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INTRODUCTION OF NEW DRUGS AND DRUG REGIMENS FOR THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS IN SOUTH AFRICA: POLICY FRAMEWORK

Version 1.1: June 2015

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Introduction of new drugs and drug regimens for the management of drug-resistant tuberculosis in South Africa: Policy framework

Chapter 1 Table of contents

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Foreword

South Africa is facing a major twin pandemic with co-infection of TB and HIV. It has the 6th highest burden of TB in the world. While the number of drug-susceptible TB cases appears to be decreasing, the number of MDR-TB patients is increasing. This undermines NTP capacity to manage and control TB in South Africa. Treatment success rate for MDR-TB has remained below 50 % despite numerous interventions.

This document aims to be a useful tool for health care workers, TB programme managers, civil society, and DR-TB patients. A clear plan is provided on how the introduction of new TB drugs will be conducted while clinical details on eligibility and referral mechanisms for participating patients are provided.

The best available evidence has been considered; however, DR-TB poses numerous unanswered questions requiring insight from experts. This document and the specific details of implementation will be updated as new evidence becomes available.

List of abbreviations

ADR, AE	Adverse drug reaction, adverse event	
AFB	Acid-Alcohol Fast Bacilli	AFB+ is also referred to as smear+
ALT	Alanine transaminase	
AM	Amikacin	Second-line injectable; aminoglycoside
ART	Antiretroviral (ARV) therapy	
BCAP	Bedaquiline Clinical Access Programme	
BDQ	Bedaquiline	Sirturo, TMC-207
BMI	Body mass index	Weight (kg) / (Height (m))^2
Ca^{2+}	Calcium (test)	
CFZ	Clofazimine	
CM	Capreomycin	Cyclic peptide
D4T	Stavudine	Zerit
DMD	Delamanid	Deltyba
DOH	Department of Health	
DOT	Directly-Observed Treatment	
DST	Drug susceptibility testing	
E, EMB	Ethambutol	
EC	Eastern Cape province	
ECG	Electrocardiogram (machine)	
EDD	Expected due date (in pregnancy)	
EDRweb	Electronic drug resistance register	National reporting system for DR TB
EFV	Efavirenz	
ETO	Ethionamide	
FS	Free State province	
GFR	Glomerular Filtration Rate	See calculation under Drug intolerance and ADR
GP	Gauteng province	
GXP	GeneXpert machine	
H, INH	Isoniazid	
Hb	Hemoglobin	
HIV	Human Immunodeficiency Virus	
HR	See context: Human resources or Heart rate	
inhA	inhA protein	Mutations in inhA gene indicate resistance to INH and ETO
K^{+}	Potassium (test)	
katG	Mycobacterial catalase-peroxidase	Mutations in katG gene indicate resistance to INH
KM	Kanamycin	Second-line injectable; aminoglycoside
KZN	KwaZulu Natal province	
LFX	Levofloxacin	Fluoroquinolone
LPV/r	Lopinavir/ritonavir	
LP	Limpopo province	
LPA	Line probe assay (Genotype MTBDR®)	
LZD	Linezolid	Zyvoxid
MCC	Medicines Control Council	
M&E	Monitory and evaluation	
MDR-TB	Multidrug-Resistant Tuberculosis	
MFX	Moxifloxacin	Fluoroquinolone

Mg^{2+}	Magnesium (test)	
MP	Mpumalanga province	
Na^{+}	Sodium (test)	
NC	Northern Cape province	
NNRTI	Non-nucleoside reverse transcriptase Inhibitors	
NTBRL	National TB Reference Laboratory	
NTP	National Tuberculosis Control Programme	
NW	North West province	
NVP	Nevirapine	
OAE	OtoAcoustic Emissions	
OBR	Optimized background regimen	
OFX	Ofloxacin	Fluoroquinolone
PAS	p-aminosalicylic acid	
PCAC	Provincial Clinical Advisory Committee	
PCR	Polymerase chain reaction	
PHC	Primary health care	
PI	Protease inhibitor	
PICT	Provider Initiated Counselling and Testing	
Plts	Platelets	
Pre XDR	Pre extensively drug-resistant TB	
PTA	Pure tone audiology testing	
PTC	Pharmaceuticals and Therapeutics Committees	
QT	Interval between start of Q wave and end of T wave	
QTcF	QT interval corrected using Fridericia formula	See calculation under Drug intolerance and ADR
R, RIF	Rifampicin	
RR-TB	Rifampicin resistant TB	
SA	South Africa, South African	
SM	Streptomycin	
TB	Tuberculosis	
TDF	Tenofovir	
TZD	Terizidone	
VL	(HIV) viral load test	
WC	Western Cape province	
WCC	White cell count	
WHO	World Health Organisation	
XDR TB	Extensively drug-resistant TB	
Xpert	Xpert MTB/RIF® test	
Z, PZA	Pyrazinamide	

Introduction and Purpose

The purpose of this framework is to provide guidance and inform practice with regards to the management of patients with drug-resistant tuberculosis (DR-TB) who will be treated with new anti-TB drugs. Current standardized regimens contain medicines with high toxicity profile and inadequate outcomes; substitutions of some drugs with available new anti-TB drugs and supported by relevant research may now be considered.

The management of DR-TB is rapidly changing. The development of new drugs to treat TB has reached a critical phase. After nearly five decades, two new agents (bedaquiline and delamanid) have been registered by regulatory authorities around the world. A few agents are in the pipeline. Therefore, we need to prepare for introduction and scale up of new drugs within the SA NTP.

In its Policy Implementation Package for New TB Drug Introduction, the WHO recommends the following pre-requisites for the introduction of new or repurposed TB drugs:

- National implementation plan for introduction of new TB drugs and/or regimens
- Monitoring and evaluation of new drugs and regimens, including active pharmacovigilance and drug resistance surveillance
- Systems approach for ensuring uninterrupted supply of quality-assured drugs

This document provides information as to how the NTP will introduce new drugs and regimens and benefits from our previous local experience gathered during the Bedaquiline Clinical Access Programme (BCAP)[2]. The Medicines Control Council (MCC) of South Africa approved a national clinical access programme to treat selected DR- TB patients with bedaquiline (BDQ) in March 2013. In October 2014, the MCC approved the use of bedaquiline for the treatment of MDR-TB.

Already before bedaquiline was introduced, the NTP has identified the need for new drugs for the treatment of TB. The 2014 WHO Global TB Report indicated that globally, treatment success rate for DR-TB is 48%. During the year 2013, of the 136,000 patients diagnosed with MDR-TB, only 97,000 received treatment. Of these 97,000 globally; 10,179 were reported from South Africa.[3] This illustrates that South Africa contributes approximately 10% of the global cohort.

There have been significant improvements in the implementation of MDR-TB case-findings strategies, diagnostics, additional agents such as PAS and clofazimine. However, the treatment success rate has remained below 50% for MDR-TB and below 25% for XDR-TB in South Africa. The reasons for this are multi-faceted, including that existing treatment regimens are sub-optimal in a DR-TB population that is largely HIV-infected.

This document aims to be a useful tool for the clinicians, healthcare workers, pharmacy staff, DR TB committees, DR-TB patients, DOH officials and others involved in the roll-out of new anti-TB drugs and drug regimens. It is based on research, available evidence, and the experience and insight of clinicians working within South Africa as well as global experts. However, as new studies are concluded, additional evidence is gathered, and further analysis informs practice and recommendations, these guidelines will be updated further. Thus, the structure of this framework is to allow for further chapters to be introduced as required.

Structure of the framework

	Title	Version, date
CHAPTER 1.	Purpose, structure	Version 1.1 June 2015
CHAPTER 2.	Effective patient management	Version 1.1 June 2015
CHAPTER 2.	Management of adverse drug reactions and ototoxicity	Version 1.1 June 2015
CHAPTER 4.	Monitoring and reporting	Version 1.1 June 2015
CHAPTER 5.	Bedaquiline	Version 1.1 June 2015
CHAPTER 6	*Linezolid*	*TBD*
CHAPTER 7	*Delamanid*	*TBD*
Annexes	Reporting templates and forms	Version 1.1 June 2015

Other anti-tuberculosis agents to be introduced

Linezolid

Linezolid, LZD, is currently in use in South Africa and is registered for specific indications such as severe and resistant respiratory and soft tissue infections. National DR-TB guidelines include recommendations for the use of linezolid although DR-TB is not an indicated use for linezolid under MCC approval. This is common to many of the repurposed medications being used for DR-TB treatment.

The use of LZD in DR-TB treatment to date has been largely restricted by the cost of the patented product from Pfizer. A more affordable, quality-assured generic LZD will be sourced for the SA NTP during the 2015 will be incorporated into treatment regimens in a controlled and systematic way, as part of the implementation plan detailed in this policy framework.

Delamanid

Following approval of delamanid (Deltyba) by major regulatory agencies, the WHO has issued interim guidelines for the use of delamanid in MDR-TB. The manufacturer, Otsuka, has been formally requested by the DOH to provide delamanid to South Africa. Otsuka and the NDOH agreed that a formal request that includes data on how delamanid will be used should be submitted before a formal response will be issued. It is expected that in 2015, delamanid will be introduced in South Africa, through a similar phased approached as is described here in detail for BDQ.

Additional agents

Pretomanid (PA-824) and sutezolid are among the drugs that are expected to be introduced through clinical trials and compassionate access initially and later programmatically.

New regimens may include the modified Bangladesh regimen (based on evidence from the STREAM trial) or other shortened regimens.

Objectives for the introduction of new drugs, regimens and management for DR-TB patients within the South African NTP

The overall aim of this policy is to:

- Increase access to new drugs and regimens for all DR-TB patients in South Africa.
- The overall aim of increasing access to new drugs and regimens is:
- To improve survival and treatment success rate of patients with DR-TB in South Africa.

The objectives of this policy are as follows:

1. To ensure the appropriate selection of DR-TB patients for new drugs, regimens and management.
2. To ensure the effective management of patients currently or previously treated for DR TB.
3. To ensure appropriate monitoring and managing of adverse events during DR-TB treatment and effective pharmacovigilance.
4. To ensure oversight and management from the national level and implementation at provincial and district levels.

Approach for implementation

Implementation of new drugs, regimens, and management will have a phased approach of which there will be four stages:

- Pre-implementation i.e. National oversight and access programmes prior to regulatory approval
- Stage I – Post approval at designated sites
- Stage II – Provincial coverage
- Stage III – District coverage

Essential reading

This framework does not stand alone and must be read in conjunction with key guidelines and standards with regards to treatment and care of DR-TB within the South African NTP, namely:

Title, website	Version date
National ART guidelines http://www.sahivsoc.org/upload/documents/2013%20ART%20Guidelines-Short%20Combined%20FINAL%20draft%20guidelines%2014%20March%202013.pdf	version March 2013
Management of drug-resistant TB: Policy guidelines http://www.hst.org.za/publications/management-drug-resistant-tuberculosis-policy-guidelines	Updated version January 2013
National tuberculosis management guidelines http://www.hst.org.za/sites/default/files/NTCP_Adult_TB-Guidelines-27.5.2014.pdf	version January 2014
Multi drug resistant tuberculosis: A policy framework on decentralized and deinstitutionalized management for South Africa http://www.health.gov.za/docs/Policies/2011/policy_TB.pdf	version August 2011
International Standards for Tuberculosis Care http://www.who.int/tb/publications/ISTC_3rdEd.pdf	3rd edition, 2014
WHO bedaquiline guideline http://www.who.int/tb/challenges/mdr/bedaquiline/en/	January 2013
WHO Policy implementation package for new TB Drug introduction http://www.who.int/tb/new_drugs	October 2014
Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis http://www.who.int/tb/publications/pmdt_companionhandbook/en/	November 2014
WHO on pharmacovigilance for TB patients http://www.who.int/medicines/publications/Pharmaco_TB_web_v3.pdf	
Guidelines for the management of tuberculosis in children http://www.sahivsoc.org/upload/documents/National-Childhood-TB-Guidelines-2013.pdf	April 2013

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Chapter 2: Effective patient management

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Chapter 2: To ensure effective DR TB patient management

The current standardised regimen recommended by the WHO and the NDOH for the treatment of MDR TB is not based on randomised clinical trial evidence but rather on expert opinion. For the treatment of even more resistant TB including XDR TB, the best data available is retrospective cohort data. While there is on-going clinical research into a shorter regimen with the current registered drugs and how to include the newer agents, the results of these studies are not likely to be available for three to five years.

In addition, the rate of adverse drug reactions (ADRs) in patients on the standardised regimen is high.

The National ART guidelines recommend that all HIV infected patients with DR TB are started on ART in an expedited manner. Interaction with ART will need to be considered when starting and/or continuing treatment for DR-TB. Prior to approval of new investigational products, an access programme may be available, as was the case of BDQ. Alignment with the ethical and regulatory framework must be followed. Thus a pragmatic approach needs to be adopted when selecting patients for the newer treatment options pending the outcomes of research.

A. Reinforcement of core principles

Guidance on how to construct a regimen is available in the **Management of drug-resistant TB: Policy guidelines**.

All patients diagnosed as rifampicin resistant by Xpert or any other diagnostic methods including Line Probe Assay or culture based drug sensitivity test, will be referred to start RR-TB treatment immediately.

At the initiating facility, a confirmatory line probe assay will be done at baseline. However this must not delay the initiation of treatment.

For patients who present for the first time and who have not had prior second line drugs exposure for more than one month, a **standardized regimen** is chosen. This consists of an intensive phase of five drugs: kanamycin, moxifloxacin, ethionamide, terizidone and pyrazinamide. This is continued for four months post culture conversion or a minimum of 6 months. The continuation phase consists of moxifloxacin, ethionamide, terizidone and pyrazinamide for 18 months post culture conversion.

In patients who have used second line drugs in the past for more than one month, or who are a contact of an MDR TB patient who resistance patterns are known, an **individualised regimen** must be used. In addition, if the line probe assay or culture based drug sensitivity test show resistance to quinolone and/or the second line injectable an individualised regimen must be used. All preXDR and XDR TB patients must have an **individualised regimen.** Guidance on how to construct **individualised regimens** is contained in the table below. This information is more up-to-date and supercedes the guidance on individualised regimens in the information about pre/XDR regimens with the newly available class 5 drugs can be found in the **'Guidance for constructing a regimen for pre-XDR/XDR TB treatment'.**

Although this framework aims to support the introduction of new medications and regimens, the core principles of TB treatment have not changed. The International Standards for Tuberculosis Care[8] sets forth the basic principles that should be followed for treatment of TB, including RR TB with the roll-out of new drugs. A few excerpts are presented here to emphasize that they continue to underpin TB management.

> **Standard 9**. A patient-centered approach to treatment should be developed for all patients in order to promote adherence, improve quality of life, and relieve suffering. This approach should be based on the patient's needs and mutual respect between the patient and the provider
>
> **Standard 11.** … An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance (if known), should be undertaken for all patients. If rifampicin resistance is detected, culture and testing for susceptibility to isoniazid, fluoroquinolones, and second-line injectable drugs should be performed promptly. Patient counselling and education, as well as treatment with an empirical second-line regimen, should begin immediately to minimize the potential for transmission.
>
> … Clinical errors that commonly lead to the emergence of drug resistance include: failure to provide effective treatment support and assurance of adherence; inadequate drug regimens; adding a single new drug to a failing regimen; and failure to recognize existing drug resistance.
>
> In addition, co-morbid conditions associated with reduced serum levels of anti-tuberculosis drugs (e.g., malabsorption, rapid transit diarrhoea, use of antifungal agents) and interruptions caused by adverse drug reactions may also lead to the acquisition of drug resistance.
>
> **Standard 12**. … At least five drugs, pyrazinamide and four drugs to which the organisms are known or presumed to be susceptible, including an injectable agent, should be used in a 6–8 month intensive phase, and at least 3 drugs to which the organisms are known or presumed to be susceptible, should be used in the continuation phase. Treatment should be given for at least 18–24 months beyond culture conversion.
>
> … Treatment success, compared with failure/relapse or death, was associated with use of later generation fluoroquinolones, as well as ofloxacin, ethionamide or prothionamide, use of four or more likely effective drugs in the initial intensive phase, and three or more likely effective drugs in the continuation phase.

B. Guidance for constructing a regimen for pre-XDR/XDR TB treatment (Adults)

Compiled by Prof Graeme Meintjes and Dr Jennifer Hughes

Go through this list one drug at a time to decide whether or not to include in the treatment regimen. Use a minimum of 4 drugs likely to be effective but preferably as many as possible that are tolerated.

FIRST LINE DRUGS	Guidance	Dosage	Duration
Pyrazinamide	Use in all XDR and pre-XDR cases, unless PZA resistance on culture-based DST or previous drug reaction due to PZA (rash, hepatitis)	30-40 mg /kg/day	24 months
Ethambutol	Consider using in all XDR and pre-XDR cases, unless ethambutol resistance on DST or patient unlikely to tolerate pill burden	15-20 mg /kg/day	24 months
INH high dose 15mg/kg	Include in regimen if inhA mutation alone is present, but exclude if katG present Exclude if previous drug reaction due to INH (rash, hepatitis, neurotoxicity)	15 mg /kg/day	24 months

SECOND LINE DRUGS	Guidance	Dosage	Duration
Kanamycin	Use only if kanamycin/amikacin susceptible on DST Avoid if severe renal impairment If hearing impairment discuss with expert – its use in such a situation depends on a number of factors (see NOTES)	>50kg: 1g/day <50kg: 500-750mg/day Reduce dosing frequency and monitor levels if renal impairment (CrCL<50ml/min)	6-8 months
Levofloxacin	Use in all XDR and pre-XDR (including ofloxacin resistant) cases unless moxifloxacin used instead (see below)	>50kg: 1g daily, <50kg: 750mg daily	24 months
Moxifloxacin	Use rather than levofloxacin if DST reports moxifloxacin susceptible and ofloxacin resistant (if moxifloxacin resistant or moxifloxacin DST not done use levofloxacin instead) When using with BDQ and/or Cfz monitor QTcF weekly for first month then monthly Avoid if QTcF> 450ms	400mg daily	24 months
Terizidone	Use in all XDR and pre-XDR cases Avoid in those with a history of psychosis	>50kg: 750mg daily <50kg: 500mg daily	24 months
Ethionamide	Use in all XDR and pre-XDR cases Avoid if inhA mutation present	>50kg: 750mg daily <50kg: 500mg daily	24 months

THIRD LINE DRUGS	Guidance	Dosage	Duration
Capreomycin	There is 80-90% cross-resistance between aminoglycosides and capreomycin, thus it is now generally not used when there is aminoglycoside resistance. When there is aminoglycoside susceptibility then aminoglycosides are used in instead. If capreomycin DST is available this could be used to direct its use. Some clinicians use it when there is aminoglycoside susceptibility but ototoxicity, but the evidence to support this practice is limited. Avoid if renal impairment	>50kg: 1g/day <50kg: 500-750mg/day	6-8 months
PAS	Use in all XDR and pre-XDR cases	Dose: 4g BD	24 months
Clofazimine	XDR: Use for all patients Pre-XDR: Not used in all patients, but use if patient cannot access or tolerate linezolid, or patient with aminoglycoside susceptible TB cannot tolerate kanamycin When using with BDQ monitor QTcF weekly for first month then monthly	Dose: 100mg daily	24 months
Bedaquiline	Use in all cases of XDR and pre-XDR Avoid if QTcF> 450msec (could start BDQ later if QTcF< 450msec provided no evidence of Rx failure)	400mg daily for 2 weeks, then 200mg daily M, W, F	6 months
Linezolid	Use in all cases of XDR and pre-XDR Avoid if severe anaemia (Hb< 7) or severe peripheral neuropathy (could start linezolid later if anaemia or neuropathy improves provided no evidence of Rx failure). Extension of treatment beyond the indicated 12 months should be reviewed by the clinical advisory committee.	>50kg: Start at 600mg daily. Reduce dose to 300mg if toxicity. Consider transfusion if anaemic. Stop if toxicity life threatening or worsens. <50kg: start at 300mg daily	12 months
Amoxycillin/ Clavulanic acid	Not recommended Exception - unless being used with meropenem in highly drug-resistant cases treated in specialised centres	-	-
Clarithromycin/ azithromycin	Not recommended (lack of clinical evidence)	-	-
Dapsone	Not recommended (lack of clinical evidence)	-	-

NOTES

1. Interpretation of INH resistance mutations from LPA

InhA = low level INH resistance; ethionamide resistance

KatG = high level INH resistance; ethionamide susceptible

2. Stopping or omitting drugs because of toxicity

Generally if toxicity occurs on any of the drugs used above, the decision on whether to continue or stop the drug will depend on severity of the toxicity, duration of Rx received, whether the patient has culture converted, how many other active drugs are in regimen, how essential the drug is to the regimen and whether it can be replaced with another active drug. Each decision is individualised. In some instances treatment is continued with a vital drug despite toxicity (e.g. Kanamycin with ototoxicity in patient who is still culture positive), whereas in other instances a non-essential drug is dropped with only moderate toxicity (e.g. PZA for moderately severe hepatitis).

"Essential" drugs are the quinolone (when susceptible), kanamycin (when susceptible), linezolid and BDQ. Sometimes it may be possible to replace with another drug (e.g. Clofazimine if it is not yet in regimen). Consult with a clinician experienced in XDR TB about this decision.

3. ART regimens

Switch TDF to AZT, ABC or D4T while patient on injectable, provided HepBsAg negative and VL lower than detectable level. Switch back afterwards provided CrCl> 50ml/min

BDQ can be used with NVP and raltegravir and rilpivarine, but not with EFZ. Lopinavir/rit increases BDQ levels 3-fold but the combination is used in patients on second line ART, monitoring QTc more frequently (weekly).

Generally avoid AZT when using linezolid as both are myelosuppressive

4. QT prolongation

The following drugs are associated with significant QT prolongation: BDQ, clofazimine, moxifloxacin. When combinations of these drugs are used ensured QTcF is monitored.

5. ETO and INH

We advise not using ethionamide and INH together, use one or the other as they have similar mechanisms of action and shared neurotoxicity.

6. Continuation of treatment beyond recommended duration

Durations listed above were recommended on the basis of available evidence. Extension of the duration should be considered an 'individualized regimen' and therefore be submitted to the clinical committee for review.

C. Guidance for constructing a regimen for pre-XDR/XDR TB treatment (Children)

Based on recommendations from Prof Simon Schaaf

Guidance specific to paediatric XDR and preXDR TB is provide below. This guidance should be used in conjunction with the overall (adult) guidance provided above).

Drug	Guidance for use in paediatric patients	Paediatric dosage	Duration
Pyrazinamide		30-40 mg /kg/day	24 months
Ethambutol		20-25 mg /kg/day	24 months
Isonaizid		15-20 mg /kg/day	24 months
Amikacin	Amikacin preferred to Kanamycin Not likely helpful if resistant to kanamycin. Not more than 6 months or 4 months after negative culture	15-20mg/kg/day	4 to 6 months
Levofloxacin	Use in all XDR and pre-XDR (including ofloxacin resistant) cases unless moxifloxacin used instead (see below)	15-20mg/kg/day	24 months
Moxifloxacin	Limited data in children; limit to children at least 8 years of age.	10mg/kg/day	24 months
Terizidone		15-20mg/kg/day	24 months
Ethionamide		15-20mg/kg/day	24 months
Capreomycin		15-20mg/kg/day	4-6 months
PAS		150-200mg /kg /day in two divided doses	24 months
Clofazimine	Because capsule size (50mg or 100mg – cannot be cut or split) – could give every second day, as has long half-life.	3-5 mg/kg/day Max 100mg/day	24 months
Bedaquiline	Not currently recommended in children.	No dosing or safety studies yet in children	
Linezolid	At recommended doses above, few adverse effects experienced and good outcome even in XDR-TB cases if used in combination with clofazimine and PAS (and other supporting drugs)	10mg/kg twice daily (suspension available) If >10years of age or weight >25kg, give 300mg daily	6-12 months

D. DR-TB Provincial Clinical Advisory Committees

Each province should establish a management team to support and advise in difficult clinical cases, as well as on medico-legal and ethical issues such as termination of MDR-TB treatment in patients who do not respond to treatment. This committee must be multi-disciplinary and should include medical officers and/or professional nurses from the DR-TB hospital, physicians, pathologists, paediatricians, cardio-thoracic surgeons, pharmacists, public health specialists, radiologists, civil society representatives, social workers, provincial management officials and a specialist in legal and ethical issues. Other representatives from government departments such as Social Development, Correctional Services, Military Health Services, South African Social Security Agency, and the mining industry may serve in this committee.

A sub-committee of clinicians should be established within the broader provincial committee in order to assess individual DR-TB cases presented by medical officers involved in the care of DR-TB patients across the province. The clinical sub-committee should advice on inter alia:

- Appropriate clinical management of individual MDR- and XDR-TB patients who may be eligible to receive treatment with new TB drugs which require committee review (please see guidelines specific to each of the drugs)
- Use of salvage regimens in individual patients with high-grade resistance
- Management of chronic drug resistant TB regarding termination of treatment and palliative care

IF COMMITTEE REVIEW REQUIRED, Patient cases should be submitted to the clinical sub-committee by the MO responsible for the patient's DR-TB care using the standard **Patient Report Form to Request Individualized Regimen** (Annex) for consideration for an individualised regimen with new drugs. The drug regimen should be tailored according to the **Guidance for Constructing a Regimen for DR TB Treatment**.

The clinical sub-committee should consist of:

- CEO or CMO of the hospitals providing DR TB treatment
- Medical officers involved in the care of DR TB patients
- NGO and university partners involved in medical care of DRTB patients, especially those in decentralised sites who will be referring centrally

The names of the identified committee members will be sent to the National DR TB Director for endorsement and appointment. Provincial MDR TB managers will provide the administrative and secretariat support for the establishment of these committees and will serve as the linkage office between the NDOH and the treating sites. The Provincial office will submit the required data to NDOH quarterly until such a time when these functions are activated on the EDRweb and can be captured accordingly.

The full committees should meet monthly (online or conference calls) and should minute their discussions. The clinical sub-committees can review cases submitted between full committee meetings via email. Email discussions should be copied to the Provincial MDR TB managers and should be cognizant of the risks to patient confidentiality when sending identifying information via email. Decisions regarding treatment regimens for patients reviewed by these committees can be taken by 3 or more persons for the clinical sub-committee via email communication. Once 3 persons have approved, then the response can be returned to the applying clinician.

Decisions taken via email should be recorded in the minutes of monthly meetings. Clinical sub-committees can begin meeting prior to the appointment of the full Provincial Committee.

For additional guidance for national and provincial committees, please see: **Management of drug-resistant TB: Policy guidelines (version 2013).**

E. Expanded capacity of clinicians and healthcare workers

In order to expand the capacity of clinicians and healthcare workers with the implementation of new drugs or regimens, training sessions and workshops will be facilitated on a regular basis.

The objectives of these trainings are to ensure that health care workers:

Understand the fundamentals concepts regarding the development of resistance and the prevention of DR TB.

Participants should be able to describe the Epidemiology of DR –TB /HIV AIDS in South Africa

The target audience will be health care workers (nurses, doctors(Including sessional Medical officers), and pharmacists, family physicians, Clinical nurse practitioners), HC managers, counsellors and NGO partners, Health care workers from other government departments as well as health care workers from the private sector. Partners can assist financially with the training. Accreditation will be sought for training sessions and information provided once accreditation is received. In all cases, persons successfully completing the training will receive an appropriate certificate. Trained clinicians will be recorded in the EDRweb register of trained healthcare workers.

A training framework could comprise:

- Fundamentals of DR TB management
- Approach to the diagnosis of TB and DR TB
- National algorithm for the diagnosis and management of TB, with emphasis on the RR-TB confirmation and diagnosis of additional resistance
- Epidemiology of TB , DR-TB and HIV
- Principles of TB treatment and DR TB treatment
- Follow up of patients (clinical monitoring, recognition and management of adverse drug events and programmatic pharmacovigilance)
- Anti – TB medications
- New developments in drugs and diagnostics, e.g. with regards to BDQ/LZD
- Management of DR TB is special situations (e.g. children, pregnancy , co-morbidities)
- Clinical case discussion that will focus on diagnosis, how to approach discordance and strategies to tackle poor follow up
- Update on new clinical developments and research
- Monitoring and evaluation requirements
- Recording and Reporting in line with the monitoring tools i.e. updated manuals and training material for EDRweb

The format of the training / workshops could be in the form of:

- Face-to-face session/ Didactic training
- Webcast
- e learning

While initial training prior to the roll-out of new medications is essential, there is also a need for repeat training, opportunities for training due to staff changes at facilities that are already offering new treatments, and ongoing support for healthcare workers who have been trained.

F. Clinical audit

In order to ensure national guidelines adhered to and implemented, regular clinical audits will be undertaken under the leadership of the DR TB Directorate. This process will review the facility staffing and equipment, monitoring and reporting, and medical files. For monitoring and reporting, in addition to counts of patients reported within the EDRweb and paper registers, medical files will be matched against the registers.

The facility capacity questions are listed below as an example.

Facility capacity questions
How many medical officers?
How many medical officers - vacant posts?
How many medical officers – sessional?
How many professional nurses - full time?
How many professional nurses - part-time?
How many professional nurses – vacant posts?
How many enrolled nurse - full time?
How many data capturers?
How many pharmacists?
Is there a Social Worker available for patients?
Is there a clinical psychologist available for patients?
Is there an audiologist?
Is there an occupational therapist?
Is there a physiotherapist?
Is there chest x-ray?
Is there emergency tray including drugs and defibrillator on site?
How many DR TB beds
Where do you collect sputum
Is there an ECG?

Chapter 3: Management of adverse drug reactions and ototoxicity

Chapter 3: To ensure appropriate management and reporting of adverse drug reactions during DR-TB treatment

A recent study has shown that two thirds of such patients have had at least one medicine stopped temporarily or permanently as a result of ADRs.[7] While some of ADRs are not serious and/or severe and can be resolved with simple interventions e.g. anti-emetics for nausea, there are severe ADRs that can produce permanent disability e.g. hearing loss. Other ADRs may result in permanent discontinuation of drugs e.g. renal dysfunction and psychosis. The following information is based on the WHO's guide for pharmacovigilance during TB treatment[9]; this guide should be read in conjunction with this section.
http://www.who.int/medicines/publications/Pharmaco_TB_web_v3.pdf

An adverse drug reaction is one type of adverse event, defined as any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.

Targeted spontaneous reporting will be used for all RR TB patients in the NTP. As per the WHO guidelines, reporting of ADRs should be part of routine monitoring of patients on RR TB treatment in order to achieve a required standard of care. Additionally, cohort event monitoring (CEM) will be implemented at capacitated sentinel sites (e.g. the BCAP sites) to have a cohort of active pharmacovigilance which can inform practice at other DR-TB treatment sites in the South Africa. Although this system will be first implemented for BDQ, the system is for the pharmacovigilance of DR-TB generally.

A. Seriousness

Each event should be graded as ***serious*** or ***not serious***. For those that are graded as ***serious***, the following reasons for grading of serious[9] should be noted:

- Results in hospitalization (caused or prolonged)
- Results in permanent disability
- Results in congenital abnormality
- Is life-threatening
- Results in death

Serious ADRs are those ADRs that are graded in any seriousness category other than the ***not serious*** category. All serious ADRs must be reported to the MCC and to the PCAC using EDRweb once the functionality is established.

B. Relationship between drug and event

Especially with new and investigational products in the treatment of RR TB, it is important to report on the causality or the relation of ADRs to drugs which the patient is taking. Is there a reasonable possibility that a TB drug caused the event? The following categories can be assigned, as per WHO guidelines[9]:

Probable

The event is an identifiable clinical or laboratory-linked phenomenon; the time elapsed between the administration of the drug and the occurrence of the event is plausible; the event cannot be explained by concurrent disease or any other drug or chemical; the patient recovered within a plausible length of time following withdrawal of the drug; re-challenge did not occur, or the result is unknown. Note that the category of 'certain' is not presented in this list of relationships. Relationships that in other reporting guidelines would be referred to as certain can be categorized as probable.

Possible

The time elapsed between the administration of the drug and the occurrence of the event is plausible; the outcome of withdrawal of the suspect medicine is not known, and/or the medicine might have been continued and the final outcome is not known; and/or there might be no information on withdrawal of the medicine; and/or the event could be explained by concomitant disease or use of other drugs or chemicals; and/or there might be no information on the presence or absence of other medicines.

Unrelated (Unlikely)

The event occurred with a duration to onset that makes a causal effect improbable with the drug being considered; and/or the event commenced before the first administration of the drug; and/or the drug was withdrawn and this made no difference to the event when, clinically, recovery would be expected; and/or it is strongly suggestive of a non-causal relationship if the drug was continued and the event resolved. This category has also been referred to as doubtful.

C. Severity and grading

Severity does not have the same meaning as seriousness, since a patient can experience a severe event such as a skin rash that is not serious. Grading is subjective, based upon perspective of the clinician and patient. Additionally, especially for measurements and laboratory results, grading may differ according to age (adult or child), gender, BMI and weight.

The following will be used for grading the severity of ADR; following common guidelines for treatment of TB and HIV/AIDS:

Mild (Grade 1)

Symptoms cause no or minimal interference with usual, age appropriate, social and functional activities (e.g. going to work, shopping, cooking, using transport, hobbies)

Moderate (Grade 2)

Symptoms cause greater than minimal interference with usual, age appropriate, social and functional activities (e.g. going to work, shopping, cooking, using transport, hobbies)

Severe (Grade 3)

Symptoms cause inability to perform usual, age appropriate, social and functional activities (e.g. going to work, shopping, cooking, using transport, hobbies)

Potentially life threatening (Grade 4)

Symptoms cause inability to perform basic, age-appropriate, self-care functions (e.g. bathing, dressing, toileting, continence, feeding, movement); OR

Medical or operative intervention required to prevent permanent impairment, persistent disability, or death

Death (Grade 5)

D. ADR Reporting

Adverse drug reactions are to be recorded and captured on EDRweb. The ADR will be reported to the MCC and the relevant drug manufacture through the EDRweb once the functionality is established.

Prior to consolidated reporting by the responsible clinician through EDRweb, the responsible clinician will need to submit to the National Pharmacovigilance Centre (NPC) and the manufacturer as per specific guidance provided during training for each new drug. ADR management of patients will be monitored and adjusted accordingly in consultation with the Provincial expert clinical sub-committees.

Required reporting for severe and serious adverse drug events:

- Patient identification
- Type of ADR (system affected)
- Grade of severe adverse drug events (mild, moderate, severe)
- Causality (unrelated, possibly, probably)
- Date of ADR start
- Outcome (e.g. recovered/resolved; permanent disability; death
- Date ADR outcome
- Date reported
- Suspected medication (dose, dates)
- Other medications
- Drug stopped
- Drug re-challenged
- Dose change

The current (12 March 2015) Suspected Adverse Drug Reaction Report form for the HIV/AIDS and TB Treatment Programme is presented below, as well as the instructions for the completion of the form. Contact information for the NPC is as follows:
TEL: 012 395 9506/ 8099

Fax2email: 086 241 2473

Email: npc@health.gov.za

Additional information may be required for specific agents or when modifications to EDRweb reporting are made. On a quarterly basis EDRweb reports on ADR should be reviewed on a national and provincial level.

E. Common ADR during DR TB treatment: grading and management

Please check the **Management of drug-resistant TB: Policy guidelines** for a comprehensive list of ADR common during DR TB treatment.

Renal dysfunction			
Increased waste products in the blood (e.g. creatinine or urea) indicates a decrease in the filtration rate of the kidneys (decreased functioning). Kidney dysfunction may also lead to hematuria, proteinuria, and/or increased potassium.			
Related drugs	Km, Am, Cm, Sm		
Monitoring tests	Glomerular Filtration Rate using the Cock Croft Gault formulation *		
Monitoring schedule	Monthly in intensive phase		
Grading	**Mild** GFR of 60 to 89 mL/min/1.73m^2 with evidence of kidney damage	**Moderate** GFR of 30 to 59 mL/min/1.73m^2	**Severe** GFR of 15 to 29 mL/min/1.73m^2 Or requiring dialysis
Indicated actions	Drug substitution for moderate to severe. Continue for mild reaction; monitor 2 weekly		

*There are different formulas to calculate creatinine clearance or estimated glomerular filtration rate (eGFR). These terms are often used interchangeably as creatinine clearance is an approximation of eGFR.

The MOST important consideration is to ensure that you are using the formula that matches the units the creatinine was reported in.

For example, in the SA 2013 ART Guidelines, creatinine values are presented in uMol/L , which relates to the following formula:

$$\text{eGFR} = \frac{(140 - \text{age}) \times \text{Mass (in kg)}}{\text{serum creatinine (in uMol/L)}} \quad \times 0.85 \text{ for female}$$

- In the SA 2013 MDR-TB Guidelines, creatinine values are presented in mg/dL and the guidelines provide this formula:

$$\text{eGFR} = \frac{(140 - \text{age}) \times (\text{ideal body weight in kg})}{(\text{serum creatinine in mg/dL}) \times 72} \quad \times 0.85 \text{ for female}$$

Neuropsychiatric			
Alteration in personality-behaviour or in mood (e.g., agitation, anxiety, depression, mania, psychosis)			
Related drugs	Terizidone		
Monitoring tests	Clinical review by medical officer		
Monitoring schedule	Monthly or as required by symptoms		
Grading	**Mild** Alteration causing no greater than minimal interference with usual social & functional activities	**Moderate** Alteration causing inability to perform usual social &functional activities	**Severe** Behaviour potentially harmful to self or others (e.g. suicidal and homicidal ideation or attempt, acute psychosis); OR Causing inability to perform basic self-care functions
Indicated actions	Drug substitution for moderate or severe.		

Hepatic toxicity			
Drug-induced liver injury. symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly			
Related drugs	Bedaquiline, PZA, PAS, ETO, INH		
Monitoring tests	alanine transaminase (ALT), aspartate aminotransferase (AST), and bilirubin(Bili)		
Monitoring schedule	Baseline, monthly while on related medications, and as needed according to symptoms An increase in serum aminotransferases to >3x upper limit of the normal should be followed by repeat testing within 48 hours. Testing for viral hepatitis should be performed and other hepatotoxic medications reviewed and be considered for discontinuation.		
Grading	**Mild** ALT 1.25 – 2.5 x ULN AST 1.25 – 2.5 x ULN Bili 1.1 – 1.5 x ULN	**Moderate** ALT 2.6 – 5.0 x ULN AST 2.6 – 5.0 x ULN Bili 1.6 – 2.5 x ULN	**Severe** ALT 5.1 – 10.0 x ULN AST 5.1 – 10.0 x ULN Bili 2.6 – 5.0 x ULN
Indicated actions	Discontinue BDQ if ALT/AST elevations severe or persist beyond 2 weeks. Consider other anti-TB drugs as cause; consider re-challenge with BDQ if another drug identified as cause.		

F. Protocol for monitoring and managing ototoxicity during DR-TB treatment

Prior to the introduction of the new drugs and drug regimens described in these guidelines, the drug regimens used to treat DR-TB in South Africa (as per 2011 and updated 2013 guidelines) involve the use of second line aminoglycoside antibiotics such as kanamycin and amikacin and the cyclic polypeptide capreomycin, also referred to as second-line injectable drugs (SLDs). These drugs are usually given for a minimum of 6 months, although in children the duration of aminoglycosides may be shorter.

A common ADR related to SLD used in DR-TB treatment is ototoxicity, or 'ear poisoning'. Exposure to ototoxic drugs damages structures of the inner ear. Symptomatic hearing loss presents as tinnitus, decreased hearing, blocked sensation, perception of fluctuating hearing and hyperacusis/recruitment.

Ototoxicity can present as cochlear toxicity leading to sensorineural hearing loss (SNHL)and/or vestibular toxicity leading disequilibrium. SNHL is a well-documented adverse event associated with aminoglycoside treatment and is most likely due to damage to the sensory hair cells and the stria vascularis in the cochlea which is permanent. There appears to be a genetic predisposition to the development of ototoxicity with aminoglycosides. Point mutations in the small (12S) ribosomal RNA gene have been described in a number of families with inherited susceptibility to ototoxicity. Genetic deafness accounts for approx. 60% of SNHL. Sustained or excessive peak serum concentrations are thought to be a risk factor. The cumulative dose plays an important role in the onset and severity of SNHL.

1. Measurement and grading of hearing loss

The major components evaluated in a hearing loss are the frequency and the intensity. The frequency refers to the pitch or tone at which the patient has lost hearing. Human hearing is typically in the range 20Hz (a low pitch sound) to 20,000Hz (a high pitch sound). The intensity refers to the loudness of the sound (expressed in decibels) required to be heard.

It is also important to classify the hearing loss in a systematic manner using a grading system. Hearing impairment can be regarded as a sufficient increase in the threshold to interfere with the understanding of speech in sentence forms in normal quiet surroundings e.g. the home. Speech ranges in frequency between 250 Hz and 5000Hz; with an acceptable, intelligible, hearing level considered at 25dB. Early ototoxic (SNHL) hearing loss may go unrecognized by the patient and initially manifests as an increase in the threshold of highest frequencies (>4000 Hz). With progression, lower speech frequencies are affected, with the patient becoming profoundly deaf. This occurs even if the offending drug is discontinued.

Hearing loss can be unilateral or bilateral. Different patterns can be present in each ear.

Loss can be sensorineural, conductive or mixed (a hearing loss with both sensorineural and conductive components).

Using otoscopy and tympanometry, it is possible, to determine whether the hearing impairment is caused by a conductive component or by a sensorineural element. This would then be confirmed by Pure Tone Audiological (PTA) testing (AC and BC testing).

OtoAcoustic Emissions (OAEs) testing can also be done. OAEs are natural sounds emitted by the cochlear when stimulated. They are extremely sensitive and can detect subtle and early changes in cochlear integrity prior to the audiogram detecting changes or the patient noting any changes. High frequency OAEs (2000, 4000, 6000, 8000, 10000 and 12 000Hz) are used at every baseline measure and can be used monitoring tool.

If Pure Tone Audiological (PTA) testing cannot be done on each patient weekly, the OAEs can be done weekly as an indicator of cochlear stability or change.

2. Definition of ototoxicity

In a review article Seddon et al (Eur Res J 2012;40(5):1277-86) discuss the American Speech-Language-Hearing Association (ASHA) guidelines regarding hearing screening for adults and children of different ages. ASHA also provides a guideline for the management of individuals receiving cochleotoxic drug therapy.

This guideline suggests that PTA testing should be carried out at 250Hz to 8,000Hz and where possible 12,000Hz. Additionally octave and inter-octave intervals (1500, 3000 and 6000 Hz) at baseline and, for ototoxic antibiotics, testing should be weekly. Ideally ultra-high frequency audiometry (>8000Hz, 12000Hz to 20000Hz) should be assessed as well as this allows for changes to be recorded and documented before frequencies in the speech spectrum become affected.

PTA should continue throughout the duration of treatment and at three and six months following discontinuation of treatment due to the lengthy half-life of ototoxic drugs.

Hearing loss should always be compared to baseline measurements and ototoxicity is defined as any of:

- 20dB decrease at any one frequency,
- 10dB decrease at any two adjacent frequencies or
- Loss of response at three consecutive test frequencies where responses were previously obtained.

Hearing loss can be unilateral (either ear) or bilateral (both ears). Ototoxicity in either ear or both ears that meets the definition above requires management as described below.

3. Recommended monitoring for ototoxicity during DR-TB treatment

The first hearing test (PTA and OAE) should ideally be done prior to the use of any ototoxic drug. However, this should not delay the start of TB treatment. In practice, the first hearing test should be done with other baseline testing or within the first week (7 days) of treatment. Hearing loss and ototoxicity from SLDs during DR-TB treatment can occur quickly in high risk patients and thus the baseline measurements should not be delayed beyond this period.

In the event that recommended testing cannot be completed as per the schedule below, a hearing handicap inventory assessment should be done (See below **Minimal screening and identification of patients at high risk of ototoxicity**).

Hearing loss is either sensorineural, conductive (normal cochlea/nerve functioning but with middle ear pathology causing hearing loss) or mixed (a hearing loss with both sensorineural and conductive components) which is why it is important to assess accurately.

If the middle ear pathology is present and is causing a conductive component to the hearing loss, hearing sensitivity must still be assessed to determine the functioning of the cochlea. Using otoscopy and tympanometry aid in diagnosing the type of hearing loss (conductive, sensorineural or mixed). However, a complete pure tone audiological testing battery (air conduction and bone conduction testing) must be performed to diagnose the type of hearing loss and accurately assess cochlear function.

If PTA cannot be done on each patient weekly, OtoAcoustic Emissions (OAEs) testing can also be done. The OAEs can be done weekly as an indicator of cochlear stability or change. OAEs are natural sounds emitted by the cochlear when stimulated. They are extremely sensitive and can detect subtle and early changes in cochlear integrity prior to the audiogram detecting changes or the patient noting any changes. High frequency OAEs (2000, 4000, 6000, 8000, 10000 and 12000Hz) are used at every baseline measure and can be used as a monitoring tool.

4. Monitoring schedule

Baseline testing:

The first hearing test (PTA and OAE) should ideally be done prior to the use of any ototoxic drug. However, this should not delay the start of TB treatment. In practice, the first hearing test should be done with other baseline testing or within the first week (7 days) of treatment. Baseline testing should be done even in patients who have pre-existing hearing loss.

During intensive phase treatment:

Monthly during treatment with ototoxic drugs. If resources allow, weekly hearing tests (with UHFA) are preferred, especially for patients at risk of ototoxicity.

Continuation phase:

Once ototoxic drugs have been discontinued (whether at the end of intensive phase or if substitution made prior to completion of intensive phase), hearing loss can continue as the damage may be from a cumulative effect. However, the priority is on identifying early signs of ototoxicity to prevent further damage, i.e. prior to the completion of the ototoxic drug treatment. Testing should be done at 3 and 6 months after discontinuation of treatment with the ototoxic drug.

5. Hearing tests

Baseline hearing test should include:

1. Case history:

- History of hearing loss
- Symptoms of damage to the ear (e.g. tinnitus, hyperacusis)
- Related medical history
- Exposure to ototoxic drugs (initiation, frequency, duration).

2. Outer and Middle ear status examination

- Otoscopy should be done at all hearing tests to exclude wax or other foreign bodies and to visualise the tympanic membrane (for middle ear pathology).
- Tympanometry must also be performed. This provides information about the integrity of the middle ear without which an accurate diagnosis could not be made. Furthermore it guides the interpretation and understanding of results from the pure tone results (conductive, SNHL or mixed).

3. Pure Tone Audiological testing

- Ultra high frequency Audiometry (UHFA) should be completed for frequencies 250Hz to 20 000Hz at octave as well as inter-octave intervals (1500, 3000 and 6000 Hz). If this is not possible, testing must at least be done for the frequency spectrum 250Hz – 8000 Hz (with inter-octaves).

4. OtoAcoustic Emissions

- High frequency OAEs (2000, 4000, 6000, 8000, 10000 and 12 000Hz) should be routinely conducted.
- Testing should continue monthly for the full duration the patient is on the injectable drug including six months after finishing the injections. Hearing loss can occur even once the drugs have been stopped.

6. Recommended management of detected ototoxicity

The options available if hearing loss is detected are:

- Stop the drug
- Reduce the dose
- Increase the length of the dose interval; or
- Retain current therapy while increasing the frequency of monitoring to identify further deterioration early.

There is no evidence from randomised controlled trials to support any of these interventions. In a paper by Peloquin et al (CID, 2004 Jun;38(11):1538–44) patients were randomized by drug to receive 15 mg/kg per day or 25 mg/kg 3 times per week of intravenous streptomycin, kanamycin, or amikacin. Ototoxicity was not associated with the size or frequency of the aminoglycoside dosage, but it was associated with older age, longer duration of treatment, and greater total dose received.

It is recommended that, patients with pre-existing hearing loss of whatever type or severity be started on BDQ and/or LZD

• If a patient on treatment has hearing loss, check that the dosage of the aminoglycoside given is appropriate for weight and age, as toxicity increases with both.

• Ototoxicity is potentiated by certain diuretics (especially loop diuretics) so these should be avoided.

If ototoxicity hearing loss occurs, the SLD should be stopped and changed to another agent e.g. BDQ or LZD

• Monitoring after hearing loss should be continued monthly even after the SLD has been stopped.

• Rehabilitation following diagnosis of hearing loss

While the benefit of hearing aids is minimal to moderate, patients with hearing loss can benefit from their use. Patients should be referred to audiologist and rehabilitation services as appropriate and available.

7. Minimal screening and identification of patients at high risk of ototoxicity

Even if hearing tests are not available at the recommended intervals above, minimal screening and identification of patients at high risk of ototoxicity can help to prioritize the available resources and prevent hearing loss.

Hearing handicap assessment:

ASHA hearing handicap assessment (mentioned above) can be performed if hearing loss suspected; however, please note that these symptoms of hearing loss would be AFTER damage has already been done at the higher frequencies.

1. Does a hearing problem cause you to feel embarrassed when you meet new people?
2. Does a hearing problem cause you to feel frustrated when talking to members of your family?
3. Do you have difficulty hearing / understanding co-workers, clients or customers?
4. Do you feel handicapped by a hearing problem?
5. Does a hearing problem cause you difficulty when visiting friends, relatives or neighbors?
6. Does a hearing problem cause you difficulty in the movies or in the theatre?
7. Does a hearing problem cause you to have arguments with family members?
8. Does a hearing problem cause you to have difficulty when listening to TV or radio?
9. Do you feel that any difficulty with your hearing limits your personal or social life?
10. Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?

Patients at high-risk for ototoxicity:

Of note, ototoxicity can be cumulative, therefore, patients who have previous exposure to SLD, including SM, KM, AM, and CM are at a higher risk of developing ototoxicity than patients never exposed to these treatments. In particular, many patients in the DR-TB treatment programme in SA would have previous exposure to SM injections. Duration of SLD treatment and number of episodes would have proportional increases to the risk of developing ototoxicity during this treatment.

Other ototoxic drugs (not used for TB or DR-TB treatment) should also be considered and history of use of these drugs obtained prior to initiating DR-TB treatment if possible: e.g. other aminoglycosides and medications containing platinum.

Patients who already have measurable (or complain of) hearing loss in one ear (unilateral) should also be managed as high-risk as unilateral loss to the other ear would be more disabling.

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Chapter 4: Monitoring and Implementation

Chapter 4: To ensure oversight and management from the national level and implementation at provincial and district levels.

A. Oversight and management of roll-out

Overall, the NTP has the responsibility for maintenance of public health in its approach to TB management and prevention. The NTP has responsibility to protect patients, minimize the risk of treatment failure, minimize emergence of DR-TB, and ensure compliance with regulatory guidance. Also, importantly, it needs to ensure fairness and equity and the principles of Batho Pele.

It is therefore important to follow the following steps in the introduction of new TB drugs:

- Formation of a working group
- Elaboration of the protocol coordinated by NTP with support from partner organizations
- NTP to appoint a national clinical advisory committee to assist with patients' selection
- Regulatory authority approval to be applied for (if required)
- Ethics approval applied for (when necessary)
- Identification of health care workers and treatment sites
- Site activation
- Involvement of provincial TB managers, provincial review committees, and pharmaceutical and therapeutic services

A plan for scale up need to be designed for each new drug or group of drugs introduced at any particular point of time.

This plan needs to:

- Be SMART
- Consider human resource Capacity
- Quantify resources required such as ECG, portable audiometry etc.
- Clearly address issues with regard to adherence to treatment
- Ensure pharmacovigilance
- Detail supply chain management
- Indicate laboratory support requirements
- Adjudge model of care: inpatient or outpatient initiation and management
- Include Standard Operating Procedure (SOP) reflecting indications, contra-indications and how to use the new drug(s), along with monitoring protocols

1. Provincial leadership:

Districts, sub-districts and facilities need to work with the provincial TB managers in the scale up of new TB drugs. Provincial review committees need to oversee the introduction and the scale of new TB drugs. Existing terms of standard operating procedures for MDR-TB provincial review committees need to be amended to include these responsibilities. Provinces should identify further expertise required to strengthen their review committees if need be, especially the clinical sub-committees. Standard operating procedures for DR-TB Provincial Clinical Advisory Committees can be found in the MDR TB guidelines. Agreement should be reached with the DR-TB Provincial Clinical Advisory Committees and CEO of each site defining programme and agreeing to referral mechanisms and budget implications. Then the drug can be distributed.

2. Expansion of capacity:

Additional training and refresher courses are necessary before introduction of new TB drugs. Partner support is required for funding and implementation of training.

Additionally, training in good clinical practice (GCP) is essential for medical practitioners, nursing personnel and pharmacists working under clinical access programme protocols. However, once the medication is registered by the MCC and the clinical access programme phased out, GCP training is optional rather than required.

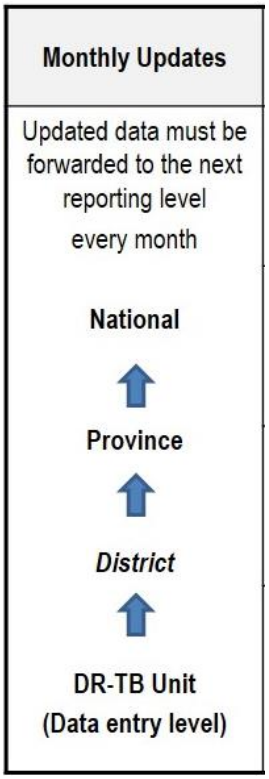
B. Reporting system: EDRweb

A national monitoring system the EDRweb has been established. This system will be further modified with the sections indicated in this framework and to support the roll-out of new drugs. Training on the revised system will follow once the updates have been made. Further, it will be important for data capturing to happen within the facility to improve the speed, accuracy, and completeness of data entry as well as the use of the data entered by healthcare workers.

1. Data management flow: Paper-based sites

Site-based datacapturer to capture within the DR TB paper register from clinic files. It is the datacapturers' responsibility to ensure information captured completely, accurately and timeously (daily updates)

On a routine basis, at least weekly, the sub-district / district / major site will ensure the paper-based register data is captured from all facilities into EDRweb.



2. Data management flow: EDRweb capacitated sites

Site-based datacapturer to capture within EDRweb daily to update new enrollments and cohort.

It is the datacapturers' responsibility to ensure information captured completely, accurately and timeously (daily updates) within EDRweb.

3. Reporting deadlines

Reporting deadlines are announced each year by the RIMES Directorate of the TB Cluster, however, generally the data submission date is on the last Friday of the month following the quarter. As with the reporting of drug-sensitive TB, data flows up from the capturing unit to the district, province and national each month. Each of the levels above the data capturing unit has specific responsibilities for data validation, verification, and quality.

4. Roles and responsibilities

Data capturer

- Capture DR TB patients into the paper-based DR TB register or EDRweb timeously
- Ensure that DRTB Register are captured completely, accurately and timeously (daily updates) onto the EDRWeb
- Report to the site data manager or information manager, regardless of the funding support
- Data capturers provided by partner NGO will be allowed 1 day per month to attend off site meetings
- DR TB initiation facilities with a 'site' established within EDRweb, should have one or more data capturers according to the number of patients (workload). Workload within the sites should be shared among the data capturers, but not assigned according to the funding support for the data capturer or the drug regimen of the patients.
- Responsible for accurate data capturing from data collection tools to the EDRWeb as per specified program guidelines

National DR TB Data Manager

- Will report to Dr Ndjeka
- Will facilitate collation of data from Provincial
- Will support the sites and oversee data capturers
- Responsible for validation and verification of data
- Report issue to relevant partner NGOs as appropriate

Partners supporting data capturing and data cleaning

- Specific working arrangements will be signed with each partners indicating that NDOH remains the custodian of the data

5. Procedures for transfer of patients

Initiation facility should record transfer out. Patient outcomes and subsequent data entry after the transfer are the responsibility of the receiving site. The treatment outcome is the responsibility of the receiving site.

Use of SA IDs is important to ensure adequate matching of patients across sites.

Matching of transfer outs to transfer in records is the responsibility of the appropriate level of data manager above the facility, i.e. district if for 'move' to a new site within the district, provincial if across districts within the province, or national if across provinces. Transfer in/outs will be merged rather than one entry deleted, so as to retain information from both periods of the patient's treatment history.

6. Procedures for deleting patients

Facility datacapturer to send identification of duplicate or error patients

Data manager responsibility for identifying duplication or errors and to confirm which entry to delete.

Data manager has responsibility for the deletion of patients and informing facility of the change in entries.

7. Standard RR-TB patient outcomes

Outcome	**Definition of criteria**
Cured	A patient who has TB culture converted, received treatment for 18 months post culture conversion, remained clinically stable **and** has 3 or more consecutive monthly negative TB culture results after the intensive phase.
Completed	A patient who has TB culture converted, received treatment for 18 months post culture conversion, **and** remained clinically stable but has only 1-2 negative TB culture results after the intensive phase.
Died	A patient who dies for any reason during the course of treatment.
Failed	Treatment terminated or need for permanent regimen change of at least 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 (ADRs).
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown). Not evaluated cases should be identified by the data capturer or data manager and evaluation requested of the treating clinician.
Culture conversion (interim outcome)	The terms “conversion” and “reversion” of culture as used here are defined as follows: Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion. Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.

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Chapter 5. Bedaquiline

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Chapter 5: Bedaquiline as a new treatment for DR-TB

Bedaquiline offers a new mechanism of anti-TB action by specifically inhibiting mycobacterial adenosine triphosphate synthase. Bedaquiline, when given with other existing MDR-TB drugs, increased the proportion of people whose sputum cultures converted to negative after 2 and 6 months of treatment. Bedaquiline, when given with other existing MDR-TB drugs (optimized background regimen, or OBR), also reduced the time to sputum culture conversion, offering the possibility of shorter treatment duration in the future.

The Medicine Control Council (MCC) of South Africa approved a national programme to treat XDR-TB or pre-XDR TB patients (defined as MDR-TB with additional resistance to either a fluoroquinolone or a second-line injectable medicine) with bedaquiline in December 2012 to allow patients with limited treatment options safe access to this drug prior to registration: the Bedaquiline Clinical Access Programme (BCAP).

Patients were presented to a virtual National Clinical Advisory Committee consisting of clinicians with experience in RR- TB. Once consensus was reached on the appropriateness of BDQ and the OBR by three of the members of this eight-member body, the case was referred to Janssen Pharmaceutical. Once both of these approvals were received by the sites, a further approval from the MCC was obtained. The duration of this process was typically 2-4 weeks, during which time the patient was initiated on the OBR.

While only early outcomes have been achieved for most of the patients in this BCAP cohort, the rate of culture conversion and the low mortality are promising in this highly resistant and often HIV-infected group of patients.

Sirturo (bedaquiline, BDQ) from Janssen Pharmaceutica, was subsequently registered in South Africa in October 2014 for use in HIV-negative or HIV-infected, ART naïve patients 18 years or older who have laboratory confirmed MDR-TB. Additionally, the World Health Organization (WHO) has issued guidance on the treatment of MDR-TB with bedaquiline.[10]

The BCAP clinicians and advisors have met the DR TB Directorate within the NDOH and together have prioritized the following inclusion and exclusion criteria for the use of BDQ within South Africa. Based upon programmatic pharmacovigilance, continued learning from the BCAP patients (many of whom are now on continuation phase treatment), and experience with the roll-out according to the guidelines below, additional guidance and expansion of these criteria may be issued in January 2016.

A. To ensure the appropriate selection of patients for BDQ treatment

1. Initial BDQ sites

The BCAP was initially started at 11 sites with at least one in each province. These sites were capacitated to treat the selected patients safely with special attention placed on monitoring the known bedaquiline ADRs. Initial Training and regular mentorship of these sites was undertaken by the National Department of Health.

Access to bedaquiline for the first year of roll out will be limited to the following 13 sites across all provinces:

- Eastern Cape - Fort Grey Hospital, Jose Pearson
- Free State – Dr JS Moroka
- Gauteng - Sizwe Hospital, Helen Joseph Hospital
- KwaZulu Natal – King Dinizulu Hospital Complex
- Limpopo – FH Odendaal
- Mpumalanga – Witbank Hospital
- Northern Cape – Harry Surtie Hospital, West End Hospital
- North West – Klerksdorp-Tshepong Hospital Complex
- Western Cape – Brooklyn Chest Hospital, MSF Khayelitsha CHC

2. Who is eligible for BDQ in the SA NTP?

Patients ≥18 years of age; *and*

Laboratory-confirmed RR-TB (at least resistance to RIF) by culture-based phenotypic drug sensitivity testing or genotypic line probe assay or PCR testing (Xpert MTB/RIF) from pulmonary and/or extrapulmonary sites ; *and*

No history or family history of QT prolongation; *and*

Baseline QTcF≤ 450 msec; *and*

Any one of the following three conditions:

a. Drug resistance in addition to RR TB:
   XDR TB; or

   preXDR TB (resistant to either fluoroquinolone or second line injectable drug); or

   both inhA and katG mutations;

b. Documented / recorded intolerance to 2nd line anti-TB treatment at baseline (prior to treatment initiation) or during RR TB treatment, e.g. hearing loss, renal dysfunction

c. History of, or surgical candidate for pneumonectomy or lobectomy

Patients who meet the above criteria, regardless of HIV infection status or concomitant treatment with ARVs can be considered eligible *for the 6 months of BDQ treatment*.

Please see *section: B. Effective management of patients currently or previously treated with BDQ* for additional guidance on HIV-infected patients.

Patients who meet the above criteria, regardless of the site of TB infection, e.g. inclusive of patients presenting with extrapulmonary TB (EPTB), should be considered eligible for BDQ.

NB: Patients who meet the above criteria are *not required* for review by the National or Provincial DR TB committees.

NB: Continuation of BDQ beyond 6 months is required to be presented for review by the clinical advisory committee.

The principle of not adding a single drug to a failing regimen applies. If the regimen is working – clinical improvement, culture conversion – but the patient needs BDQ for toxicity or surgical reasons, then single drug substitution can be warranted.

3. Which cases should be reviewed by a DR TB clinical advisory committee prior to prescribing BDQ?

1) Patients has already had > 3 months of pre-XDR or XDR treatment prior to BDQ initiation; OR
2) Patient has fewer than 2 of the following 4 drugs 'counted' to be effective in regimen:

Drug	Count if
Injectable	Only count if no documented resistance to any second line injectable on DST (specimen taken within last 3 months)
Quinolone	Only count if no documented resistance to any fluoroquinolone on DST (specimen taken within last 3 months)
Bedaquiline	Do not count if exposed to clofazimine for more than 3 months previously
Linezolid	Do not count if exposed to linezolid previously for DR TB

***Note**: 'counting as effective' does not mean that a drug which is 'not counted as effective' should not be prescribed; it means that further clinical review is needed for these patients to address the appropriate regimen.*

3) Patients does not have at least one other drug (in addition to those listed in table above) to which their TB is susceptible or predicted susceptible (because not previously exposed); OR
4) Age < 18 years; *or*
5) Pregnant; *or*
6) Patients with MDR treatment failure (smear or culture positive at 8 months on MDR treatment) without proven 2nd line resistance.

Additionally, extension of BDQ treatment beyond the current standard of 6 months must be submitted for review by the DR TB clinical advisory committee.

These cases may be presented by MOs using the same Patient Report Form as Annex: **Request for individualised patient regimen**. Approval does not have to wait for the next meeting but can be done by the same method as employed by BCAP, e.g. electronic approval by a quorum of 3/8 membership.

4. Contraindications

The WHO companion guide on the use of BDQ classifies the contraindications for BDQ as as absolute or relative. The absolute contraindications for use within the SA NTP are as those recommended by WHO:

Absolute contraindications:

- **Patient refuses consent.** The patient decides to not accept treatment after being properly counselled and informed about the benefits and risks associated with its use.
- **High risk for cardiac complications.** Patient has a QT interval greater than 500 ms, history of torsades de pointes or cardiac ventricular arrhythmias or severe coronary artery disease.
- **History of severe allergic reaction to bedaquiline.**

Special note should be made of drugs that are commonly prescribed during DR-TB treatment which are contraindicated with BDQ, namely tricyclic antidepressants, including amitriptyline and neuroleptics, such as haloperidol.

Package insert

Prescribing clinicians should refer to the package insert for further information. According to the package insert at the time of these guidelines, the following drugs are contraindicated:
Class 1a or Class III antiarrhythmic drugs (such as amiodarone, sotalol, procainamide, dysopyramide and quinidine)

Tricyclic antidepressants, including amitriptyline, doxepin, desipramine, imipramine, clomipramine; the non-sedating antihistamines astemizole and terfenadine;

Neuroleptics, such as phenothiazine, thioridazine, haloperidol, chlorpromazine, trifluoperazine, percycline, prochlorperazine, fluphenazine, sertindole, and pimozide;

Prokinetic cisapride

Quinolone antimalarial (e.g., chloroquine and quinacrine)

Patients with known allergies, hypersensitivity, or intolerance to BDQ or its excipients should not be put on BDQ.

Relative contraindications:

For relative contraindications, BDQ could be used in situations where the options of treatment are extremely limited and the benefit outweighs the potential risks; in these cases, the case should be reviewed and approved by either the PCAC or the National Clinical Advisory Committee.

Concomitant use with the following QTc prolonging medications should be avoided:

Moxifloxacin: Levofloxacin should be substituted for MFX when possible; **LFX is the quinolone of choice when using BDQ**, as MFX may also prolong the QTc interval. However if the DST indicates MFX sensitivity and LFX/OFX resistance, MFX should be used with weekly QTc monitoring for the first month.

Breastfeeding females, as per national guidelines for treatment of DR-TB **Management of drug-resistant TB: Policy** guidelines, should be advised and supported to formula feed to minimize exposure of the infant to DR TB.

For HIV-infected patients on ART: BDQ can be used with NVP and raltegravir, but not with EFV. It is reported that co-administration with of efavirenz (EFV) and BDQ may result in reduced bedaquiline exposure and loss of efficacy and therefore is not recommend. Please see *section:* **Objective 2.To ensure the effective management of patients currently or previously treated with BDQ** for additional guidance on additional guidance on appropriate ART regimens for HIV-infected patients.

As per the package insert for Kaletra (Lopinavir/ritonavir (LPV/r)): QT interval may be prolonged on LPV/r. Please see *section:* **Objective 2.To ensure the effective management of patients currently or previously treated with BDQ** for additional guidance on appropriate ART regimens for HIV-infected patients.

B. Effective management of patients currently or previously treated with BDQ.

1. Additional safety investigations

Patients initiated on BDQ should be managed as inpatient or outpatient depending on the existing national guidelines and programmatic implementation and capacity within the provinces.

All standard safety investigations as per the national guidelines for DR TB treatment **Management of drug-resistant TB: Policy guidelines** are applicable for patients treated with BDQ, special note should be made of follow-up investigations for patients with abnormal or outside the upper limit of normal results.

Additional safety investigations required for BDQ:

- ECG prior to starting BDQ (baseline)
- Monthly thereafter unless clofazimine or moxifloxacin is used. In this case, weekly ECGs should be done for the first month.

2. Background regimen

In patient who has MDR TB, the standardized regimen should be used with the exception of moxifloxacin. The quinolone that should be used with BDQ is levofloxacin.

As per national guidelines the standard regimen should be constructed with at least 3 anti-tuberculosis drugs to which the patient is known to be susceptible on DST or likely to be susceptible, based on known treatment history.

In cases where both INH mutations are present, neither ethionamide nor high dose INH should be used as these are unlikely to be effective.

In cases where one of the drugs in the standard regimen are not tolerated, this drug may be replaced by BDQ.

For patients with preXDR or XDR an individualized regimen will be constructed according the algorithm. Please see the **Guidance for pre/XDR TB regimens**.

3. Management of HIV-infected patients

HIV infected patients who are ART naïve or currently on ART may be started on BDQ. As per national ART guidelines, HIV-infected patients not yet on ART should be initiated on ART.

For patients requiring ART the following are options

- NVP and two appropriate NRTIs if the CD4 is <250 in women and <350 in men
- LPV/r-containing regimen with two appropriate NRTI for patients that require second line therapy or have CD4 is greater than 250 in women and 350 in men
- Rilpivirine and raltegravir can be considered if available.

As per the package insert under US approval of Sirturo[11]:

Efavirenz (EFV) co-administration with BDQ may result in reduced bedaquiline exposure and loss of efficacy. Efavirenz is a moderate inducer of CYP3A activity and co-administration with BDQ may result in reduced BDQ exposure. This may cause a loss of efficacy of BDQ and is not recommended.

Nevirapine (200 mg twice daily for 4 weeks) was co-administrated with bedaquiline in HIV-infected patients with no clinically relevant effect on BDQ exposure (AUC increased by 3%, Cmax decreased by 20%) Lopinavir/ritonavir (400/100 mg twice daily) was co-administered BDQ to 16 HIV/TB-negative subjects causing an increase in BDQ AUC by 22% and had no effect on Cmax.

Should a patient who is already on ART need to start BDQ, a viral load test must be done. If the patient has a suppressed VL and a nadir CD4 less than 250 in women and 350 in men, the patient can be changed to NVP. If the patient does not have full viral suppression or a higher nadir, the option of LPV/r should be considered.

4. Surveillance of BDQ drug resistance

The introduction of bedaquiline (BDQ) into the MDR treatment program in South Africa is an important step towards potentially improving patient outcomes. However, concerns of drug resistance emerging are real and such resistance has been recently documented, though the occurrence is very low. Additionally, evidence has emerged that efflux pumps associated with clofazamine resistance may also confer resistance to BDQ.

Thus surveillance to monitor the emergence of drug resistance to BDQ is an essential component to the large scale programmatic roll out of the drug in South Africa. Currently there exists no validated method for testing BDQ resistance and this weakness has been noted in the WHO interim guidance document. This is being addressed through collaboration within the Supranational Reference Laboratory Network, including the SA National TB Reference Laboratory (NTBRL).

As the introduction of BDQ is set to begin early in 2015, an interim measure is required. All patients receiving the new drug should have the following BDQ MIC testing performed:

1. Baseline testing coupled with a laboratory request form indicating prior use of clofazimine (as these drugs share metabolic pathways).
2. Testing at week - 8 (2 months)
3. Testing at week-24 (6 months) (indicative of treatment failure)

Initial testing would be performed at the NTBRL in the first quarter of 2015 while the major referral laboratories get ready to perform testing. After this period, these selected referral laboratories will test BDQ at three concentrations ranging from 0.03 – 0.12 µg/ml (as supplied by the NTBRL). Any isolates with an MIC of >0.06µg/ml would be sent to the NTBRL for confirmation and testing over a wider concentration range (0.03 – 1.0 µg/ml).

A review of MIC data should be performed on a quarterly basis and any cases where the MIC increased 4 fold from baseline or has an MIC above 0.25ug/ml should be notified immediately to the attending clinician and the National Clinical Advisory Committee. Enhanced surveillance in such cases would be warranted as well as implementation of higher levels of infection control interventions.

C. Appropriate monitoring and managing of adverse drug reactions during DR-TB treatment and effective pharmacovigilance for BDQ.

A process for improved programmatic pharmacovigilance is in progress and guidelines related to sentinel sites and reporting may be issued to update the information is this section. Baseline intolerance and ADRs on RR TB treatment is an indication for use of BDQ and therefore targeted monitoring and management of potential drug toxicity is important for all RR TB treatment. In addition to the ADR which are common during treatment with previous DR TB regimens, the following should be monitored for patients treated with BDQ:

QTc prolongation			
QT interval measures the time between the start of the Q wave and end of the T wave; a lengthened QT interval is a marker for potential tachyarrhythmia and a risk factor for sudden death.			
Related drugs	BDQ, CFZ, MFX		
Monitoring tests	ECG – the QTcF* interval (QT interval corrected using Fridericia formula)		
Monitoring schedule	Baseline and monthly during BDQ treatment. Increased monitoring if MFX is used		
Grading	**Mild** Asymptomatic; QTc interval 450 – 470 msec; OR increase in interval <30 msec	**Moderate** Asymptomatic; QTc interval 450 – 470 msec; OR increase in interval 30-50 msec	**Severe** Asymptomatic; QTc interval ≥500 msec; OR increase in interval ≥50 msec; OR Life-threatening consequence, e.g. Torsades de pointes or other associated serious ventricular dysrhythmia.
Indicated actions	Drug withdrawal for moderate and severe. Consider rechallenge if moderate reaction resolves. Mild reactions should be monitored.		

Many ECG machines calculate the QT interval corrected for the heart rate, however, as there are different calculations used and it is important to identify whether the ECG is producing the QTcF or the QTcB (QT interval corrected using Bazett's formula).

If the ECG does not generate the QTcF automatically, there may be settings that can be adjusted for the reporting. Alternatively, the QT (seconds) and heart rate (beats per minute) can be collected and the QTcF calculated as follows:

RR = 60 / HR QTcF = QT / $\sqrt[3]{RR}$

1. Special situations

In addition to adverse events, the following categories of data are considered to be 'special situations' and also require reporting to MCC and Janssen:

- Drug exposure during pregnancy (maternal and paternal)
- Exposure to bedaquiline from breastfeeding
- Overdose of bedaquiline
- Suspected abuse/misuse of bedaquiline
- Inadvertent or accidental exposure to bedaquiline (e.g., occupational exposure)
- Any failure of expected pharmacological action (i.e., lack of effect) of bedaquiline
- Medication error involving a Janssen medicinal product (with or without patient exposure to bedaquiline, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of bedaquiline
- Unexpected therapeutic or clinical benefit from use of bedaquiline
- Off-label use of bedaquiline

D. Monitoring and reporting

1. BCAP data

NDOH and the partners involved in BCAP have undertaken initial analysis of the learnings and early outcomes of this programme. Ongoing lessons learned, continued follow-up of BCAP patients, and final outcomes will be used to further inform the overall roll-out of BDQ and national DR TB policy. Any publication of the outcomes of these findings will be at the discretion of the NDOH. The National BCAP Committee should, on an annual basis, assess the data and outcomes from BCAP and inform plans for publication as appropriate.

2. Roll-out data

In the first year BDQ roll-out, all designated BDQ treatment sites should provide weekly initiation data to the National DR TB Data Manager. This will form the basis of clinical audits and possible revisions to policy.

The first 500 BDQ patient records will be audited by the NDOH DR TB Directorate.

3. Bedaquiline patient registry

A BDQ registry will be established within EDRweb with additional data entry requirements for all patients who are initiated on EDRweb.