshay
3. *Proportion of DR-TB patients with sputum culture conversion by the end of BDQ containing phase of treatment regimen*	Number of DR-TB patients registered on BDQ containing regimen who achieved sputum culture conversion by the end of BDQ containing phase of treatment regimen	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay

Case fatality indicators			
4. *All-cause case fatality rate by the end of BDQ containing phase of treatment regimen*	Number of DR-TB patients registered on BDQ containing regimen who died due to any reason by the end of BDQ containing phase of treatment regimen	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay
5. *BDQ attributable* case fatality rate by the end of BDQ containing phase of treatment regimen*	Number of DR-TB patients registered on BDQ containing regimen who died due to reasons attributable* to BDQ by the end of BDQ containing phase of treatment regimen	Number of DR-TB patients registered on BDQ containing regimen who died due to any reason by the end of BDQ containing phase of treatment regimen	PMDT TB register/ Nikshay /CEM follow up format
6. *All-cause case fatality rate by the end of full DR-TB treatment course*	Number of DR-TB patients registered on BDQ containing regimen who died due to any reason by the end of full DR-TB treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
7. *BDQ attributable* case fatality rate by the end of full DR-TB treatment*	Number of DR-TB patients registered on BDQ containing regimen who died due BDQ attributable* reason by the end of full DR-TB treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
8. *All-cause case fatality rate by 6m after completion of BDQ containing phase of treatment course*	Number of DR-TB patients registered on BDQ containing regimen who died due to any reason by 6m after completion of BDQ containing phase of treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
9. *BDQ attributable* case fatality rate by 6m after completion of BDQ containing phase of treatment course*	Number of DR-TB patients registered on BDQ containing regimen who died due to BDQ attributable* reason by 6m after completion of BDQ containing phase of treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
Indicators on Serious Adverse Events (SAEs)			
10. *All-cause SAEs rate by the end of BDQ containing phase of treatment regimen*	Number of DR-TB patients registered on BDQ containing regimen who reported SAEs due to any reason by the end of BDQ containing phase of treatment regimen	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format

11. BDQ attributable SAEs rate by the end of BDQ containing phase of treatment regimen*	Number of DR-TB patients registered on BDQ containing regimen who reported SAEs due to reasons attributable* to BDQ by the end of BDQ containing phase of treatment regimen	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
12. All-cause SAEs rate by the end of full DR-TB treatment course	Number of DR-TB patients registered on BDQ containing regimen who reported SAEs due to any reason by the end of full DR-TB treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
13. BDQ attributable SAEs rate by the end of full DR-TB treatment course*	Number of DR-TB patients registered on BDQ containing regimen who reported SAEs due BDQ attributable* reason by the end of full DR-TB treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
14. All-cause SAEs rate by 6m after completion of BDQ containing phase of treatment course	Number of DR-TB patients registered on BDQ containing regimen who reported SAEs due to any reason by 6m after completion of BDQ containing phase of treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
15. BDQ attributable SAEs rate by 6m after completion of BDQ containing phase of treatment course*	Number of DR-TB patients registered on BDQ containing regimen who reported SAEs due to BDQ attributable* reason by 6m after completion of BDQ containing phase of treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
Indicators on Adverse Events			
16. All-cause AEs rate by the end of BDQ containing phase of treatment regimen	Number of DR-TB patients registered on BDQ containing regimen who reported AEs due to any reason by the end of BDQ containing phase of treatment regimen	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
17. BDQ attributable AEs rate by the end of BDQ containing phase of treatment regimen*	Number of DR-TB patients registered on BDQ containing regimen who reported AEs due to BDQ attributable* reason by the end of BDQ containing phase of treatment regimen	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format

18. All-cause AEs rate by the end of full DR-TB treatment course	Number of DR-TB patients registered on BDQ containing regimen who reported AEs due to any reason by the end of full DR-TB treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
19. BDQ attributable AEs rate by the end of full DR-TB treatment course*	Number of DR-TB patients registered on BDQ containing regimen who reported AEs due BDQ attributable* reason by the end of full DR-TB treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
20. All-cause AEs rate by 6m after completion of BDQ containing phase of treatment course	Number of DR-TB patients registered on BDQ containing regimen who reported AEs due to any reason by 6m after completion of BDQ containing phase of treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
21. BDQ attributable AEs rate by 6m after completion of BDQ containing phase of treatment course*	Number of DR-TB patients registered on BDQ containing regimen who reported AEs due to BDQ attributable* reason by 6m after completion of BDQ containing phase of treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
Indicator on discontinuation of BDQ			
22. Proportion of DR-TB patients in whom BDQ was stopped permanently before completion of BDQ containing phase of treatment course	Number of DR-TB patients in whom BDQ was stopped permanently before completion of BDQ containing phase of treatment course	Number of DR-TB patients registered on BDQ containing regimen during the period of assessment	PMDT TB register/ Nikshay /CEM follow up format
23. Mean time taken for stopping BDQ permanently before completion of BDQ containing phase of treatment course	Sum of difference in days between the date of start and date of stopping for all the DR-TB patients for whom BDQ containing regimen was permanently stopped before completion of BDQ containing phase of treatment course	No of the DR-TB patients for whom BDQ containing regimen permanently before completion of treatment	PMDT TB register/ Nikshay /CEM follow up format

* Attribution will include causality assessment grades of definite or probable.

Safety assessment measure is the proportion of patients experiencing a grade 3 or greater adverse event, as defined by the DAIDS (Division of AIDS) criteria during treatment and follow-up [18].

14. MANAGEMENT OF TREATMENT INTERRUPTIONS, LOSS TO FOLLOW-UP AND RECURRENT DR-TB

BDQ: If a dose is missed during the first 2 weeks of treatment, one should not make up for the missed dose but should continue the usual dosing schedule.

From the third week onwards, if a 200 mg dose is missed, one should take the missed dose as soon as possible, and then resume the 3 times a week regimen.

Patients who interrupt treatment during the first 2 weeks of BDQ course and returns to resume the treatment:

- If interruption is up to 7 days, BDQ containing regimen will be continued to complete the doses and the duration of treatment will be extended to complete IP. Follow-up cultures will be done as per the revised schedule.
- If interruption is more than 7 consecutive days, BDQ course will be re-loaded (started afresh) and a sputum sample will be collected for culture. The culture isolate must be stored for BDQ DST in future. In addition, serum sample will be collected and transported to the concerned lab within 6 hrs for BDQ levels for correlation with outcomes, wherever feasible and lab capacity is available.

Patients who interrupt treatment during 3-24 weeks of BDQ course and returns to resume the treatment:

- If interruption is up to 2 month, BDQ containing regimen will be continued to complete the doses and the duration of treatment will be extended to complete IP. Follow-up cultures will be done as per the revised schedule.
- If interruption is more than 2 months, BDQ will be permanently discontinued. Such patients will be given an outcome of “Lost to follow up” (LTFU) based on the duration of LTFU and managed as per RNTCP PMDT Guidelines for DST guided treatment and registered afresh. A sputum sample will be collected for culture. The culture isolate must be stored for BDQ DST in future. In addition, serum sample will be collected and transported to the concerned lab within 6 hrs for BDQ levels for correlation with outcomes, wherever feasible and lab capacity is available.

Further treatment: If the patient has any indication of a treatment failure or recurrence, the DR-TB Centre Committee will be contacted to discuss whether the patient should be re-treated. The decision will be made on a case-by-case basis using all the available bacteriological and clinical data.

15. SALVAGE REGIMEN

Salvage regimens may be needed for patients who receive BDQ under RNTCP conditional access but fail treatment. A standardized salvage treatment strategy may not be feasible, as all these patients have already been treated for DR-TB using second-line drugs. Salvage regimens will be DST-guided treatment regimens based on expanded panel of standardized DST for all available first- and second-line drugs. Given that the number of drugs that could be used for salvage regimens is limited and that these reserve drugs are less potent, drugs of uncertain effectiveness may be included. Further details of anti-tuberculosis drugs that may be used for salvage regimens should follow the RNTCP PMDT DST guided treatment guidelines. This would guide careful selection of sensitive first- and second-line drugs including group 5 drugs to scientifically design an appropriate regimen wherever possible. In patients requiring surgical intervention, the feasibility of surgery should be evaluated.

16. RECORDING, REPORTING AND MONITORING

In order to avert duplication and overburdening the programme staff with additional sets of records and reports, the existing PMDT records and reports have been updated to record the diagnostic and treatment services-related information for patients who would be managed with a BDQ-containing regimen. For every patient enrolled on a BDQ-containing regimen, a separate folder of all patient records as listed below must be maintained at the DR-TB centres.

16.1 Updated PMDT records and reports

Appropriate modifications have been incorporated pertaining to this guideline on use of BDQ under RNTCP PMDT services, the updated outcome definitions in line with the WHO companion handbook on PMDT and the RNTCP DST guided treatment guidelines. The following table enlists the RNTCP PMDT records and reports that have been comprehensively modified:

S No	Existing RNTCP PMDT records & reports	Appendix No
1	Request for Culture and DST form (Annexure I) - renamed	5
2	Referral for Culture and DST register (Annexure III)	6
3	C & DST Laboratory Register (Annexure IV)	7
4	PMDT referral for treatment form (Annexure V)	8
5	PMDT treatment card (Annexure VIII)	9
6	PMDT treatment register (Annexure IX)	10
7	PMDT patient identity card (Annexure X)	11
8	RNTCP PMDT Quarterly Report on Case Finding (Annexure XI)	12
9	RNTCP PMDT Six Month Interim Report (Annexure XII)	13
10	RNTCP PMDT Twelve Month Culture Conversion Report (Annexure XIII)	14
11	RNTCP PMDT Report on Treatment Outcomes of M/XDR TB patients (Annexure XIV)	15
12	Monthly Stock Report for Stocks & Indenting of Second line drugs at DR-TB Centre	16
13	Monthly Stock Statement of Second line drugs from State Drug Store	17

16.2 Additional records and reports for BDQ

In addition to the above, the following two new forms would be introduced for patients treated with BDQ containing regimen:

- **Patient Education Booklet for BDQ-containing regimen under PMDT (RNTCP) and Informed Consent Form**

A detailed patient education booklet has been developed for educating the patient on the use of BDQ (Appendix 18) and for obtaining informed consent (Appendix 19).

The patient education booklet (Appendix 18) must be provided to the patient along with the patient identity card (Appendix 11) that contains the list of drugs contraindicated or to be used with caution with BDQ. The patient must be motivated to carry these documents at every visit to any health care provider throughout the treatment course.

The informed consent must be filled with signature / thumb impression of the patient after educating the patient with counseling before initiation of treatment with BDQ containing regimen. The consent form must be maintained in the patient folder.

– **Cohort Event Monitoring Form:**

The standard formats for cohort event monitoring (Appendix 20) as prescribed in the WHO Guidelines would be used at all the sites. Every AE or SAE including death needs to be promptly reported by the sites to RNTCP using the standard format. The data of CEM form will be entered into NIKSHAY on a real-time case to case basis. Hard copies need to be maintained at each of the sites in the individual patient folders of records. The process of data entry and analysis for active pharmacovigilance and event based ADR reporting using NIKHSAY and Vigiflow has been described in details in section 12.4 above.

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APPENDICES

Appendix 1:

Bedaquiline information BDQ storage
All supplies of BDQ must be stored at 15–30 °C (59–86 °F), in a limited access area or in a locked cabinet under appropriate environmental conditions. Access to BDQ should be restricted to designated personnel. All medication should remain in the original packaging in which it was delivered. Storage conditions and expiry date will be supplied with the medication. Should a deviation in storage conditions of BDQ occur, the site should refrain from any further dispensation of the affected medication and immediately provide the information on the nature of the deviation to CTD. Upon review of this information, a decision will be made regarding further use of the affected medication.

Concomitant medications
This list of disallowed medication is based on established or theoretical interactions with BDQ. The prescribing information for all co-administered medication should be consulted and reviewed carefully. The determinations listed in the respective contraindicated, warning and precaution sections must be respected in order to prevent any potentially serious and/or life threatening drug reactions.

The current package inserts should be consulted for concomitant use of the OBR with other medication and for contraindicated medication or medication that is not recommended for concomitant use. Please also consult national TB and HIV programme treatment guidelines.

The following medications are disallowed during the 24-week administration of BDQ and up to 1 month after the last dose of BDQ because of potential drug–drug interactions:

- The systemic use of moderate and strong CYP3A4 inhibitors, e.g. azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolides such as telithromycin and macrolide antibiotics other than azithromycin for more than 2 consecutive weeks;
- The systemic use of strong CYP3A4 inducers, e.g. phenytoin, carbamazepine, phenobarbital, St. John's wort and rifamycins (rifampin, rifabutin, rifapentine);
- The use of antiretroviral (ARV) medication (except for the triple nucleoside regimen AZT/3TC/ABC, or an NVP- or LPV/RTV-containing regimen (in combination with NRTIs);
- Cholesterol lowering medications of the “statin” class.

The following medications should not be used during the 24-week administration of BDQ because of their potential to prolong the QT interval:

- Class 1a or Class III antiarrhythmic drugs such as amiodarone, sotalol, procainamide, dysopyramide and quinidine;
- Tricyclic antidepressants, including amitriptyline, doxepin, desipramine, imipramine and clomipramine;
- The non-sedating antihistamines—astemizole and terfenadine;
- The neuroleptics-phenothiazines—thioridazine, haloperidol, chlorpromazine, trifluoperazine, percycline, prochlorperazine, fluphenazine, sertindole and pimozide;
- The prokinetic cisapride;
- Quinoline antimalarials, e.g. chloroquine and quinacrine.

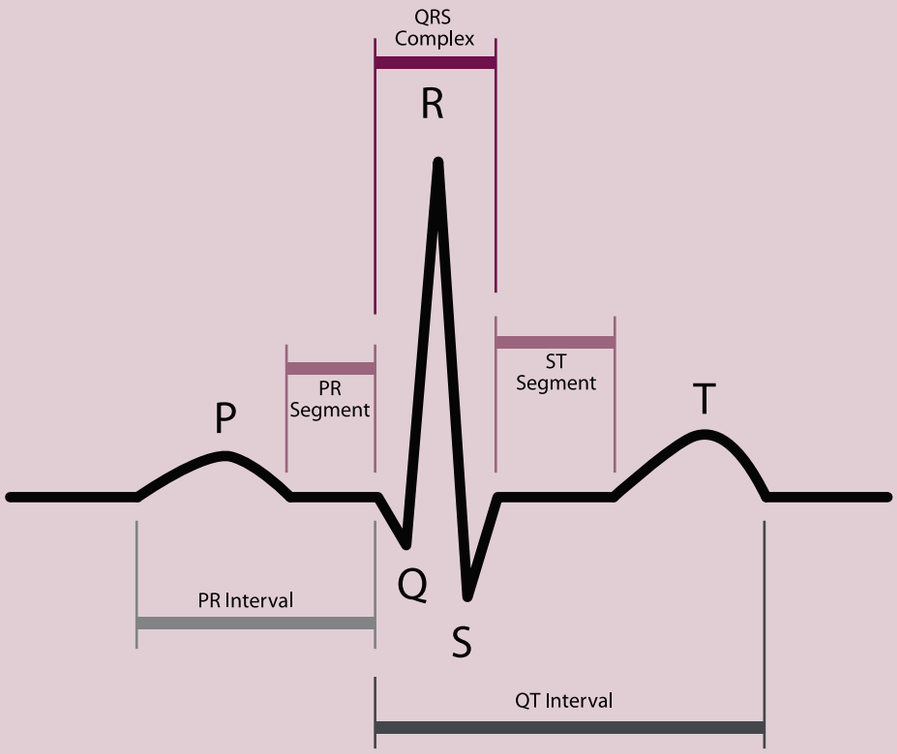
Some of these drugs may be required for management of side-effects. Concomitant administration of these drugs must be decided by the DR TB center committee on a case to case basis, if necessary, by consulting the specialist concerned. The patient may need to be admitted in the DR TB center and the frequency monitoring of the patient may also be increased by the committee in case such a medicine(s) is/are required to be given along with BDQ.

BDQ drug information

BDQ supplied for this programme is formulated as a tablet containing 120.89 mg of the fumarate, equivalent to 100 mg of the active free base and additionally composed of lactose monohydrate, unmodified maize starch, hypromellose 2910 15 mPa.s, polysorbate 20, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate. Purified water is used in the manufacturing process but is not present in the final formulation. BDQ will be provided in bottles. One bottle contains 188 tablets.

Appendix 2: Definition of QTc interval

■ The QT interval in an ECG is measured from the start of the Q wave to the end of the T wave (see diagram below).



■ When monitoring the effect of bedaquiline, the QT interval needs to be adjusted (corrected) for the heart rate. Many ECG machines today provide an output of the corrected QT interval (QTc) automatically. If you are using a machine that does not, the following instructions can help you make the necessary correction.

- The preferred way to calculate the QTc is the Fredericia method (QTcF), which is derived by dividing the QT interval by the cubed root of the interval in seconds between the peak of two successive R waves (RR) read from the ECG strip:

$$QT_{cF} = \frac{}{\sqrt{}}$$

■ Whenever an abnormal QTc value is found, the ECG and calculations should be repeated.

■ A normal value for the corrected QTcF interval is equal to or less than 0.45 seconds (450 ms) in males or 0.47 seconds (470 ms) in females.

Appendix 3: The most common adverse effects, the offending drugs and their management strategies [18]

Common adverse effects/ reactions	Responsible agent	Management	Comments
Seizures	Cs Trd FQs	1. Rule out other likely causes. 2. Treat any suspected causes. 3. Initiate anticonvulsant treatment phenytoin 3–5 mg/kg/day; valproic acid 750–1250 g/kg/day; carbamazepine 600–1200 mg/day; phenobarbitol 60–120 mg/kg/day. 4. Increase pyridoxine to 200 mg daily. 5. Lower dose of offending drug. 6. Discontinue offending drug.	Clinical evaluation is generally sufficient unless there is high suspicion of infectious, malignant, vascular or metabolic cause. Anticonvulsant must be continued until MDR-TB treatment is completed or suspected agent is discontinued. History of prior seizure disorder is not a contraindication for the use of the offending TB drugs if the patient's seizures are well-controlled and/or the patient is receiving anticonvulsant treatment. Patients with a history of prior seizures may be at increased risk for development of seizures during MDR-TB treatment. Seizures are not a permanent sequela of MDR-TB treatment.
Peripheral neuropathy	Cs Trd S Km Amk Cm Eto/Pto FQs	1. Increase pyridoxine to 200 mg daily. 2. Begin exercise regimen, focus on affected regions. 3. Initiate therapy with tricyclic antidepressant drugs. 4. Lower dose of suspected drug. 5. Discontinue suspected drug. 6. Initiate therapy with gabapentin 300 mg qid initially, and increase by 600 mg every 3–7 days; max dose 1200 mg tds.	Patients with co-morbid disease, e.g. diabetes, HIV or alcoholism are more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the offending TB drugs. Neuropathy is generally not reversible, but only a minority (approximately 10%) of patients require continued intervention to keep symptoms controlled once MDR-TB treatment is completed.

Hypothyroidism	PAS Eto / Pto	Initiate thyroxine.	Completely reversible upon discontinuation of offending drug. The use in combination of PAS and Eto or Pto is more frequently associated with hypothyroidism than their individual use.
Hearing loss	S Km Amk Cm	1. Conduct audiometry and compare with baseline. 2. Consider reducing the frequency of the drug administration to five times or even three times per week. 3. Lower the dose of the suspected drug if this will not compromise the regimen. 4. Discontinue the suspected drug if this will not compromise the regimen.	Patients with prior exposure to aminoglycosides may have baseline hearing loss. Hearing loss is generally not reversible. The risk of further hearing loss should be weighed against the risk of stopping the drug in the regimen.
Psychosis	Cs Tdr FQs Eto / Pto	1. Refer to a psychiatrist for assessment. 2. Hold the suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. 3. Initiate anti-psychotic drugs, e.g. risperidone 0.5–2 mg po bd; haloperidol 1–5 mg po or IV or IM repeated every hour as needed. 4. Lower dose of suspected agent if this will not compromise the regimen. 5. Discontinue use of suspected agents and replace accordingly.	Some patients will need to continue anti-psychotic treatment throughout the MDR-TB treatment. Prior history of psychiatric disease is not a contraindication to the use of the offending TB drugs, but may increase the likelihood of development of psychotic symptoms. Psychotic symptoms are generally reversible upon MDR-TB treatment completion or discontinuation of the offending agent.

Depression	Cs Trd FQs Cm Eto / Pto	1. Rule out side-effects of concomitant medications, e.g. Amx/clv, penicillin, benzodiazepines. 2. Refer to a psychologist or psychiatrist for assessment. 3. Initiate group or individual psychological therapy. 4. Initiate anti-depressant drugs, e.g. amytriptyline, nortriptyline, fluoxetine, sertraline, but use with caution when there is a history of convulsions. 5. Increase pyridoxine to 200 mg daily. 6. Lower dose of the offending drug if this will not compromise the regimen. 7. Discontinue the offending drug if this will not compromise the regimen.	Importance of personal socioeconomic conditions and confinement to hospital should not be underestimated as contributing factors to depression. Depression and depressive symptoms may fluctuate during treatment. History of prior depression is not a contraindication to the use of the offending TB drugs; however, these patients may be at increased risk for developing depression during MDR-TB treatment.
Nausea and vomiting	Eto/Pto PAS Cm E Z	1. Assess for dehydration and rehydrate if indicated. 2. Initiate anti-emetics 30 min prior to administering MDR-TB drugs. 3. Administer Eto in 3 separate doses. 4. Administer Eto at night with short-acting benzodiazepine. 5. Lower dose of offending drug. 6. Discontinue use of offending drug.	Nausea and vomiting is common in the early weeks of treatment and usually abates with time on treatment or supportive therapy. Electrolytes should be monitored and replenished if vomiting is severe. Reversible upon discontinuation of suspected agent.

Gastritis	PAS Eto/Pto E Z	1. Administer MDR-TB drugs with a small amount of food. 2. Caffeine and cigarettes should be avoided. 3. Consider use of: • Antacids, e.g. calcium carbonate, aluminium hydroxide, magnesium-hydroxide. • H2-blockers, e.g. cimetidine, ranitidine; proton-pump inhibitors, e.g. omeprazole. 4. Withhold offending drug (s) for short periods of time (1–7 days). 5. Lower dose of offending drug. 6. Discontinue the offending drug.	Severe gastritis or gastric ulcers as manifested by haematemesis, melena or haematechezia is rare. Dosing of antacids should be carefully timed so as not to interfere with the absorption of MDR-TB drugs. Ancillary drugs should be taken 2 hours before or 3 hours after the TB medication. Reversible upon discontinuation of offending drug(s).
Hepatitis	Z FQs Eto / Pto PAS E	1. Stop treatment pending resolution of the hepatitis. 2. Rule out other potential causes of hepatitis. 3. Consider suspending the causative drug permanently. 4. Re-introduce drugs individually while monitoring liver function, with the most likely drug introduced first. 5. Monitor liver function every 1–2 months.	History of prior hepatitis should be carefully analysed to determine the most likely causative drug(s); these should be avoided in future regimens. Generally reversible upon discontinuation of offending drug.
Renal failure and nephrotoxicity	S Km Amk Cm	1. Discontinue the causative drug. 2. Consider dosing 3 times per week and monitor creatinine clearance. 3. Adjust dose of all the drugs according to creatinine clearance. 4. Consider use of Cm if patient was on aminoglycoside.	History of diabetes or renal disease is not a contraindication to the use of the offending TB drugs, although patients with co-morbidities may be at increased risk for developing renal failure. Renal impairment may be permanent.

Optic neuritis	E	1. Stop agent. 2. Refer patient to ophthalmologist.	Usually reverses with cessation of the drug.
Arthralgia / arthritis	Z FQs	1. Initiate therapy with non-steroidal anti-inflammatory drugs. 2. Initiate exercise regimen physiotherapy where necessary. 3. Lower dose of offending drug, if this will not compromise the regimen. 4. Discontinue offending drug, if this will not compromise the regimen.	Symptoms of arthralgia/arthritis generally diminish over time, even without intervention. Uric acid levels may be elevated in some patients but are of little therapeutic relevance. Anti-gout treatment, e.g. allopurinol and colchicines does not correct the uric acid levels in these cases.
Electrolyte disturbances (hypokalaemia, hypomagnesaemia)	Cm Km Am S	1. Replenish potassium po or IV. 2. Treat associated vomiting or diarrhoea. 3. Check magnesium levels if potassium levels do not improve. 4. Discontinue arrhythmogenic drugs, e.g. digoxin, amyltriptyline, cisapride and haloperidol if the patient is taking them. 5. Discontinue aminoglycosides if the condition is severe.	Hypokalaemia can occur within clinical signs and symptoms and may be life-threatening. Amiloride 5–10 mg qid or spironolactone 25 mg qid may decrease the potassium and magnesium wasting and is useful in refractory cases.

Appendix 4 – RNTCP Verbal Autopsy Form for Bedaquiline CAP

PMDT Number: PMDT NIKSHAY ID: YEAR:

Name of the head of household :

Full Name of the deceased:

Section 1: Details for respondent and deceased

Details of respondent

1. Name of respondent

2. Relationship of respondent with deceased
- ☐ 1. Wife/Husband
- ☐ 2. Brother/Sister
- ☐ 3. Son/Daughter
- ☐ 4. Mother/Father
- ☐ 5. Grandchild
- ☐ 6. Son-in-law/ Daughter-in-law
- ☐ 7. Brother-in-law/ Sister-in-law
- ☐ 8. Parent-in-law
- ☐ 9. Grandfather/Grandmother
- ☐ 10. Other relative
- ☐ 11. Neighbour/No relation
- ☐ 99. Unknown

3. Did the respondent live with the deceased during the events that led to death?
☐ 1. Yes ☐ 2. No ☐ 99. Unknown

4. Respondent's age in completed years

5. Respondent's sex ☐ 1. Male ☐ 2. Female

6. What is the highest standard of education the respondent has completed?
- ☐ 0. Illiterate and literate with no formal education
- ☐ 1. Literate, Primary or below
- ☐ 2. Literate, Middle
- ☐ 3. Literate, Matric Class-X
- ☐ 4. Literate, Class XII
- ☐ 5. Graduate and above
- ☐ 99. Unknown

7. Religion of the head of the household
- ☐ 1. Hindu
- ☐ 2. Muslim
- ☐ 3. Christian
- ☐ 4. Sikh
- ☐ 5. Buddhist
- ☐ 6. Jain
- ☐ 7. No religion
- ☐ 8. Other
- ☐ 99. Unknown

Details of deceased

8. Deceased's Sex ☐ 1. Male ☐ 2. Female

9. Age of Deceased Years: ☐☐

10. Relationship of the deceased with the head of the household
- ☐ 1. Wife/Husband
- ☐ 2. Brother/Sister
- ☐ 3. Son/Daughter
- ☐ 4. Mother/Father
- ☐ 5. Grandchild
- ☐ 6. Son-in-law/ Daughter-in-law
- ☐ 7. Brother-in-law/ Sister-in-law
- ☐ 8. Parent-in-law
- ☐ 9. Grandfather/Grandmother
- ☐ 10. Other relative
- ☐ 11. Neighbour/No relation
- ☐ 12. Self
- ☐ 99. Unknown

11. What is the highest standard of education the deceased had completed?
- ☐ 0. Illiterate and literate with no formal education
- ☐ 1. Literate, Primary or below
- ☐ 2. Literate, Middle
- ☐ 3. Literate, Matric Class-X
- ☐ 4. Literate, Class XII
- ☐ 5. Graduate and above
- ☐ 99. Unknown

12. What was the occupation of the deceased?
- ☐ 1. Non-worker
- ☐ 2. Salaried
- ☐ 3. Wage earner
- ☐ 4. Profession/Business
- ☐ 5. Cultivator/farmer
- ☐ 6. Agricultural wage labour
- ☐ 7. Non agricultural wage labour
- ☐ 8.. Student
- ☐ 9. Other
- ☐ 99. Unknown

13. Date of death D D / M M / Y Y ☐☐

14. How many years did the deceased live at this address?

15. Place of death?
- ☐ 1. Home
- ☐ 2. On way to health facility
- ☐ 3. PHC/CHC/Rural Hospital
- ☐ 4. District Hospital
- ☐ 5. Private Hospital
- ☐ 6. Other place
- ☐ 99. Unknown

16A. House address of the deceased

16B. PIN ☐☐☐ ☐☐☐

17. What did the respondent think that this person died of?
(Allow the respondent to tell the illness in his or her own words)

Section 2: Past History

Had a doctor EVER stated that the deceased had the following diseases?

	1. Yes	2. No	99. Unknown
18. Hypertension	☐	☐	☐
19. Heart disease	☐	☐	☐
20. Stroke	☐	☐	☐
21. Cholesterol problem	☐	☐	☐
22. Diabetes	☐	☐	☐
23. Tuberculosis	☐	☐	☐
24. HIV/AIDS	☐	☐	☐
25. Cancer (write site in narrative)	☐	☐	☐
26. Asthma	☐	☐	☐
27. Other chronic illness (specify in narrative)	☐	☐	☐

28. Was the deceased taking any medications regularly during the last five years? (Record up to three in Hindi or English only).

1. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

2. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

3. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

First, ask the following questions for the deceased (First Column), and then ask them for the main respondent (second column)

Tobacco, alcohol and diet	Deceased (Ask first)	Respondent (Ask second)
29A. Did s/he smoke tobacco within the last 5 years?	1. Definite Yes 2. Definite No 99. Unknown	1. Definite Yes 2. Definite No 99. Unknown
29B. If yes, how many bidis per day?		
29C. If yes, how many cigarettes per day?		
29D. Any other tobacco smoked?	1. Definite Yes 2. Definite No 99. Unknown	1. Definite Yes 2. Definite No 99. Unknown
30A. Did s/he chew tobacco within the last 5 years?	1. Definite Yes 2. Definite No 99. Unknown	1. Definite Yes 2. Definite No 99. Unknown
30B. Did s/he apply tobacco within the last 5 years?	1. Definite Yes 2. Definite No 99. Unknown	1. Definite Yes 2. Definite No 99. Unknown
31A. Did s/he normally drink alcohol (use local term) at least once a week during most weeks in the last 5 years?	1. Definite Yes 2. Definite No 99. Unknown	1. Definite Yes 2. Definite No 99. Unknown
31B. If yes, what was the average no. of days per week s/he drank?	_____days OR Unknown	_____days OR Unknown
31C. If yes, what type of alcohol was most commonly consumed?	1. Country liquor 3. Indian made foreign liquor 2. Toddy 4. Beer 5. Other	1. Country liquor 3. Indian made foreign liquor 2. Toddy 4. Beer 5. Other
32. Was s/he a pure vegetarian (consumed no egg, meat or f i sh) for the last 5 years?	1. Definite Yes 2. Definite No 99. Unknown	1. Definite Yes 2. Definite No 99. Unknown

For female deaths aged 15-49 ask:

33. Was she either known or suspected to be pregnant or within 42 days of delivery or abortion?

1. Yes 2. Definite No *If YES to question Q33 then DO NOT complete narrative below. Instead complete Form 10D and copy the Form 10D number here*

34. Key symptoms preceding death (check all that apply, and then use symptom list for narrative)

1. Coughing of blood	2. Severe shortness of breath	3. Fainting or giddiness
4. Vomitting, loss of appetite, pain in abdomen	5. Yellowish discolouration of eyes and urine	6. Sudden chest pain
7. Irrelevant behavior or talk	8. Palpitations	9. Seizures/fits
10. Fever	11. Weight loss	12. Paralysis/stroke
13. Urinary problems	14. Diarrhoea/dysentery	15. Odeme (swelling)
16. Severe Weakness		

35. Narrative language code

Section 3: Written narrative in local language

Please describe the symptoms in order of appearance, doctor consulted or hospitalization, history of similar episodes, enter the results from reports of the investigations if available.

Respondent's cooperation: 1. Good 2. Poor

Interviewer name: Desig:

Date: D D / M M / Y Y

Signature/Impresion

Respondent

Interviewer