Introduction of bedaquiline for the treatment of multidrug-resistant tuberculosis at country level

Implementation plan

Introduction of bedaquiline for the treatment of multidrug-resistant tuberculosis at country level

World Health Organization

Contents

Abbreviations and acronyms

aDSM	active tuberculosis drug-safety monitoring and management
AE	Adverse event
ADR	Adverse drug reaction
DOTS	directly observed treatment, short-course
DRS	Drug Resistance Surveillance
DST	drug susceptibility testing
ECG	electrocardiogram
EMA	European Medicine Agency
EQA	external quality assurance
FM	fluorescent microscopy
GDF	Global Drug Facility
Global Fund	Global Fund to fight AIDS, Tuberculosis and Malaria
Hgb	haemoglobin
HIV	human immunodeficiency virus
IDA	International Dispensary Association
ISTC	International Standards for Tuberculosis Care
LPA	line-probe assays
MDR-TB	multidrug-resistant TB
ms	milliseconds
NGO	nongovernmental organization
NPVC	national pharmacovigilance centre
NRA	national regulatory authority
NTP	national TB programme
PAS	para-aminosalicyclic acid
PMDT	programmatic management of drug-resistant TB
QT interval	start of Q wave to the end of the T wave on the electrocradiogram
QTc	QT-corrected
QtcF	Fredericia correction method for measurement of QTc interval
RR-TB	rifampicin-resistant TB
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SNRL	supra-national reference laboratory
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TB	tuberculosis
TSH	thyroid stimulating hormone
USFDA	United States Food and Drug Administration
WBC	white blood cell
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB
Xpert® MTB/RIF	assay for *M. tuberculosis* and rifampicin resistance mutations
ZN	Ziehl–Neelsen

Definitions

Active TB drug-safety monitoring and management (aDSM): Active and systematic clinical and laboratory assessment of patients on treatment with i) new anti-TB drugs; ii) novel MDR-TB regimens; or iii) XDR-TB regimens; to detect, manage and report suspected or confirmed drug toxicities.

Adverse drug reaction (ADR): A response to a TB medicine which is noxious and unintended, and which occurs at doses normally used in humans.

Adverse event (AE): Any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.

Extensively drug-resistant tuberculosis (XDR-TB): TB due to a strain of *M. tuberculosis* resistant to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin) in addition to multidrug resistance.

Risk factor: A characteristic associated with an increased probability of occurrence of an event. In the presence of a risk factor, a patient is more likely to develop an adverse reaction.

Signal: Reported information on a possible causal relationship between an adverse event and a TB medicine, the relationship being unknown or incompletely documented previously or representing a new aspect of a known association. The information may arise from one or multiple sources that is judged to be of sufficient likelihood to justify verification.

Monoresistance: Resistance to one first-line anti-TB drug only.*

Multidrug-resistant TB (MDR-TB): TB due to a strain of *M. tuberculosis* that is resistant at least to both isoniazid and rifampicin, which are the two most important first-line drugs to treat drug-susceptible TB.

Polydrug resistance: Resistance to more than one first-line anti-TB drug other than both isoniazid and rifampicin.*

Rifampicin-resistant TB (RR-TB): Resistance to rifampicin with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of monoresistance, polydrug resistance, multidrug resistance, or extensive drug resistance and is detected using phenotypic or genotypic methods.

Serious adverse event (SAE): An adverse event which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. Serious events which do not result immediately in one of these outcomes but which might require an intervention to prevent it from happening are included. SAEs may require a drastic intervention such as termination of the drug suspected of having caused the event.

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* While it has been the practice until now to limit the definitions of monoresistance and polydrug resistance to first-line drugs only, future drug regimens may make it important to classify patients by their strain resistance patterns to fluoroquinolones, second-line injectable agents, as well as any other anti-TB drug for which reliable drug susceptibility testing (DST) becomes available.

Acknowledgements

Introduction: why an implementation plan?

The emergence of drug-resistant tuberculosis (TB) is a major threat to global TB care and control. In 2014, the World Health Organization (WHO) estimated that 480 000 people developed multidrug-resistant TB (MDR-TB), of which 190 000 died *(1)*. MDR-TB is a form of TB caused by a *Mycobacterium tuberculosis* strain resistant to at least rifampicin and isoniazid. Current treatment regimens for MDR-TB patients are far from satisfactory. These usually require at least 20 months of treatment with a combination of second-line drugs, that are more toxic and less effective than the drugs used to treat drug-susceptible TB *(2, 3)*. In the 2012 global cohort of detected cases, only 50% were successfully treated, as a result of high frequency of death (16%), treatment failure (10%) and loss to follow-up (16%) commonly associated with adverse drug reactions, among other factors. One hundred and five countries have reported at least one case of extensively drug-resistant TB (XDR-TB), a form of MDR-TB with additional resistance to fluoroquinolones and second-line injectable drugs (amikacin, kanamycin or capreomycin). On average, an estimated 9.7% of MDR-TB cases have XDR-TB. Treatment options for XDR-TB patients are even more limited with lower cure rates compared to MDR-TB. In a subset of 200 XDR-TB patients in 14 countries, treatment success was achieved in only 33% while 26% of the patients died *(4)*.

In addition to the problems described above, second-line drugs may have important interactions with other drugs used to treat comorbidities often associated with TB, such as antiretroviral treatment for human immunodeficiency virus (HIV) co-infected subjects. These drug interactions may be responsible for limited drug efficacy, or cause increased organ toxicity, and/or overlapping side-effects, thus posing an additional challenge to treatment completion in co-infected patients. For all these reasons, new TB drugs and novel regimens are urgently required to enable faster, safer, less toxic and more effective treatment for persons with drug-resistant TB.

Much progress has been made in research and development of new drugs and regimens for TB over the past decade. Two new drugs – bedaquiline and delamanid – have been granted regulatory approval under accelerated or conditional procedures by the United States Food and Drug Administration (USFDA) and the European Medicine Agency (EMA). This was based on results of Phase IIb clinical trials. Novel drug combinations for shortened treatment of drug-resistant TB, including the above mentioned two drugs or other new or re-purposed drugs are currently under investigation.

To facilitate the introduction of these new drugs or treatment regimens and ensure wide accessibility to patients in need, a number of issues of public health relevance need to be addressed. These include: (i) the identification of optimal combination regimens to be used

according to the type of TB; (ii) the likely implications of drug profiles and safety aspects on patients' eligibility criteria; and (iii) the need to ensure the safety of patients exposed to new drugs while preventing the emergence of resistance to the new compounds. In terms of access, it is essential to ensure programmatic feasibility and cost-effectiveness of newly developed TB drugs and treatment regimens, and to preserve these new therapeutic options from irresponsible use that may hamper their efficiency. Therefore, the following key questions need to be addressed before introducing new drugs at the country level:

- How can countries enable **optimal introduction and use of new TB drugs**, as part of programmatic management of MDR-TB (through programme design, provider regulation and capacity building)?
- How can countries **build capacity** to introduce the new drugs and monitor their use, enable necessary drug safety monitoring and conduct more complex surveillance of drug resistance?
- How can countries ensure that the recommended use of the new drugs maximizes benefits for patients and programmes while **minimizing the risks to the patients and further emergence of drug resistance**?

To assist countries preparing for introduction of new drugs or treatment regimens under programmatic conditions, the WHO initiated a process in 2012 with the view to develop ad hoc policy recommendations for TB treatment with new drugs and assist countries to prepare for safe and effective uptake of these new drugs or regimens under programmatic conditions *(5)*. A *WHO Policy implementation package for new TB drug introduction* was developed to support country efforts towards the implementation of recommended new drugs or treatment regimens *(6)*. This package provides the key elements of a roadmap for introduction of new TB drugs and/or treatment regimens in countries. It also aims to complement existing and new policy guidance on the use of new drugs for the treatment of TB or MDR-TB.

Objective of the implementation plan

The aim of this implementation plan is to assist countries (particularly high MDR-TB burden countries) in the preparation and conduct of necessary activities for the introduction of bedaquiline to **ensure that patients in need get access to bedaquiline and are treated in a way that maximizes the benefits for patients and the programme.** It provides a logical and comprehensive framework, adaptable to a large diversity of country and programme settings.

The implementation plan includes the following series of five logical steps:

- Step 1: Establishing the framework for the introduction of bedaquiline at country level.
- Step 2: Meeting the minimal requirements for introduction of bedaquiline.
- Step 3: Developing a national plan for introduction of bedaquiline.
- Step 4: Implementing the introduction of bedaquiline.
- Step 5: Generating evidence for scale-up.

Target audience for the implementation plan

The implementation plan is targeted at national TB programme (NTP) managers, their public and private partners and all stakeholders involved in the detection and management of MDR-TB at the country level. It is also relevant for drug procurement managers, technical advisors, specialist clinicians, laboratory technicians, other services providers, relevant government officers, as well as individuals responsible for programme planning, budgeting, resource mobilization and training activities. Guidance for the clinical use of bedaquiline as well as clinical recommendations that have programme implications can be found in the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (hereafter referred to as *WHO Companion handbook for PMDT*) *(7)*.

WHO recommendation for the use of bedaquiline

Bedaquiline (also known as TMC207) is the first new anti-TB drug to be introduced into the market in almost 50 years. The drug belongs to the diarylquioline family and has a novel mechanism of action against *M. tuberculosis (8)*. The drug is given daily for two weeks and then thrice-weekly for a total of six months *(9)*. It has a long half-life of almost five-and-a-half months. The drug was tested in a Phase IIb trial in addition to background therapy in patients with MDR-TB. It demonstrated improved efficacy compared to that from only background therapy for MDR-TB using a surrogate marker to measure treatment efficacy *(10)*. Primary adverse events (AE) included liver function abnormalities, prolongation of the cardiac QT interval on the electrocardiogram (ECG) and pancreatitis. All-cause death rate in the group of patients receiving bedaquiline in the Phase IIb trial was higher than among patients who did not receive bedaquiline *(11)*.

Bedaquiline was approved under an accelerated procedure by the USFDA in December 2012 *(12)* and conditionally approved by the EMA in February 2014 *(13)*. In June 2013, the WHO issued **interim policy guidance** on **the use of bedaquiline in the treatment of MDR-TB** *(14)*. The guidance was the product of an expert group meeting convened by the WHO to assess all available data on bedaquiline. Since efficacy and safety data were available from only Phase IIb studies (i.e. no Phase III trial), the potential guidance is provisional until further efficacy and safety data, particularly from a Phase III trial, become available. The WHO document specifies the essential conditions for the use of bedaquiline and is targeted at NTPs, public health agencies, as well as public and private partners involved in planning, implementing and monitoring MDR-TB control activities. A *brief summary* of the main recommendations of the interim guidance can be found in **Box 1** below. The full recommendation is provided in the WHO interim policy guidance on the use of bedaquiline in the treatment of MDR-TB *(14)*.

Further to this guidance, an instructional document on '***How-to use bedaquiline?***' has been developed and is available in the *WHO Companion handbook for PMDT (7)*.

BOX 1. BRIEF SUMMARY OF THE MAIN RECOMMENDATIONS OF THE INTERIM POLICY GUIDANCE ON THE USE OF BEDAQUILINE IN THE TREATMENT OF MDR-TB *(13)*

WHO recommends that bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation, very low confidence in estimates of effects).

The WHO recommendation for the inclusion of bedaquiline in the adult treatment regimen of MDR-TB is subject to the following five conditions being met:

1. Proper patient inclusion (special caution in persons above 65 years of age or adults living with HIV; use not advised in pregnant women and children).

2. Signed patient informed consent obtained after detailed explanations on the novel nature of the drug, the reasons why it is added to the regimen, and its risks and benefits have all been provided to the patient.

3. 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: a fluoroquinolone (preferably later generation), a second-line injectable agent and two bacteriostatic drugs, preferably prothionamide or ethionamide plus cycloserine or para-aminosalicylic acid. Bedaquiline may be 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).

4. Treatment administered under closely monitored conditions to enable optimal drug effectiveness and safety (sound treatment and management protocols must be in place, preferably submitted and approved by the relevant national ethics authority; review of treatment and management programmes by an independent group of experts in clinical management and public health, such as the national MDR-TB advisory group is recommended).

5. Active pharmacovigilance and proper management of adverse drug reactions and prevention of complications from drug–drug interactions.*

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*   The WHO interim policy on bedaquiline recommends active pharmacovigilance as one of the five conditions when using this new drug. The national TB programme should thus actively monitor drug-safety to ensure proper patient care, to report any adverse drug reactions to the responsible drug-safety authority in the country, and to inform national and global policy. (See section 2.7 of this document, page 17).

Since the results from the Phase IIb trial were published, bedaquiline has been used in a series of patient cohorts as part of compassionate use or expanded access programmes, and the results so far have been encouraging. A recent publication of results from 35 patients with MDR-TB and XDR-TB in France showed that those who received bedaquiline as part of a four-drug combination regimen (usually including linezolid) had high rates of culture conversion (97%) by six months and only two patients needed to stop bedaquiline during the course of therapy *(15)*. Data on bedaquiline use in more than 90 patients with XDR-TB from an Expanded Access Programme in South Africa showed a treatment success rate of 83% among patients who received bedaquiline (compared with 20% in a similar population of historical controls) with only one patient requiring cessation of bedaquiline due to QTc prolongation *(16)*.

Step 1: Establishing the framework for the introduction of bedaquiline at country level

Prior to the introduction of bedaquiline, a series of activities should be undertaken to **establish the framework at country level.** Many of these are usually part of routine programme activities for drug-resistant TB and will simply need to be reviewed prior to the introduction of bedaquiline.

STEP 1.
Recommended activities to establish the framework for the introduction of bedaquiline at country level

1. Assess the national context

2. Contact relevant units/departments at the health ministry

3. Identify implementing partners

4. Create a national implementation Task Force and a Technical Working Group

5. Coordinate with the national regulatory authority

6. Establish a dialogue with pharmaceutical companies

7. Ensure appropriate procurement system for bedaquiline

8. Organize sensitization workshops

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1. Assess the national context

The *first required activity* is the assessment and understanding of the national health environment. This activity includes a detailed assessment of: (i) the general health infrastructure under which healthcare is being organized and provided to patients; (ii) a review of the organization of the NTP; and (iii) TB epidemiological and programmatic data (see **Box 2**). Much of this information already exists in a number of documents, including NTP reviews, Green Light Committee monitoring reports, and/or applications to the Global Fund to fight AIDS, Tuberculosis and Malaria (Global Fund) and only require updating and review as part of bedaquiline implementation.

Detailed **background information** is required in the following areas:

Health system infrastructure

- General healthcare system organization and structure at different levels; health system geographical coverage, access to health system in urban/rural areas and referral system;

- Treatment and care delivery models (such as role of primary health care, role of private sector, mechanism of social protection, existence of health insurance).

NTP infrastructure

- Organization of NTP at national/regional/provincial/district level (staffing, roles and responsibilities).
- Characteristics of TB diagnostic and treatment facilities at various levels of care (such as reference TB/MDR-TB hospital, dedicated TB wards, TB diagnostic centres, TB treatment centres).
- Geographical DOTS (directly observed treatment, short-course) coverage and access to diagnostic and treatment facilities; access to diagnostic/treatment facilities for affected populations (including prisoners, displaced people, migrants and ethnic minorities, nomadic groups, elderly persons).
- Financing/resources (domestic/external, funding gap).
- National and international key partners, including their roles and responsibilities.
- Role of private sector in TB control (and information on public–private mix approaches if available).

Burden of TB at country level

- TB burden indicators (estimated TB prevalence, incidence and mortality rates)[1] *(17)*
- Results from a recent TB prevalence survey at national or subnational level (if available) and related programme implications.
- TB/HIV coinfection rate; incidence and mortality estimates for HIV-positive TB cases.
- Estimated percentage of new and retreatment cases with MDR-TB.
- Baseline levels of resistance to first- and second-line drugs from Drug Resistance Survey (DRS) (ideally implemented in the past 2–3 years).

NTP performance

- TB case notification, proportion of notified TB cases enrolled on treatment and treatment outcome of drug-susceptible TB over recent years.
- MDR-TB, XDR-TB case notification, proportion of notified MDR-TB, XDR-TB cases enrolled on second-line treatment and treatment outcome of MDR-TB over recent years.
- TB/HIV interventions (proportion of notified TB patients tested for HIV, proportion of TB/HIV coinfected patients put on cotrimoxazole preventive therapy and antiretroviral treatment).
- NTP performance gaps identified and recommendations provided during recent joint programme review.
- Assessment of the surveillance system using the Impact Measurement Task Force's checklist and user guide on *Standard and benchmarks for tuberculosis surveillance and vital registration systems (18).*

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[1] http://www.who.int./tb/country/data/profiles/, accessed 13 August 2015.

TB case management at country level

- National TB diagnostic algorithms and TB treatment guidelines.
- TB and MDR-TB model of care (hospital/outpatient-based; centralized/decentralized).
- Existence, composition, role and responsibilities of a Clinical Review Committee (e.g. MDR-TB Consilium[2]); case holding strategy (such as enablers, psychosocial support, adherence measurement), including retrieval of patients lost to follow-up.

Pharmacovigilance

Existing pharmacovigilance system in place.

BOX 2. WHAT NTP/COUNTRIES SHOULD KNOW BEFORE INTRODUCTION OF BEDAQUILINE

Know your system. Healthcare providers, regulation, and financing of TB care at country level, including laboratory network, procurement system, private sector, health insurance, donors.

Know your epidemic. The following key epidemiology indicators at country level must be considered:

- Estimated incidence, prevalence and mortality of TB

- Estimated percentage of new and retreatment cases with MDR-TB

- TB drug resistance patterns at country level from latest available drug resistance survey (burden of mono/polyresistance, MDR-TB, MDR-TB with additional resistance to second-line drugs, XDR-TB)

- TB case notification rate; number of MDR-TB cases notified

- Proportion of notified drug-susceptible TB and drug-resistant TB cases enrolled on treatment

- Treatment outcome of drug-susceptible TB and drug-resistant TB

- HIV prevalence in TB cases; coinfected patients enrolled on cotrimoxazole preventive therapy and antiretroviral treatment.

Know bedaquiline. Characteristics of bedaquiline in the context of existing tools (drugs and diagnostics) and its added value as a new drug for MDR-TB. For additional information, see the *WHO Companion handbook for PMDT (7).*

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2. Contact relevant units/departments at the health ministry

While the NTP usually has a clear idea about the need for a drug in their specific setting, the higher-level (health ministry) officials may see the drug as either "experimental" or "too costly" – or both. Smooth introduction of the drug would require contact with relevant units/ departments at health ministry level, such as planning, finance, hospital and pharmaceutical

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[2] The MDR-TB Consilium is a specialized team in charge of management and supervision of all MDR-TB patients at country level. It usually consists of a chairperson, a secretary, physicians with clinical experience in MDR-TB/XDR-TB, a radiologist, a microbiologist, a specialist from drug management, monitoring and evaluation, and surgeons.

services, primary healthcare, disease surveillance, pharmacovigilance, procurement, as well as the national drug regulatory authority. Updating and involving them in the process will help ensure that they support both the introduction of bedaquiline and the steps necessary to start using the drug in the country.

3. Identify implementing partners

Introduction of bedaquiline should be led by the NTP, but other partners in the country can help support various aspects of drug introduction. This is essential given the multiple components that are needed for successful bedaquiline introduction and the costs associated with each of these. Potential partners include organizations with experience in drug-resistant TB clinical management, active pharmacovigilance (for TB or other diseases), operational research and laboratory management. Most NTPs already work with implementing partners in the management of drug-resistant TB and it would be important to identify the roles and resources of each partner agency.

4. Create a national implementation Task Force and a Technical Working Group

At country level, the NTP (or the national health authority responsible for TB control) is the focal point for the preparation and implementation of the plan. To assist the NTP, the creation of a high level *national implementation Task Force* is strongly recommended. This Task Force has the mandate to oversee the preparation, planning, implementation and evaluation of bedaquiline introduction, as well as other new TB drugs/regimens as appropriate.

It is essential to engage stakeholders at an early stage, even before bedaquiline is ready for deployment. The process of engaging key stakeholders should include advocacy for timely evaluation and adoption of the product at country level, and should continue with activities that are required for programme introduction and implementation.

The Task Force should foster a multisector process resulting in an explicit country policy decision to access and use bedaquiline, following the analysis of:

- the benefits, risks and costs of the drug;
- the health system's capacity to finance, manage and appropriately use bedaquiline;
- the drug management system's capacity to ensure timely procurement, quality assurance, inventory control and sustainable access to bedaquiline; and
- the acceptance of bedaquiline by healthcare providers and domestic markets.

The Task Force should be **chaired by the health minister** or **his/her representative** and have its **secretariat within the NTP**. High-level involvement of the health ministry will ensure planning and coordination of the introduction process across the various offices and implementers of the healthcare system nationally. The Task Force is expected to meet twice a year, with ad hoc meetings and other communications as needed.

Membership of the national implementation Task Force

It is recommended that the Task Force be composed of representatives from:

· the relevant **health ministry units/departments** (such as planning, finance, hospital and pharmaceutical services, primary healthcare, disease surveillance, pharmacovigilance, procurement, and drug regulatory authority)

· **national technical stakeholders** (such as academia, professional associations, ethical committees, technical partners, major private sector healthcare provider groups)

· **donors**

· **civil society** (such as patient support groups, NGOs)

· **international stakeholders/technical partners.**

It will also be useful to create a specific Technical Working Group to develop the preparatory steps for the introduction of bedaquiline (i.e. adaptation of WHO interim guidance, development of a national plan for introduction of the drug, revision of treatment guidelines and clinical tools, development of training materials, revision or adaptation of recording and reporting forms, etc.). While the Task Force will provide the *framework* for bedaquiline implementation and ensure political support, the Technical Working Group will focus on the *practical aspects* with the production of tools and materials needed for implementation. Furthermore, the Technical Working Group may be asked to provide support during the training of healthcare workers and for supervision of implementing centres. The Technical Working Group should be chaired by the NTP and include the NTP manager, technical partners and stakeholders, academia, clinicians and pharmacists. The Technical Working Group should meet on a regular basis, preferably once a month.

It may take several months to garner the high level support needed for bedaquiline introduction and to have members officially appointed to the Task Force. Thus, the Technical Working Group can do the initial work on bedaquiline introduction (described below) while the Task Force is being formed and officially sanctioned. As long as a dialogue is in place with the potential members of the Task Force, bedaquiline introduction should proceed.

5. Coordinate with the National Regulatory Authority

Introduction of bedaquiline in a country requires close coordination between the NTP and the national regulatory authority (NRA) to ensure that the development of the implementation plan fits the timeline of registration of the drug. The objectives of coordination with the NRA are:

● to ensure timely registration of bedaquiline (including temporary import permissions if needed) so that the drug is available at the time of planned NTP introduction;

● to prepare inclusion of bedaquiline in the national Essential Medicines List (if applicable);

- to discuss plans to avoid irresponsible use of bedaquiline, including limiting its prescription by accredited centres/providers, if applicable; and
- to plan for active drug-safety monitoring as needed.

> Registration, inclusion in the Essential Medicines List, regular procurement and distribution, prevention of inappropriate marketing, responsible prescription as well as drug-safety monitoring must apply **not only to bedaquiline but also to all the accompanying drugs included in the drug-resistant TB regimen.** On the 8th May 2015, the 20th WHO Expert Committee meeting on the selection and use of essential medicines has recommended the inclusion of bedaquiline (together with delamanid, linezolid, rifapentine and terizidone) in the anti-tuberculosis medicines section of the WHO Model List of Essential Medicines.

6. Establish a dialogue with pharmaceutical companies

When deemed appropriate by the NTP, and depending on the country's choice for procurement of bedaquiline (e.g. special access scheme with waiver for import), dialogue with the manufacturing company at country level should be directed to:

- encourage timely filing for registration (if not ongoing yet);
- provide timely and adequate supply according to the needs;
- ensure that internationally agreed price discounts (or more favourable conditions) become available nationally;
- prevent prescription and sale in the private sector before the NTP plan is in place;
- prevent inappropriate marketing;
- discuss collaboration on drug-safety monitoring; and
- ensure assessment of resistance to the new drug.

7. Ensure appropriate procurement system for bedaquiline

Countries procure anti-TB drugs on a routine basis, and the procurement mechanisms largely vary between countries, and depend on the drug. When introducing bedaquiline at the country level, an effective and sustainable procurement and supply chain management (PSCM) system must be in place, preferably building upon existing mechanisms. The following aspects should be considered:

- Regulatory issues (including waivers, permission, formal registration, procurement model)
- Quantification of needs (of new drug AND complementary drugs)
- Funding
- Logistic issues (custom fees, storage, etc.)
- Distribution to selected centres
- Buffer level (stock pile).

It is advisable to enter into a dialogue with the Global Drug Facility (GDF)[3] for drug procurement of bedaquiline. GDF is the procurement arm of the Stop TB Partnership. It provides quality assured anti-TB medicines and related supplies at affordable prices to approved NTPs and nongovernmental organizations (NGOs). Since its establishment, the GDF is authorized by the WHO to procure anti-TB medicines and diagnostics. The International Dispensary Association (IDA) provides GDF with procurement agent services, including logistics and arranging for transport and quality control.

Standard procurement process through the GDF

1. Complete drug requirements are calculated using GDF-approved tools.

2. The calculations and the signed Technical Agreement are sent to the GDF.

3. GDF generates an order in the GDF Order Management System.

4. GDF requests its procurement agent (the IDA) to provide a price quote.

5. GDF shares the price quote with the country.

6. The country approves the price quote and transfers funds to the IDA.

7. Upon receipt of funds by the IDA, the order is placed with the suppliers.

8. Once the medicines are produced and quality control is carried out, IDA sends an authorization request to the country and arranges delivery as soon as the country confirms its readiness to accept the medicines.

Standard lead time is approximately four to six months (depending on the destination and mode of transport) as of confirmation of the order and fulfillment of payment obligations (as applicable). The lead time may be longer than six months for bedaquiline. Lead time comprises production, quality control, pre-shipment inspection, internal processing and transport to destination.

8. Organize sensitization workshops

In the early preparatory phase of bedaquiline implementation, it is advisable to organize sensitization workshops targeting high-level decision makers at the health ministry, professional associations, various regions/provinces and stakeholders. The workshops inform them about the national plan to introduce bedaquiline at country level and provide a general overview of the introduction process. Advocacy activities should start in the early stage of preparation to ensure sensitization and collaboration of all actors involved at the different levels. The sensitization workshop should be organized and carried out by the NTP with the support of the national implementation Task Force. Patient representatives and civil society organizations should be involved in the preparation and conduct of these workshops.

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[3] For further details on GDF please refer to http://www.stoptb.org/gdf/ and http://www.stoptb.org/gdf/whatis/default.asp, accessed 15 March 2015.

Step 2. Meeting the minimal requirements for introduction of bedaquiline

This section presents the *minimum basic package* that countries should have in place before introducing bedaquiline. The main issues to be addressed are related to the organizational, technical and logistical aspects for country preparedness.

Note: *The introduction of bedaquiline should always take place within a functional PMDT programme organized according to WHO guidelines (2, 3), and many of these minimal requirements will already be in place as part of a robust PMDT.*

STEP 2.
Recommended activities for meeting the minimal requirements for introduction of bedaquiline should be in place in the following domains:

1. Laboratory capacity
2. Drug resistance surveillance
3. Clinical Review Committee
4. Case management
5. Recording and reporting system
6. Monitoring and evaluation
7. Drug-safety monitoring
8. Budget
9. Technical assistance
10. Drug supply system
11. Checklist for country preparedness and planning

The second step comprises several key domains under which specific questions need to be addressed to have an understanding of the environment in which bedaquiline will be introduced, and to assess where improvements may be needed for bedaquiline introduction and scale-up.

In each area, there is baseline data or evidence needed to prepare the implementation plan and a minimum package of activities required to be in place for the introduction of bedaquiline at the country level. These are summarized in *Step 2.11* below (***Checklist for country preparedness and planning***).

1. Laboratory capacity

In planning the introduction of bedaquiline, the design and quality of the supporting laboratory network at national, regional and treatment centre levels is crucial for both the programme and the patient. This includes TB laboratories as well as general laboratories. Specific processes to ensure adequate laboratory support may need to be put in place prior to implementation by the NTP, though ideally this would be linked to strengthening the diagnostic capacities of

the health system in general. If applicable, specific action(s) may be needed to upgrade the laboratory capacity with reference to available models.[4] This would need to be appropriately conducted without unnecessarily burdening the NTP or delaying deployment of bedaquiline in countries. Wherever possible, existing structures of quality assurance should be used/ upgraded and duplication must be avoided.

Background information

At *individual level,* laboratory tests need to be available for *patient assessment and review*:

- Prior to treatment initiation, laboratory tests are needed to:
  - identify patients eligible for bedaquiline and select appropriate companion drugs, for which drug susceptibility testing (DST) to first- and second-line drugs is needed; and
  - exclude patients with contraindications (e.g. liver impairment).

- During treatment, laboratory tests are needed to:
  - monitor the response to treatment (sputum culture);
  - identify adverse drug reactions or drug–drug interactions (biological safety checks); and
  - monitor the potential emergence of drug resistance during treatment (DST to second-line drugs and bedaquiline).

For these reasons, it is crucial to have reliable and quality assured laboratory services in place at the bedaquiline implementation sites level and establish optimal linkages with the reference laboratory for tests that are not available at site level.

From a *programmatic* point of view, background information should be collected on general and TB-specific laboratory aspects.

- TB laboratory infrastructure
  - Organization of the TB laboratory network at various levels (i.e. National Reference Laboratory; regional, provincial, district laboratories, sputum collection centres; geographical and population coverage).
  - Specification of the diagnostic tests available at each level (i.e. smear microscopy, sputum culture – solid/liquid, rapid molecular tools – Xpert® MTB/RIF (assay for *M. tuberculosis* and rifampicin resistance mutations), line-probe assays (LPA)).
  - Availability of DST for first- and second-line drugs at the country level.
  - Implementation of an external quality assurance (EQA) system.
  - Linkage with supra-national reference laboratory (SNRL).

- Availability of the following tests in laboratories that are certified through national standards.
  - Haematology and biochemistry tests as requested by treatment protocol (see **Annex 2**).
  - HIV diagnostic tests (HIV test, CD4 cell count, HIV viral load).

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[4] http://www.who.int/tb/laboratory/tool_set/en/index.html and http://www.who.int/tdr/publications/documents/gclp-web.pdf, accessed 21 March 2015.

Minimal requirements

Prior to the introduction of bedaquiline, the following **minimal requirements** should be in place **at country level**:

- WHO International Standards for Tuberculosis Care (ISTC) *(19)*.
- Decentralized access to rapid molecular tests.
- National reference laboratory with sufficient capacity for culture and storage of samples.
- DST for first-line drugs (at least rifampicin and isoniazid) and timely access to DST for second-line drugs (at least ofloxacin/levofloxacin, moxifloxacin, amikacin/kanamycin, capreomycin) (see **Annex 2**).
- Documented EQA system under supervision of a SNRL.

In addition, at the **implementing site level**, the following capacities must be in place:

- TB diagnostic capacity: i.e. smear microscopy (Ziehl–Neelsen (ZN) and/or fluorescent microscopy (FM)), rapid molecular tests (e.g. Xpert® MTB/RIF), culture (solid and/or liquid media).
- Timely access to DST for first- and second-line drugs either on site or via linkage with a reference laboratory for drug resistance monitoring during treatment.
- Timely access to general laboratory monitoring (haematology, liver function tests, kidney function tests, electrolytes, pregnancy test and any other laboratory test required by the bedaquiline treatment protocol).
- HIV test and monitoring test (CD4 cell count, HIV viral load) or linkage with HIV laboratory.

Should the potential pilot sites not meet the minimal requirements requested by the protocol, a detailed plan of activities to reinforce the system prior to the introduction of bedaquiline must be developed as part of the national implementation plan. The introduction of a new TB drug/regimen can be seen as an opportunity to strengthen the diagnostic capacity of the health system in general and/or in EQA processes.

Minimal laboratory requirements are detailed in **Annex 2**.

2. Drug resistance surveillance

Patients treated for TB should be closely monitored to detect emergence of drug resistance so that an adequate regimen can be offered in a timely fashion. It is crucial to monitor the use of bedaquiline and assess potential emergence of resistance at population and programme level. When piloting the introduction of bedaquiline for the treatment of TB, drug resistance surveillance has two major objectives:

i. to assess **baseline** levels of drug resistance to all TB drugs in the population targeted to receive bedaquiline; and

ii. to monitor **emergence of resistance** to bedaquiline.

To meet these objectives, two complementary surveillance approaches are needed, at patient and programme levels.

Patient level approach: continuous surveillance of drug resistance in patients receiving bedaquiline. All patients receiving bedaquiline should be closely monitored to document emergence of drug resistance. DST for first- and second-line drugs (as appropriate) should be performed **before treatment initiation and during treatment** (all strains should be stored and DST should be repeated on the last positive culture isolate). In the event that laboratory capacity for susceptibility testing to selected drugs is not available at country level, the strains should be sent to the SNRL for testing. All phenotypic and molecular tests endorsed by the WHO can be used for this purpose.[5]

It is likely that DST for bedaquiline will be beyond the means of many laboratories serving the programmes where the drug has been introduced. Evidence of resistance to bedaquiline should be sought by measuring minimum inhibitory concentration. It is advisable to store culture isolates from patients receiving bedaquiline (at −20°C) in designated laboratories until DST for bedaquiline becomes available. All DST done for bedaquiline should comply with WHO-recommended standards and laboratory processes, which should be quality-assured in cooperation with a designated SNRL.

Country level/programme approach: Population-representative drug resistance surveys are routinely conducted in most countries every 3–5 years. Existing data should be reviewed prior to the introduction of bedaquiline and can be used for planning purposes.

After the introduction of bedaquiline, drug resistance surveys should be repeated every 3–5 years according to national plan. When possible, a sample of strains should be stored or tested for bedaquiline resistance to track any emerging resistance that may be developing.

3. Clinical Review Committee

At country level, the implementation of bedaquiline requires strict monitoring and supervision that should be provided by an independent group of experts in clinical management of TB, MDR-TB and public health. Countries may already have a Clinical Review Committee in place (such as an MDR-TB Consilium for MDR-TB patients). If not, this committee would need to be established. The aim of this process is to ensure the best possible treatment results for patients through expert review on individual clinical data.

The Clinical Review Committee shall preferably be composed of clinicians with experience in managing TB, TB/HIV, MDR/XDR-TB, and other personnel with relevant experience (i.e. pharmacists, nurses, social workers). The Committee must have in place a chairperson and secretary and should meet regularly (in person or through the Internet) to evaluate the records of each patient eligible for bedaquiline. The Committee should consider the patient's history, laboratory results, eligibility criteria and potential contraindications and then take a decision on whether or not the patient would benefit from bedaquiline. The Committee should then state the approval/refusal decision on using bedaquiline and the suggested treatment regimen

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[5] http://www.who.int/tb/laboratory/en/, accessed 21 March 2015.

composition (**Annex 10**). All evaluated cases should be recorded in a dedicated register according to standard operating procedures of the Clinical Review Committee.

Physicians in charge of treatment are requested to regularly update the Committee about the treatment response and/or AEs experienced by the patients, and to consult the Committee for any decision on treatment change or interruption as well as on treatment completion.

4. Case management

Case management strategies for patients on bedaquiline should be developed by clinical specialists in the country in line with WHO recommendations and ISTC both at country and implementing site levels *(20, 21)*. Patients should be appropriately evaluated at treatment initiation and during treatment through recommended tests and medical evaluation at scheduled times. The details of such case management are described in the WHO *Companion handbook for PMDT,* with specific attention to the bedaquiline guidance in the annex section of that document.

Minimal requirements. The following capacities should be in place at implementing site level.

- *Mandatory*: laboratory tests (as described above), chest radiograph, ECG, audiometry, vision tests, access to psychosocial evaluation, access to psychiatric evaluation if necessary and/or access to neurologic evaluation if necessary.
- *Suitable (or be able to access nationally):* bronchoscopy, ultrasound, surgery and histopathology.

As part of case management, ancillary drugs to manage AEs and comorbidities must be available. In addition, appropriate methods should be in place to maximize patients' adherence to treatment (e.g. DOTS, psychosocial support, incentives/enablers, etc.) and for regular adherence measurements.

5. Recording and reporting system

A recording and reporting system for the use of bedaquiline should be established at country level for PMDT *(22).* This should include:

- Standardized definitions for cases and treatment outcomes as recommended by WHO in 2013.
- Standardized registration of cases in line with WHO recommendations.
- Generation of interim results and treatment outcome indicators as recommended by WHO.

The use of **electronic systems** is indispensable for proper collection, storage, management, transfer and analysis of data and should be developed where they do not yet exist, as described in the WHO recommendation for electronic recording and reporting for TB care and control *(23).*

6. Monitoring and evaluation

Countries introducing bedaquiline should have a robust and efficient monitoring and evaluation system in place as part of PMDT. Such a system, when efficient, would ensure safe implementation of bedaquiline and prevention of misuse, and would provide reliable data about its safety and effectiveness.

Standard routine **MDR-TB programme** indicators must continue to be used when bedaquiline is introduced. These indicators should be regularly generated at country level, as recommended in the *WHO Companion handbook for PMDT* (see **Annex 5** for details).

The assessment of treatment outcomes in patients receiving bedaquiline and comparison with other WHO recommended regimens for MDR-TB is of critical importance to guide country decisions in terms of policy and scale-up (see **Step 5** in this document). Therefore, it is essential that data on response to treatment are properly collected for the cohort of patients treated with bedaquiline, as well as for the cohort of patients treated with standard MDR-TB regimens.

Additionally, apart from indicators collected on a routine basis, countries may decide to select additional indicators at **programmatic level** so as to measure the cost and cost-effectiveness of the bedaquiline intervention. Therefore, when evaluating the use of bedaquiline at the national level, it may be helpful to determine what information already exists on key activities, such as human resources and training requirements, stock of pharmaceuticals, laboratory reagents, chest radiographs and consumables, as well as unit costs for these components that could be improved upon.

To ensure appropriate introduction of bedaquiline at country level, a regular supportive supervision schedule by the NTP is required. The existence of such a system needs to be documented in the *background information* collected prior to the implementation of bedaquiline.

7. Drug-safety monitoring

The occurrence of adverse events (AEs) during anti-TB treatment can contribute to additional morbidity, treatment interruption before completion, treatment failure, emergence of drug resistance, reduced quality of life, and/or death. For these reasons, it is important that adverse drug reactions be routinely monitored for TB patients on treatment. The introduction of new drugs in the context of complex regimens for drug-resistant TB, the concomitant use of antiretroviral treatment in patients with HIV-associated TB, or other drugs in case of comorbidities, make the case for this *drug-safety monitoring* even stronger. Furthermore, as the complete safety profile of bedaquiline has not yet been developed, there is a need for prioritizing detection, reporting and monitoring of serious adverse events (SAE) among patients receiving these new drugs.

Monitoring of *AEs or any other drug-related problems* is a fundamental public health surveillance activity, to inform the management of patient safety measures in healthcare settings. This is intended to enhance patient care and safety in relation to the use of medicines and to support

public health programmes by providing reliable information for the effective assessment of the risk–benefit profile of medicines.

In accordance with WHO's interim guidance, it is recommended that countries conduct rigorous **active monitoring of AEs for the introduction of bedaquiline** *(13)*. This recommendation was supported by independent experts who reviewed available information on safety of bedaquiline during the Guideline Development Group meeting held in January 2013 in Geneva. Bedaquiline is still relatively new and only a limited number of patients have been treated with the drug. Its accelerated marketing approval by stringent drug regulatory authorities ahead of the completion of Phase III trials took into account the serious nature of MDR-TB and the unsatisfactory outcomes obtained when regimens composed solely of older second-line drugs are used. When introducing bedaquiline, a clear plan for implementing active drug-safety monitoring is essential to record in a reliable way any evidence of AEs or drug–drug interactions and use this information to inform policy decisions, clinical guidelines and treatment recommendations. NTPs should conduct the systematic assessment of patients receiving bedaquiline as recommended in the framework for *active TB drug-safety monitoring and management* (aDSM) *(24)*.

An aDSM system is performed as an observational study of a group (cohort) of patients who are taking a particular medication or regimen. aDSM is necessary when patients are treated with a medicine for which the drug safety profile is incomplete, as is the case of bedaquiline. This does not depend on the number of patients enrolled. Monitoring needs to be closely associated with early action to prevent and manage any serious consequences to the patient. It is to be conducted under programmatic conditions, without any randomization of study subjects to intervention or to any control/comparison arms. The national programme also should strive to capture data from the private sector as well as from public–private partnership structures.

It is also important to collect safety data accurately to ensure that at least SAEs are properly investigated and no hasty conclusions are drawn on the causative medicine. Every person receiving bedaquiline should be registered and data collected on a periodic as well as a sporadic event-driven basis. A cohort approach is essential to avoid bias in selection of patients or in measurement of events. It is also best suited to make preliminary conclusions about the potential association of an event with the given exposure. Lastly, it provides denominators and baseline data for analysis.

Drug-safety monitoring requires recording clinical events that occur while patients receive bedaquiline. It requires active and systematic reports of AEs occurring while drugs are being administered and provides a method that facilitates reporting. All deaths are to be reported and all efforts should be made to ascertain the immediate and contributing causes of death, including determining if death could be linked to TB or TB treatment. This may require recovering information from vital registration coding. Reporting of other SAEs is also required, primarily based on what is known about the safety profile of the new agent and other possible harms that have not yet been described.

Many countries implementing PMDT have a form of spontaneous (or passive) reporting of suspected AE already in place *(14)*. Here clinicians already assess patients clinically for AEs on a regular basis, both at initiation and during follow-up visits. They do not, however, record AE systematically and/or report them on a national level and in a standardized way. The presence or absence of these clinical findings is often documented in medical records as part of routine clinical care in most settings. The use of bedaquiline will require monitoring for expected AEs in a more standardized and systematic approach (i.e., aDSM). It requires an *active search of AEs* through regular queries for clinical signs or routine laboratory tests and formal *recording* of these events on standard forms and *reporting* of these events to a central focal point.

As part of readiness planning for bedaquiline introduction, **it is necessary to assess what drug-safety monitoring experience already exists in the country** *(7).* While countries may not be monitoring safety for anti-TB drugs as part of routine activities within the TB programme, countries may have a pharmacovigilance system in place. The NTP should liaise with the pharmacovigilance structures (if in place) in order to better coordinate planning, mobilize existing expertise and avoid overlapping of functions. Concurrently, the NTP must assign someone to coordinate the necessary aDSM activities or assign the responsibility for the coordination of aDSM at national level to an existing TB expert body, such as the MDR-TB committee (or *consilium*) or the technical working group on new drugs.

It is important that measures are taken to ensure that essential drug-safety monitoring elements are in place so that key safety data are collected for all patients started on regimens containing a new drug. There needs to be a broad agreement between essential stakeholders on the process to implement drug-safety monitoring for new TB drugs, preparation for the collection of data (e.g. forms), and training of staff to collect the data properly *(24).*

8. Budget

Adequate financial resources should be allocated to ensure successful introduction and sustainable implementation of bedaquiline at country level.

Background information. This should be sought for sources of funding for NTP activities (domestic, external donors), as well as for potential strategies to mobilize funding for implementation of a new drug/regimen.

Minimal requirements. Funding sources for the introduction of bedaquiline should be identified and funds secured at the time of preparation. The budget should include the following items:

- Costs of medicines and pharmaceutical products (bedaquiline, companion drugs and ancillary drugs).
- Supply and management costs (procurement, storage, distribution).
- Costs of preparation activities (e.g. Task Force meetings, Technical Working Group meetings, sensitization workshops, communication material, training, development of national plan, administration, technical assistance).

- Costs of system strengthening to meet the minimum requirements (e.g. upgrading / renovating infrastructure, maintenance, equipment needed for laboratory and for patient monitoring – such as ECG, drug-safety monitoring, etc.).
- Costs of implementation (e.g. human resources, technical and management assistance, training, laboratory reagents and consumables costs, drug-safety monitoring, supportive supervision and monitoring visits to implementing sites, patient transport or incentives).

The *WHO Planning and budgeting tool for TB control activities* is a helpful resource to estimate the required budget at country level *(25)*.

9. Technical assistance

The introduction process requires a multidisciplinary approach, multisector involvement and support from various technical partners at all stages, from preparation to implementation. It is therefore recommended to identify all potential partners and clarify specific roles and responsibilities according to available competencies and resources. Activities such as laboratory or health system strengthening, staff training, active TB drug-safety monitoring and management, drug resistance surveillance may require specific technical support and involvement of multiple partners. It is hence advisable to involve country level technical partners at an early stage, reaching out also to nongovernmental organizations (NGOs), donors and civil society. Donors such as the Global Fund may play a critical role in facilitating the implementation. The NTP and the national implementation Task Force should coordinate all technical partners.

10. Drug supply system

To successfully introduce bedaquiline for treatment of MDR-TB in a country, a functioning drug procurement system must be in place. Most countries have a procurement system in place for MDR-TB drugs, which should form the basis for bedaquiline procurement. Prior to implementing bedaquiline, the current procurement system should be reviewed and updated. Special attention must be given to changes required in the procurement system to obtain bedaquiline and other related materials and medications that should be prescribed as companion drugs.

Even if a full procurement and supply chain management (PSCM) system for TB drugs is already in place, new challenges can arise when bedaquiline is to be introduced in a country. For example, procurement regulation may need to be amended to allow direct procurement from an international (single) source with additional costs justified; or the use of bedaquiline may require use of other second-line drugs (such as moxifloxacin, capreomycin).

Prior to the introduction of bedaquiline, the following **minimal requirements** must be in place:

- Adequate PSCM system in place to guarantee regular drug supply and distribution.
- Absence of stockout for one year (**i.e. one year buffer stock of existing/companion TB drugs should be always in place**).

A review of past medication stockouts should be undertaken with a focus on why stockouts occurred (if any) and what steps were taken to solve the relevant problems. As part of this review, an assessment of existing buffer stocks should be done, with documentation of current supplies and plans for ongoing procurement. Existing drug forecasting needs should be reviewed to ensure that buffer stock for a minimum period of one year is available for bedaquiline.

11. Checklist for country preparedness and planning

To guide countries to assess the level of preparedness and plan for the introduction of new TB drugs/regimen, a detailed **checklist for country preparedness and planning** has been developed. As noted above, much of the required information will exist as part of routine documentation of the PMDT programme into which bedaquiline is being introduced. The checklist is articulated into seven domains that need particular attention during the preparatory phase:

i.   Health and regulatory environment

ii. Laboratory capacity

iii. Drug procurement and supply chain management

iv. Case management

v.   Monitoring and evaluation

vi. Drug-safety monitoring

vii. Financial resources and country support.

How to use the checklist ?

The checklist should be compiled with and used by the NTP/partners as a means to assess whether all essential aspects are in place or need to be established or improved prior to the introduction of bedaquiline (see **Table 1**).

Once compiled, the checklist should be evaluated by the national implementation Task Force together with national and international partners, to streamline the preparation, planning and implementation phases.

If the minimal requirements are not met or are not in place at the time of preparation, a specific plan and timeline for addressing the gaps and weaknesses should be developed by the Technical Working Group with support from the Task Force. Progress should be periodically assessed to ensure all minimal requirements are in place.

Table 1. Checklist for country preparedness and planning

DOMAIN	MINIMAL REQUIREMENTS FOR INTRODUCTION OF BEDAQUILINE	IN PLACE/ AVAILABLE	TO BE STRENGTHENED	TO BE SET-UP/ ESTABLISHED
Health and regulatory environment	Background information on health system infrastructure			
	Background information on NTP infrastructure			
	Background information on PMDT in the country			
	TB burden indicators			
	NTP performance indicators			
	Background information on TB case management at country level			
	Background information on national drug regulatory process			
Laboratory capacity	*At country level*			
	Background information on general laboratory infrastructure			
	Background information on TB laboratory infrastructure			
	WHO/ISTC standards for TB diagnosis			
	Decentralized access to rapid molecular tests			
	Reference laboratory with appropriate capacity for culture			
	DST to determine resistance to first line drugs (at least rifampicin and isoniazid) and second-line drugs (at least ofloxacin/ levofloxacin, moxifloxacin, amikacin/ kanamycin, capreomycin)[a]			
	Quality assurance system through an established link with a SNRL			
	At implementing site level			
	Sputum smear microscopy or other WHO-recommended initial diagnostic test			
	Rapid molecular tests: Xpert® MTB/RIF and/or LPA technology			
	Culture (solid and/or liquid)			
	Access to DST to first- and second-line drugs (as per national treatment protocol)[a]			
	Haematology (white blood count, haemoglobin, platelet count)			

DOMAIN	MINIMAL REQUIREMENTS FOR INTRODUCTION OF BEDAQUILINE	IN PLACE/ AVAILABLE	TO BE STRENGTHENED	TO BE SET-UP/ ESTABLISHED
Laboratory capacity	Biochemistry (kidney function tests, liver functions tests, pancreatic function tests, electrolytes)			
	HIV test, CD4 cells count, HIV viral load			
	Pregnancy test			
	Other tests as per treatment protocol (e.g. thyroid stimulating hormone (TSH), lactic acid, serum glucose)			
Drug procurement and supply chain management	Adequate PSCM system in place to guarantee regular drug supply and distribution			
	Absence of stockouts for one year			
Case management	*At country level*			
	WHO/ISTC standards for treatment			
	Clinical Review Committee (e.g. MDR-TB Consilium)			
	Appropriate case holding strategy			
	At implementing site level			
	Chest radiographs			
	ECG and access to continuous ECG monitoring			
	Audiology[a]			
	Visual acuity tests[a]			
	Psychosocial evaluation			
	Ancillary drugs			
	Measures to maximize treatment adherence and adequate patient support systems in place			
	Access to psychiatric evaluation if needed[a]			
	Access to neurologic evaluation if needed[a]			
	Access to bronchoscopy if needed[a]			
	Access to surgery and histopathology if needed[a]			
	Access to ultrasound if needed[a]			

DOMAIN	MINIMAL REQUIREMENTS FOR INTRODUCTION OF BEDAQUILINE	IN PLACE/ AVAILABLE	TO BE STRENGTHENED	TO BE SET-UP/ ESTABLISHED
Monitoring and evaluation	Recording and reporting in line with revised WHO recommendations			
	Electronic recording and reporting system			
	Minimum indicators routinely generated			
	Regular supervision plan (minimum 2 rounds/year) to each implementing site			
	Regular cohort data analysis			
	Drug resistance survey in the past 2–3 years			
	Plan to repeat drug resistance survey 3–5 years after new drug/regimen introduction			
Drug-safety monitoring	Background information on pharmacovigilance system at country level			
	Minimal requirements in place *(7)*			
	Availability of a system for active drug-safety monitoring, if yes, specify.			
Financial resources and country support	Background information on NTP budget			
	Budget for introduction of bedaquiline developed			
	Funds for bedaquiline introduction secured			
	Technical assistance partners identified			
	Plan for technical assistance developed			

[a] These are the required tests and diagnostics at the implementing site level during the pilot phase of the programme. As more experience is gained with bedaquiline, the country may consider allowing scale-up sites without some of these tests to use bedaquiline provided they are able to send samples and receive results in a timely fashion.

Step 3: Development of a national plan for the introduction of bedaquiline

The aim of this section is to guide countries to develop a logical and concise implementation plan, after all the minimum requirements have been checked. It describes the various preparatory activities to enable the introduction of bedaquiline. The different aspects to be considered are listed in chronological order, although activities may be implemented in parallel, if required, to make the process more efficient. All these steps should ideally follow the establishment of a national framework for the introduction of bedaquiline that includes the creation of a national **implementation Task Force** and a **Technical Working Group**, as described in **Step 1**.

Countries should adapt the implementation plan to their specific environment and settings

Selection of model of introduction and pilot sites

Bedaquiline can be introduced according to various models, but it is recommended that a *pilot site approach* be used for the following reasons:

- Need for careful screening of patients according to the established eligibility criteria.
- A lack of staff experience in handling bedaquiline and managing its AEs as the drug is new.
- Additional demands for recording and reporting.
- Need for close supervision and monitoring.

Pilot sites should preferably be MDR-TB specialized centres or tertiary/referral hospitals with good diagnostics, monitoring and evaluation systems, and recording capacity. The experience of these pilot sites can then be used to **scale-up** bedaquiline at national level after collection of suitable evidence about the feasibility and effectiveness of adding the drug to MDR-TB treatment regimen.

Selection of pilot sites

The selection of **pilot sites** requires a careful assessment of the following parameters:

- The centre's infrastructure and catchment population.
- The annual number of MDR-TB patients diagnosed in the past five years.
- The annual number of MDR-TB patients enrolled for treatment in the past five years and the related treatment outcomes.
- The recording and reporting capacities.

The centre(s) selected for pilot implementation should ideally meet the following **minimal requirements**:

- Adequate infrastructure (including TB dedicated ward, ambulatory care, laboratory, staff).
- Appropriate TB diagnostic and treatment capacities according to WHO/ISTC standards (**Annex 2**).
- WHO recommended revised recording and reporting system *(26)*.
- Access to quality assured TB drugs through an efficient procurement system in place.
- Active drug-safety monitoring system available.
- Good performance indicators (case notification; treatment outcomes).
- Good patient support.
- Referral system from decentralized centres in place.

The **location** of pilot centres is crucial. It is advisable to start at sites that are experienced in PMDT and have an adequate patient population (i.e. 5–10% of the patients being treated for drug-resistant TB in the country). Once experienced sites have access to bedaquiline, additional pilot programmes targeting other populations (e.g., urban vs rural, HIV-infected) can be started.

> Centres to be involved as pilot sites should be carefully selected by the NTP, with the support of the national implementation Task Force. **The appropriate selection of pilot sites where bedaquiline will be introduced is a critical step.**

The **modality of treatment administration** (hospital- or outpatient-based) should be also considered, based on the country policy on MDR-TB treatment. WHO recommends outpatient management for MDR-TB, wherever possible (reserving hospitalization only for severe cases), but in some countries the management of MDR-TB, at least during the initial intensive phase, is done at the hospital level. The introduction of bedaquiline may require hospitalization at least in the initial phase, to strictly observe patient's tolerability and monitor the potential occurrence of AEs and drug–drug interactions. If, per country policy, bedaquiline has to be administered in a hospital, appropriate infrastructure (TB ward bed capacity, isolation rooms, infection control measures, etc.) needs to be assessed prior to selecting the specific implementing sites.

Expansion phase

Data from the initial phase of introduction of bedaquiline at pilot sites level should be properly collected and analysed. Based on results and lessons learned, a country may decide to scale-up the intervention (see **Step 5**: *Generating evidence for scale-up*). A second group of centres could be selected and appropriate measures taken to ensure that they meet the minimal requirements. Cascade training, visit tours and inter-centre collaboration may greatly help this expansion process. Close staff supervision as well as monitoring and evaluation of newly selected centres are advisable to ensure smooth expansion.

At initial stage, it is recommended to introduce bedaquiline **in centres accreditated** by government authorities only, as misuse or occurrence of AEs may jeopardize patients' safety and increase the risk of drug resistance, with dramatic consequences for the individual and for the community at large. In many contexts, the engagement of the private sector should preferably be planned in the second phase, after initial introduction of bedaquiline in government facilities has been shown to be successful.

During the expansion phase, the NTP should consider the role of private providers in the scale-up of bedaquiline. Engaging all relevant healthcare providers in TB care and control through public–private mix approaches is an essential component of global TB control. Introduction and use of bedaquiline in the private sector should be done in liaison with the health ministry and the NRA as appropriate. Although the NTP may have input on how bedaquiline is introduced in the private sector, it is generally beyond the scope of the NTP to oversee the use of bedaquiline in these conditions. As such, it is important for the NTP to know and communicate with the entities that will oversee bedaquiline implementation in the private sector and maximize opportunities for open communication. Engaging the private sector in the introduction of bedaquiline should always **build on existing collaboration**, beginning with those providers that are already collaborating with the NTP for management of TB or drug-resistant TB, to ensure that there is a foundation for engagement, capacity-building, and monitoring and evaluation. Detailed information on public–private mix in the implementation of bedaquiline is provided in **Annex 12.**

Developing a national plan for introduction of bedaquiline

A technically sound national plan describing in detail the various phases of bedaquiline introduction at country level must be developed. The treatment plan should follow specific WHO recommendations and guidelines for bedaquiline and reinforce principles of PMDT.

The national plan should include the aspects highlighted below.

STEP 3.
Recommended activities for developing a national plan for the introduction of bedaquiline

1. Rationale for the introduction of bedaquiline at country level
2. Development or update of national clinical guidelines
3. Development of plans for laboratory needs
4. Recording and reporting
5. Monitoring and evaluation
6. Drug-safety monitoring

7. Ethical aspects
8. Calculation of drug needs
9. Training of managers and staff
10. Human resources development plan
11. Timeline development
12. Budget development
13. Obtaining consensus from donor agencies

1. Rationale for the introduction of bedaquiline at country level

The rationale for the introduction of bedaquiline at country level should build on the national context assessment previously described. Also, the reasons why the NTP is planning to introduce the new treatment should be elaborated.

2. Development or update of national clinical guidelines

Most countries introducing bedaquiline will have established clinical guidelines for the management of patients with drug-resistant TB as part of a national PMDT programme. These national guidelines should be updated to include guidance on the clinical use of bedaquiline, with clear indication of patients' eligibility and exclusion criteria, optimal use of bedaquiline, case management, informed consent and treatment monitoring, as specified below:

- Eligibility criteria should define the population to be treated with bedaquiline and specify who should <u>not</u> be treated with the drug, following interim guidance issued by the WHO.
- Optimal use of bedaquiline should describe preferred methods for administration, the type of companion drugs, as well as the treatment duration and case-holding strategies, in line with WHO recommendations.
- Case management strategies should describe how patients should be evaluated prior to and during treatment with bedaquiline and should provide guidance on patient management. These strategies should follow WHO recommendations as detailed in the *WHO Companion handbook for PMDT (7)*.
- Informed consent guidance should specify the information given to patients about bedaquiline and outline the process by which a signed/thumbprinted informed consent will be obtained from each patient prior to receiving the drug.
- Treatment monitoring should include content and frequency of clinical and diagnostic monitoring. Monitoring should also include assessment of interim and final treatment outcome in accordance with WHO recommendations *(2, 3)*.

- Indication of alternative regimen(s) should be given for treatment failure or poor tolerability of the proposed regimen.
- The strategies for enhancing and monitoring adherence to treatment, including patient psychosocial/economic support, and other aspects of patient-centred care should be specified.

Guidance for the clinical use of bedaquiline can be found in the *WHO Companion handbook for PMDT* (Chapter 11) *(7)*.

In addition to updating the clinical guidelines, the NTP needs to develop training materials (such as training manuals, slides for workshops and training courses) for different cadres of health system management and healthcare providers (such as physicians, clinical officers, nurses, pharmacists, laboratory staff). Training materials should include the development of practical clinical tools (such as flipcharts, leaflets, hand books), bedaquiline indications and contraindications, companion drugs to be chosen in different scenarios and their dosage, patient monitoring information, as well as AEs and their management.

3. Development of plans for laboratory needs

A thorough review of laboratory capacity will be done as part of the assessment of readiness for introducing bedaquiline in the country. This review may identify areas that need improvement or strengthening. A clear plan for improving the laboratory capacity should be integrated in the national implementation plan, including the activities to undertake, funding sources and timeline for introducing improvements.

4. Recording and reporting

All patients receiving bedaquiline should be assembled in a ***cohort*** for collection of specific data. Recording the outcome of treatment for the cohort should follow the routine system in use at country level, according to WHO recommendations (see WHO documents: *Revised TB recording and reporting forms and registers – version 2006 (26)* and *Definitions and reporting framework for tuberculosis – 2013 revision (22)*; see also **Annexes 3** and **4**). Existing systems for PMDT recording and reporting should form the basis of reporting on patients receiving bedaquiline, and such patients should be flagged or marked in the system using current tools so as to be specifically assembled for cohort analysis. The use of electronic systems – such as e-TB manager – is encouraged *(27)*.

5. Monitoring and evaluation

In addition to standard monitoring and evaluation tools used in PMDT, countries may decide to set specific targets for the first three years of bedaquiline implementation to monitor drug introduction according to the plan. Some suggested indicators are listed in **Table 2**.

Table 2. Suggested indicators for monitoring and evaluation

INDICATOR	SUGGESTED FREQUENCY OF MONITORING
Number of national implementation Task Force meetings	Annually
Number of Technical Working Group meetings	Quarterly
Number of sites with patients receiving bedaquiline	Twice a year
Number of providers trained on bedaquiline	Quarterly
Number of patients screened for bedaquiline	Quarterly
Percentage of eligible patients receiving bedaquiline	Quarterly
Number of patients receiving bedaquiline	Quarterly
MDR-TB patients on bedaquiline included in aDSM	Quarterly
MDR-TB patients on bedaquiline retained in the cohort for event monitoring	Yearly
Time to stopping bedaquiline	Quarterly
MDR-TB patients included in aDSM with any serious adverse event	Quarterly
Frequency of bedaquiline-associated adverse drug events	Quarterly
Time to development of bedaquiline-associated adverse drug reactions	Quarterly
Buffer stock of bedaquiline	Quarterly
Buffer stock of companion drugs	Quarterly
Number of technical assistance missions	Twice a year
Number of support/supervisory visits to pilot sites	Twice a year

In terms of supervisory and support visits, it is recommended that such activities occur at least twice a year in sites introducing bedaquiline. These visits should build upon those used in routine PMDT supervision and support.

6. Drug-safety monitoring

As mentioned previously, the introduction of bedaquiline requires the establishment of a rigorous drug-safety monitoring mechanism to systematically identify the occurrence of AEs and collect information on the safety profile of bedaquiline, as well as providing adequate management of AE *(13)*. This is done through the careful implementation of the aDSM framework *(24)*.

Annex 6 summarises the essential steps for the establishment of aDSM; these are addressed ahead of patients' recruitment and are built upon the strengths of the monitoring framework that NTPs are accustomed to when following up their patients. There is a substantial amount of additional work required to establish and maintain an aDSM system. As mentioned previously (see *Step 2.7* above), it is important to ensure that the following essential aDSM elements are

in place before enrolling patients on bedaquiline: i) creating standard data collection materials; and ii) training staff on the collection of data.

7. Ethical aspects

Most countries implementing PMDT have some sort of formal ethical review body with which they can consult. As part of this review, the national bedaquiline implementation plan could be submitted to the nationally recognized ethical committee to ensure that ethical principles are duly respected during bedaquiline implementation.

The use of bedaquiline will require that patients sign an informed consent form, acknowledging their agreement to be treated with the new medication. In many PMDT programmes, patients sign a general consent form in which they agree to receive treatment (see **Annex 9**). The use of bedaquiline, however, requires additional specifications to be duly acknowledged (see **Annex 10**).

8. Calculation of drug needs

The GDF will provide bedaquiline as a six-month treatment regimen. Given this, countries will need to order the number of regimens for the target patient goal. For example, if the goal is 100 patients, then the country will order 100 regimens of bedaquiline, which will contain the required number of tablets.

If specific calculations for the quantity of tablets is needed, the following should be taken into account: bedaquiline comes in a 100 mg tablet form; each patient will take four tablets (400 mg total) daily for two weeks (14 days), which is a total of 56 tablets for the first two weeks of treatment; following that, each patient will take 200 mg of bedaquiline thrice a week (i.e. six tablets of 100 mg per week) for a total of 22 weeks – which is 132 tablets. Thus, for a complete treatment course, each patient will require 56 + 132 = 188 tablets of bedaquiline. Appropriate buffer stock should be planned in the calculations and ordered according to standard practice also for second-line drugs taking into account spillage, breakage or other types of loss of medication.

9. Training of managers and staff

The NTP, in collaboration with the treatment centres, should identify: (i) where bedaquiline will be introduced, and (ii) where staff need to be trained. It is advisable to organize training for the various cadres of health providers (such as clinicians, clinical officers, nurses, pharmacist, laboratory technicians), and for NTP teams working at central/regional/decentralized level depending on the model of introduction adopted. Also, specific training of NTP and the national pharmacovigilance centre (NPVC) staff on the principles of aDSM and on causality assessment would be useful, if needed.

Health provider training should take place few weeks/months before the introduction of bedaquiline. International technical assistance to carry out training on bedaquiline utilization is advisable. Members of the Clinical Review Committee may be involved as facilitators in the training.

10. Human resources development plan

Ensuring competent and sufficient human resources in all categories of personnel involved in the programme at all levels (clinical, laboratory, pharmaceutical and managerial) is key for high quality implementation of a new drug/regimen. Central management should estimate staff requirements for all aspects of introduction of bedaquiline according to the type of activities to be undertaken.

11. Timeline development

The development of a clear timeline including all steps needed **before** the introduction of bedaquiline will greatly help the preparation process. This should be the responsibility of the national implementation Task Force, with the support of the Technical Working Group or NTP.

The timeline should spell out a clear schedule for **preparatory and implementation activities**. Many of these activities can be done in parallel to speed-up the preparatory phase of the introduction.

For **preparatory activities:**

- Establishment of the national implementation Task Force and Technical Working Group
- Drug regulatory procedures
- Arrangements for drug procurement
- Development of a national treatment plan
- Meeting ethical requirements
- Selection of pilot sites
- Laboratory preparation and system strengthening
- Establishment of the Clinical Review Committee (if not yet available)
- Establishment of an active TB drug-safety monitoring and management system (as needed)
- Securing the required budget
- Organization of sensitization workshops.

For **implementation activities**:

- Training of healthcare providers and health managers
- Introduction of bedaquiline at pilot site level
- Supportive supervisory visits
- Monitoring and evaluation
- Evaluation of collected data and generation of evidence for scale-up
- Designation of the scale-up phases and implementing sites
- Expansion of the use of bedaquiline to new sites.

The implementation plan should be adequately reflected in the country's national strategic plan to ensure proper coordination and evaluation of implementation within the framework of programmatic activities.

12. Budget development

Once the national implementation plan has been developed, a detailed budget for each of the items should be developed using standard budgeting tools. In addition to the expected cost of planned items, the confirmed or possible sources of funding should be noted in the budget plan. This will allow for targeted fund raising and advocacy to ensure that the cost of bedaquiline implementation will be covered throughout the implementation period.

13. Obtaining consensus from donor agencies

Multiple donors are supporting the introduction of bedaquiline globally, including the Global Fund, United States Agency for International Development (USAID), and UNITAID. Each will have their own processes and mechanisms for countries to use funding to procure bedaquiline as well as for activities to support introduction (i.e. funding for active drug-safety monitoring). In the past, donors had to request proof of approval from the WHO Green Light Committee to release funding. With bedaquiline, however, the WHO is no longer "approving" projects. Donors may still want some confirmation that the plan is technically sound, and whenever possible, countries should involve donors in discussions about bedaquiline introduction. A copy of the the bedaquiline implementation plan should be provided to donors to document the due process the country went through for the optimal introduction of bedaquiline.

Step 4: Implementing the introduction of bedaquiline

This section describes the successive practical activities to be carried out at the implementation site level in accordance with the national implementation plan. Implementation is expected to start after all the preparatory activities outlined in the precedent sections have been carried out, bedaquiline has been made available, and the health staff has been properly trained. As noted in previous sections, bedaquiline should be introduced in settings with robust PMDT programmes and should be implemented according to WHO guidelines.

STEP 4.
Recommended activities for meeting the minimal requirements for introduction of bedaquiline

1. Identify patients eligible for treatment with bedaquiline

2. Obtain informed consent

3. Consult with Clinical Review Committee

4. Initiate treatment

5. Monitor treatment response

6. Ensure active drug-safety monitoring (detection, management and reporting of adverse events)

7. Monitor individual drug resistance

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1. Identify patients eligible for treatment with bedaquiline

Following WHO recommendations, bedaquiline should be utilized as an add-on to treatment in patients with a confirmed diagnosis of pulmonary MDR-TB, provided they meet defined eligibility criteria. Details of patient screening procedures are included in the *WHO Companion handbook for PMDT* (see also **Annex 7**).

Patient eligibility

Patients to be started on bedaquiline must meet the general requirements for enrolment in PMDT and follow WHO recommendations. These recommendations were developed based on registration trials for the drug. Certain populations of patients were excluded from these trials.

In accordance with WHO recommendations, a patient is declared eligible for bedaquiline treatment if he/she meets the following criteria:

- Confirmed pulmonary MDR-TB.
- Age 18 years or above.
- An effective treatment regimen (as per WHO recommendations) containing four second-line drugs in addition to pyrazinamide cannot be designed. This is due to known adverse drug reactions, poor tolerance, documented drug resistance to any fluoroquinolone or

second-line injectable, or contraindication to any component of the combination regimen, or unavailability or lack of a guaranteed supply of a drug.

- Baseline and repeat ECG show normal QTc interval (≤ 440 milliseconds (ms) for males, ≤ 470 ms for females) and no obvious signs of arrhythmia;
- A signed informed consent is provided by the patient or his/her legal guardian.

Exclusion criteria

The following exclusion criteria should be considered:

Absolute contraindications.

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

Relative contraindications. Bedaquiline should be used with "extreme caution" in the following populations, as the studies leading to the approval of bedaquiline did NOT include patients with any of the following conditions:

- **Children or persons below 18 years of age.** The safety and dosing of bedaquiline has not been established in children and its use in this group should be avoided until further evidence is made available.
- **Geriatric use (patients above 65 years of age).** Clinical studies of bedaquiline did not include a sufficient number of patients aged 65 years and above to determine whether they respond differently from younger patients.
- **Pregnancy.** Reproduction studies performed in rats and rabbits revealed no evidence of harm to the foetus due to bedaquiline. In these studies, the corresponding plasma exposure was twofold higher in rats compared to humans. There are, however, no adequate and well-controlled studies of bedaquiline among pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if absolutely needed.
- **Nursing mothers.** It is not known if bedaquiline and its metabolites pass into human breast milk. Because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug in curing the mother.

Caution: Bedaquiline should only be used with "caution" in patients with the following conditions, as the studies leading to the approval of bedaquiline did NOT include patients with these conditions:

- **Hepatic impairment.** No dose adjustment is necessary for bedaquiline in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and should be used with caution in these patients only when the benefits outweigh the risks.

- **Renal impairment.** No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease requiring haemodialysis or peritoneal dialysis, bedaquiline should be used with caution.
- **HIV infection.** Clinical studies on bedaquiline did not assess the long-term use with anti-retroviral drugs. For information on recommended antiretroviral treatment, please consult the *WHO Companion handbook for PMDT.*

For relative contraindications, bedaquiline should be avoided but could be used in situations where the options for treatment are extremely limited and the benefits of bedaquiline would definitely outweigh the potential risks. In these settings, a risk–benefit determination should emerge through discussion with the patient and the MDR-TB Clinical Review Committee, based on the patient's clinical situation and the programmatic policy on bedaquiline use. For patients falling into the "caution" category, a decision to use bedaquiline should be taken on case-by-case basis after weighing the risk/benefits. In both situations, increased patient monitoring (especially ECG, liver function) is advisable.

In addition, the following should be ensured.

- The drugs included in the regimen that are known to prolong the QTc interval should be minimized. Clofazimine and moxifloxacin should be avoided if possible, due to potential overlapping cardiotoxicity, unless an adequate MDR-TB treatment regimen cannot be constructed without them.
- Aminotransferases are less than thrice the upper limit of normal and total bilirubin is less than twice the upper limit of normal.
- The patient's serum potassium, calcium and magnesium have been obtained at baseline and levels are within normal limits or the patient has received appropriate electrolyte repletion to bring their laboratory values within normal limits.

> Bedaquiline should be reserved for the treatment of MDR-TB when a WHO standard recommended regimen cannot be otherwise provided; it cannot be utilized to treat drug-susceptible TB or drug-resistant TB cases in which another satisfactory regimen is available.

2. Obtain informed consent

Patients declared eligible for treatment with bedaquiline should be informed about the novel nature of the drug/regimen, the reason why it is being proposed and its benefits and potential harms. Information should be provided in the local language of the patient, ensuring he/she can understand what is being explained. Written information detailing the potential side-effects should be provided to patients (see *WHO Companion handbook for PMDT* and **Annex 9** for an example of an information note). It is important to communicate to patients the name/surname and contact details of their treating physicians.

The lack of written informed consent represents an absolute contraindication for treatment with bedaquiline.

A written informed consent should be sought from each patient who is being started on bedaquiline. If he/she is illiterate, a literate witness must sign (if possible, this person should be selected by the patient and should have no connection to the care providers). Patients who are illiterate should provide a thumbprint.

Confidentiality of information as well as the possibility for the patient to withdraw consent at any point in time must always be ensured (see **Annex 9** for a sample informed consent form).

3. Consult with Clinical Review Committee

The clinical dossier of every patient declared eligible for a bedaquiline-containing regimen, and who provided informed consent should be presented to the Clinical Review Committee (or MDR-TB Consilium). This dossier includes all patient clinical records, laboratory investigations, results of DSTs, ECG, chest radiograph, as well as information on past history of TB, past TB treatment, and the reasons for bedaquiline treatment request.

The Committee is asked to provide **individual written feedback** (in paper and/or electronic format), within a short period of time (ideally within 48 hours), to the clinician who has presented the case. The Committee should use their standard communication and feedback forms, however for patients being considered for bedaquiline, the following information should additionally be included (see **Annex 10**):

- Clinical Review Committee decision on bedaquiline treatment (approval/refusal).
- Reasons for approval/refusal of bedaquiline treatment.
- Companion drugs recommended with doses.
- Any other information deemed relevant by the Committee.

Details of all evaluated patients must be recorded in the Clinical Review Committee register, including the final decision, treatment regimen and date.

4. Initiate treatment

After approval by the Clinical Review Committee, the patient can be started on treatment. Baseline data to be collected at treatment initiation include those collected for patients under PMDT. In addition, information on the reasons for bedaquiline prescription, baseline ECG results, and presence of a signed informed consent should be documented. The routine second-line treatment card should be used, and a system for identifying patients on bedaquiline should be developed (such as coloured highlighting, or tabs in e-databases).

Bedaquiline must be used for a maximum length of 24 weeks (six months) at the start of treatment in addition to the WHO-recommended MDR-TB regimen, which lasts for about 20 months.

Table 3. Length of treatment for bedaquiline-containing regimens

DRUG	SUGGESTED DURATION OF TREATMENT IN MONTHS WHEN BEDAQUILINE IS ADDED TO THE STANDARD WHO REGIMEN*																			
Bedaquiline (oral)	1	2	3	4	5	6														
Second-line injectable drug	1	2	3	4	5	6	7	8												
Other oral anti-TB drugs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

* With XDR-TB, the total treatment can be extended to 24 months; however, bedaquiline is still used only in the initial six months.

> **Warning:** Bedaquiline should not be introduced into a regimen in which the other companion drugs are known or believed to be ineffective or are failing to show effectiveness. This implies that bedaquiline should not be added alone to a failing regimen, and should be introduced well before the regimen fails completely.

Bedaquiline must not be added in the middle of treatment. Instead, when it is determined that there is an indication for bedaquiline, a new regimen is designed according to the different scenarios described in the *WHO Companion handbook for PMDT (7)*.

Bedaquiline is available as 100 mg tablets. Bedaquiline must be taken at the recommended dose and indicated frequency of administration. The six-month dosing schedule of the medication is as follows:

- **Week 0–2:** Bedaquiline 400 mg (four tablets of 100 mg) daily (seven days per week).
- **Week 3–24:** Bedaquiline 200 mg (two tablets of 100 mg) thrice a week (with at least 48 hours between doses) for a total dose of 600 mg per week.
- **Week 25 (start of month seven) to end of treatment:** Continue other second-line anti-TB drugs only, as per WHO standard recommendations. Bedaquiline is NOT used in this phase of treatment.

Bedaquiline can be taken together with other anti-TB drugs with a light meal (bedaquiline is better absorbed with food).[6]

Currently, dose adjustment is not a requirement in any circumstance, even if concomitant agents are known to affect bedaquiline bioavailability. If a dose is missed during the first two weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From the third week onwards, if a 200 mg dose is missed, patients should take the missed dose as soon as possible, and then resume the thrice-weekly regimen *(11)*.

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[6] If taking a light meal with bedaquiline 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 fluoroquinolones. Also, large fatty meals should be avoided as these can impair absorption of some of the other anti-TB drugs (cycloserine, isoniazid, etc).

Administration of MDR-TB treatment containing bedaquiline (hospital-based or outpatient-based) should be arranged according to the treatment protocol and country policy.

For HIV-positive patients on antiretroviral treatment, consideration should be given to potential drug interactions and overlapping toxicities between bedaquiline and antiretroviral drugs. Therefore, caution should be used when designing regimens for patients on antiretroviral treatment (refer to *WHO Companion handbook for PMDT (7)* for further details).

At the time of treatment initiation and during follow-up visits, relevant patient details, comorbidities, laboratory test results and AEs need to be collected. PMDT forms already in use should be adapted to incorporate additional data fields required for drug-safety monitoring (see *Meeting report of the inter-regional workshop on pharmacovigilance for TB (28)* for the minimum data collection elements; and the *Sample data collection forms for active TB drug-safety monitoring and management* (**Annex 11**). Patients on bedaquiline should be flagged as such and drug-safety monitoring data preferably entered in the routine recording and reporting system. Thus, additional data fields related to drug-safety monitoring need to be included both in the paper and electronic recording and reporting systems.[7]

5. Monitor treatment response

Patient level

It is recommended that patients receiving bedaquiline be regularly monitored during and after treatment, according to the standard monitoring schedule for patients on PMDT. In addition, patients on bedaquiline should be seen *at least* on a *monthly* basis while they are receiving the drug. Patient monitoring should include:

- Clinical evaluation (daily if the patients is hospitalized; weekly if on an outpatient model of care during the intensive phase; then monthly after the patient has stabilized on bedaquiline).
- Weight (baseline, then every two to four weeks).
- Height (baseline, then monthly – only for children).
- Assessment of treatment adherence and tolerance to drugs (i.e. regular check of treatment card).
- Laboratory tests to assess response to TB therapy:
  - Sputum smears and culture (ideally every month throughout the treatment)
  - DST at baseline – should be repeated if patient remains positive or reverts to positive culture after month four.
- Laboratory tests to check for AEs, including creatinine, electrolytes, thyroid function, liver function, complete blood count, audiometry, visual acuity and ECGs. The timing of these routine assessments is described in **Annexes 4 and 11**.
- Chest radiograph: baseline, then every six months .

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[7] The *Hanoi workshop report* provides a list of essential data elements and a data dictionary to facilitate incorporation of drug-safety monitoring data fields in a standardized manner across countries *(27)*.

At the end of treatment, the patient's clinical response to bedaquiline will be evaluated using standard clinical indicators as described in the national PMDT guidelines. In particular, the following will be assessed:

- Adherence to treatment: number of bedaquiline doses received compared to prescribed amount per patient.
- Sputum culture conversion: occurrence and date.
- Patient survival: if the patient has died, all efforts should be made to ascertain the immediate and contributing causes of death and determine if it were linked or not to TB or to treatment. The International Classification of Diseases coding of the cause of death should always be recorded. As death is by definition considered a SAE, all legal requirements on reporting of SAEs should be obeyed.
- Has the patient been lost to follow-up? If yes, all effort should be made to find the patient and to determine why he/she has not continued to receive care for drug-resistant TB.

Programmatic level

The treatment response in the **cohort** of patients treated with bedaquiline will be evaluated in terms of effectiveness and safety through routine PMDT indicators of treatment response, as described in **Annex 5**. These include detection indicators (such as confirmed MDR-TB cases detected among TB patients tested for susceptibility to isoniazid and rifampicin), enrolment indicators (such as presumed or confirmed MDR-TB cases started on treatment), interim results (such as MDR-TB patients on treatment with a negative culture at six months), and final outcomes (such as cured, failed or other).

In addition, **the following indicators** should be assessed to evaluate the feasibility and effectiveness of bedaquiline implementation at country level:

- **Enrolment indicators**
    - Number of MDR-TB patients declared eligible for treatment with bedaquiline by the Clinical Review Committee who have indeed started treatment with bedaquiline
    - Interval of time between MDR-TB diagnosis and start of MDR-TB treatment containing bedaquiline.

- **Treatment monitoring indicators**
    - Time to culture conversion
    - Proportion of patients on bedaquiline who developed SAEs
    - Proportion of patients on bedaquiline who changed treatment regimen due to AEs
    - Proportion of expected monitoring visits/tests that have been performed
    - Proportion of patients who developed resistance to bedaquiline during treatment
    - Rate of disease recurrence or relapse one year after successful completion of treatment.

Specific pharmacovigilance indicators can be found in the *WHO Companion handbook for PMDT (7)* and the *Hanoi Workshop Report (28)*.

Lastly, the NTP should evaluate the following aspects in the pilot sites where bedaquiline was introduced:

- Number of pilot sites identified and equipped to introduce bedaquiline vs planned.
- Number of health providers trained.
- Number of eligible MDR-TB patients started on bedaquiline in year 1, 2 and 3, respectively.
- Whether the drug-safety monitoring indicators are being generated or not.
- Number of supportive supervision visits performed (at least two supervision rounds per year to each implementing site are recommended).
- Number of drug stockouts and reasons.

6. Ensure appropriate implementation of active TB drug-safety monitoring activities

Special attention should be paid to ensure that AEs – in particular hepatic and cardiac events – are detected early and promptly managed. Patients receiving bedaquiline are to be monitored closely throughout their treatment, and AEs promptly recorded and reported through active drug-safety monitoring, preferably using the aDSM approach (see Step 2.7 in previous section). AEs monitoring should take place within the context of PMDT. The recommended AE monitoring schedule for patients with MDR-TB should be used.

In addition, patients on bedaquiline will need the following monitoring:

Adverse event monitoring

For AE monitoring the following are required.

- Monthly monitoring of liver function tests.
- ECG monitoring to assess cardiotoxicity and potential drug-induced QT prolongation: at baseline and then at two, eight, 12 and 24 weeks after initiating bedaquiline. Because of the long half-life of bedaquiline (5.5 months) additional ECG monitoring could be considered as part of routine monitoring (i.e. at weeks 36 and 48) or in any patient who becomes symptomatic.
- Clinical monitoring for haemoptysis, pancreatitis and pleuritic chest pain, with symptom-directed testing based on clinical evaluation.

Annex 4 provides details on recommended tests to monitor AEs during MDR-TB treatment.

Adverse event management

For each AE, it is necessary:

- to analyse the type, severity and relation of the event with the drugs provided;
- to treat the event;
- to monitor the evolution (and outcome) of the event; and
- to report the event in the routine electronic reporting and recording system.

Adverse event recording and reporting

Data on AE must be actively collected at initiation, during treatment monitoring visits and recorded at each follow-up visit. This information must also be collected during unscheduled follow-up visits (e.g. for the treatment of an AE). Clinical information must be complemented by details on laboratory tests and other measurements before and during treatment (e.g., biochemistry, ECG (see **Annexes 3** and **4**)).

NTPs are required to record and report clinical events that may arise once patients are started on bedaquiline. When reporting the event, it is essential that patient and event data be accurately identified and all due information reported. Ideally, ALL AE should be actively identified, properly managed and reported, but the extent or capacity to carry out drug-safety monitoring activities (i.e., aDSM) will rely on country's financial resources and human capacity. Hence, three levels of aDSM are recommended according to needs and capacity of countries introducing new TB drugs and/or regimens:

- a core package, requiring monitoring and reporting of all SAEs;
- an intermediate package, which includes SAE as well as AE of special interest; and
- an advanced package aiming at identifying all AEs of clinical significance.

Except in special projects in which data on AE of special interest or those of clinical significance are being collected, at leas**t ALL** SAE (such as AE which either lead to death or are life-threatening; hospitalization or prolongation of hospitalization; persistent or significant disability; or a congenital anomaly) must be reported. Completed forms should be sent to the centre responsible for drug-safety monitoring, according to each country's policy. For countries adopting the aDSM framework, an aDSM committee composed of national experts in both DR-TB and drug-safety will conduct a formal causality assessment. This would help assess the potential relationship between reported AEs and drugs taken by the patient.

For further details on levels of monitoring in aDSM, refer to the *Framework for implementation of active tuberculosis drug-safety monitoring and management* (aDSM) *(24)*. More information on data that should be recorded can also be found in the report of the *Inter-regional workshop on pharmacovigilance for new drugs and novel regimens for the treatment of drug-resistant tuberculosis* held in Hanoi, Viet Nam 12–14 November 2014 *(28)*.

7. Monitor individual drug resistance

It is important to monitor the occurrence of resistance to bedaquiline and to companion drugs by comparing the baseline DST to repeated DST during treatment. It is advisable to store all the strains collected for testing during treatment with bedaquiline. In addition, the repeat DST for first- and second-line drugs (including bedaquiline) should be done on the last positive culture isolate. If laboratory capacity for susceptibility testing to selected drugs is not available at country level, then the strains should be sent to the SNRL for testing.

Step 5: Generating evidence for scale-up

As countries start to introduce bedaquiline for the treatment of MDR-TB, they may face operational and logistical challenges related to drug procurement, introduction of new tests for patient screening, varied protocols for treatment monitoring, including drug-safety monitoring. In addition, human resources capacity building processes and supportive supervision activities may require exceptional efforts, especially in the first phase. It is therefore recommended that implementation of bedaquiline at country level be started in a phased manner (with a pilot phase) and monitored in a systematic way before scaling up at country level. Documenting the pilot phase experience by collecting key data related to programmatic implementation will assist countries to plan proper scale-up introduction of bedaquiline (as well as other new TB drugs/regimens). This will ultimately be very useful to inform wider expansion.

Key data to collect and analyse are data on *outcomes* of patients receiving bedaquiline (including safety, efficacy, and tolerability) and data on *process* of bedaquiline implementation (identifying facilitators and barriers to the use of bedaquiline in the country). These indicators are detailed below. As in any programmatic assessment, it is crucial to ensure that the data are of the best possible quality. A baseline set of data should be collected once, at the time of bedaquiline treatment initiation. Ongoing review datasets should be collected throughout the programme at specific time periods according to the national plan on bedaquiline implementation.

Outcome indicators

Many of the outcome indicators will be collected as part of routine recording and reporting, as discussed in the previous sections.

- **Safety outcome indicators.** These include percentage of patients receiving bedaquiline who develop: (i) SAEs (particularly related to heart and liver); (ii) bedaquiline-associated adverse drug reactions; and (iii) time to development of bedaquiline-associated adverse drug reactions.
- **Efficacy outcome indicators.** These include: (i) percentage of patients on bedaquiline with successful treatment outcomes (cure and completed treatment); (ii) percentage of patients on bedaquiline with unsuccessful treatment outcomes (treatment failure, lost to follow-up and death); (iii) average time to sputum culture conversion; and (iv) percentage of patients treated with bedaquiline who developed resistance to the medication.
- **Tolerability outcome indicators**. These include: (i) percentage of patients defaulting from treatment; (ii) number of missed doses of bedaquiline in the six-month treatment period; and (iii) qualitative assessment of the patients' experience with bedaquiline.

When evaluating outcome indicators, it might be helpful to have a "comparison group" to which the data on bedaquiline can be compared. For example, when assessing the safety of bedaquiline, a group of patients not receiving bedaquiline could be assessed to see if there are

fewer, more, or similar rates of AEs in the two groups, and if the events are similar. This could be historic data collected at the same site, before the introduction of bedaquiline or a comparable cohort of patients treated with the standard regimens. However, caution should be made in drawing conclusions about differences between the groups, especially if the populations being compared are not similar (i.e. patients receiving bedaquiline might have more clinically advanced disease than those not receiving the drug, given the requirements for the use of bedaquiline in individual patients). To minimize the risk of bias when comparisons are made between groups, the "control" populations should as much as possible match the cohort of patients receiving bedaquiline in terms of age, sex, HIV status, disease severity (cavitation), etc.

Process indicators

Assessing the process by which bedaquiline was implemented and is being used in a country is key to generating evidence for national and global scale-up. Process indicators provide valuable information on what worked well with bedaquiline implementation and what needs to be strengthened or changed as the programme is expanded in the country and throughout the world. Process indicators should include:

- number of patients screened for bedaquiline eligibility;
- percentage of patients screened by the Clinical Review Committee who are declared eligible for bedaquiline and reasons for prescribing bedaquiline;
- percentage of eligible patients enrolled on treatment with bedaquiline;
- percentage of patients eligible for treatment with bedaquiline who were NOT enrolled on treatment, and reasons why;
- percentage of MDR-TB patients on bedaquiline included in the cohort;
- percentage of MDR-TB patients started on bedaquiline retained in the cohort; and
- stockouts of bedaquiline.

In addition, operational challenges (such as human resources constraints, laboratory issues, challenges in supportive supervisory visits) should be described.

Additional information is crucial to take informed decisions on scale-up. These include:

- *Data on the costs and benefits of bedaquiline use.* Clearly, the use of bedaquiline may incur upfront costs, including purchase of the drug, purchase of companion drugs, increased patient monitoring, development of clinical and training materials, and development of a drug-safety monitoring framework. Programmes should monitor the costs of implementation of the drug to have a realistic sense of budget planning and resource allocation for wider introduction. Programmes need to consider that there may be great benefits to using bedaquiline, including: (i) a more rapid time to culture conversion (thus ensuring less transmission in the community provided diagnosis is made and therapy is given in a timely fashion); (ii) a treatment option for "untreatable" patients (thus saving lives and decreasing transmission); and (iii) the return to health of persons in their most productive years of life. Some of these benefits and savings may not be apparent in the first few years of bedaquiline implementation but should be considered if programmes are to have a realistic view of how useful bedaquiline is in their settings.

- *Qualitative information.* While many of the variables discussed above are numeric and can be collected through a variety of treatment registers, qualitative data obtained by speaking to individuals receiving bedaquiline and those caring for them can help provide a more holistic picture of bedaquiline introduction. For example, interviewing patients about their experience with taking bedaquiline, their understanding of the informed consent process, and their ideas about how patient care can be improved, can provide important data for programmes. Health care personnel should also be interviewed about their experience in delivering bedaquiline, including their assessment of a change in the workload, their experience with the informed consent process, and their thoughts on the role of drug-safety monitoring in MDR-TB treatment.

Data for both outcome and process indicators that are most likely to be valuable should have the following features:

- They should come from treatment centres with reliable access to good quality drugs and monitoring facilities run by staff with good proficiency in clinical care;
- They should be collected using a quality-assured methodology for the variables and the organization of data, respecting ethical norms and standards for data management;
- They should represent a series with relatively large numbers of patients of a diverse age and gender profile; and
- Lastly, they should be carefully checked and analysed with an understanding of the potential limitations of the results.

Results from these early implementation projects should be considered for publication in peer-reviewed journals, provided proper ethical approval is given from relevant review boards and informed consent is obtained from all patients and other participants. Publishing such results allows the global community to share in the findings of the implementing sites. Checklists on how to report the different types of observational studies are available as part of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement *(29)*.

A summary of activities for introduction and use of bedaquiline at country level is given in **Table 4** below.

Table 4. Summary of activities for implementation of bedaquiline at country level

KEY ACTION STEPS				
BEFORE/DURING IMPLEMENTATION	**STEP**	**DOMAIN**	**RESPONSIBLE BODY**	**ACTIVITIES**
Preparation	Step 1	Establish the framework for bedaquiline introduction	National level (health ministry, NTP, implementation Task Force)	1. Assess the national context
				2. Contact relevant units/ departments at the health ministry
				3. Identify implementing partners
				4. Create a national Implementation Task Force and Technical Working Group
				5. Coordinate with the National Regulatory Authority
				6. Establish a dialogue with pharmaceutical companies
				7. Establish appropriate procurement system for bedaquiline
				8. Organize sensitization workshops
	Step 2	Meet the minimal requirements (see checklist, pages 23–25)	National level (health ministry, NTP, implementation Task Force)	1. Laboratory capacity
				2. Drug resistance surveillance
				3. Clinical Review Committee
				4. Case management
				5. Recording and reporting system
				6. Monitoring and evaluation
				7. drug-safety monitoring
				8. Budget
				9. Technical assistance
				10. Drug supply system
				11. Checklist for country preparedness and planning

BEFORE/DURING IMPLEMENTATION	STEP	DOMAIN	RESPONSIBLE BODY	ACTIVITIES
Preparation	Step 3	Develop a national plan for the implementation of bedaquiline	National level (health ministry, NTP, implementation Task Force, Technical Working Group)	Identify pilot/implementing sites
				Develop specific plan elements
				1. Rationale for introduction of bedaquiline at country level
				2. Development or update national clinical guidelines
				3. Development of plans for laboratory needs
				4. Reporting and recording
				5. Monitoring and evaluation
				6. Drug-safety monitoring plans
				7. Ethical aspects
				8. Calculation of drug needs
				9. Training of managers and staff
				10. Human resources development plan
				11. Timeline development
				12. Budget development
				13. Obtain consensus from donor agencies
Implementation	Step 4	Implement bedaquiline use	NTP, implementation Task Force, Technical Working Group, pilot/ implementing site level staff	1. Identify patients eligible for treatment with bedaquiline
				2. Obtain signed informed consent
				3. Consult with Clinical Review Committee
				4. Initiate treatment
				5. Monitor treatment response
				6. Ensure active drug-safety monitoring (detection, management and reporting of adverse events)
				7. Monitor individual drug resistance
	Step 5	Generate evidence for scale-up	National level (NTP, implementation Task Force, Technical Working Group)	

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Annex 1. Further reading

WHO website

1. Introduction and rational use of new drugs and drug regimens for TB treatment – 2013 (http://www.who.int/tb/publications/newdrugs_factsheet.pdf, accessed 16 October 2015).

2. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis, Interim policy guidance (http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf, accessed 10 September 2015).

3. Policy Implementation Package for new TB drug introduction (http://www.who.int/tb/PIPnewTBdrugs.pdf, accessed 16 October 2015).

4. Tuberculosis and pharmacovigilance. [website] Geneva: World Health Organization; 2015 (http://www.who.int/tb/challenges/pharmacovigilance/en/, accessed 27 August 2015).

Working Group on new TB drugs of the Stop TB Partnership

5. Working Group on new TB drugs (http://www.newtbdrugs.org, accessed 19 March 2015).

6. Global TB drug pipeline (http://www.newtbdrugs.org/pipeline.php, accessed 19 March 2015).

New drugs and regimens framework

7. Lienhardt C, Raviglione M, Spigelman M, Hafner R, Jaramillo E, Hoelscher M, et al. New drugs for the treatment of tuberculosis: needs, challenges, promises and prospects for the future. J Infect Dis 2012;205(S2):S241–9.

8. Wong EB, Cohen KA, Bishai WR. Rising to the challenge: new therapies for tuberculosis. Trends Microbiol 2013;21(9):493–501.

9. Dooley KE, Mitnick CD, Ann DeGroote M, Obuku E, Belitsky V, Hamilton CD, et al. Efficacy Subgroup, RESIST-TB. Old drugs, new purpose: retooling existing drugs for optimized treatment of resistant tuberculosis. Clin Infect Dis 2012;55(4):572–81.

Drug-safety monitoring

10. Framework for implementation of active tuberculosis drug-safety monitoring and management (aDSM). (WHO/HTM/TB/2015.28). Geneva: World Health Organization; 2015.

11. Companion handbook to the WHO guidelines for the programmatic management of drug resistant tuberculosis (WHO/HTM/TB/2014.11). Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf, accessed 16 October 2015).

12. Inter-regional workshop on pharmacovigilance for new drugs and novel regimens for the treatment of drug-resistant tuberculosis. Hanoi, Viet Nam 12–14 November 2014. Meeting report (WHO/HTM/TB/2015.07) (http://www.who.int/tb/challenges/meeting_report_pv_workshop_hanoi_2014.pdf?ua=1, accessed 1 October 2015).

Main publications on bedaquiline

- Andries K, Verhasselt P, Guillemont J, Göhlmann HW, Neefs JM, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. Science 2005;307(5707):223–7.
- Diacon AH, Pym A, Grobusch M, Patientia R, Rustomjee R, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009;360(23):2397–405.
- Diacon AH, Dawson R, Von Groote-Bidlingmaier F, Symons G, Venter A, et al. Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum microscopy smear-positive pulmonary tuberculosis. Antimicrob Agents Chemother 2013;57(5):2199–203.
- Diacon AH, Donald PR, Pym A, Grobusch M, Patientia RF, Mahanyele R, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob Agents Chemother. 2012;56(6):3271–6.
- Diacon, A. H., Pym, A., Grobusch, M. P., de los Rios, J. M., Gotuzzo, E., et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014; 371(8): 723–732.
- Guglielmetti L, Le Dû D, Jachym M, Henry B, Martin D, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: an interim analysis of a French cohort. Clin Infect Dis. 2015 Jan 15;60(2):188–94. doi: 10.1093/cid/ciu786. Epub 2014 Oct 15.
- Gras J. Bedaquiline for the treatment of pulmonary, multidrug-resistant tuberculosis in adults. Drugs Today (Barc) 2013;49(6):353–61.
- Ndjeka, N., Conradie, F., Schnippel, K., Hughes, J., Bantubani, N., et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. Int J Tub Lung Dis. 2015;19(8): 979–985
- Rouan MC, Lounis N, Gevers T, Dillen L, Gilissen R, et al. Pharmacokinetics and pharmacodynamics of TMC207 and its N-desmethyl metabolite in a murine model of tuberculosis. Antimicrob Agents Chemother 2012;56(3):1444–51. doi: 10.1128/AAC.00720–11. Epub 2011 Dec 12.
- Tiberi S, De Lorenzo S, Centis R, Viggiani P, D'Ambrosio L, et al. Bedaquiline in MDR/XDR-TB cases: first experience on compassionate use. Eur Respir J 2014; 43(1):289–92. doi: 10.1183/09031936.00122313. Epub 2013 Aug 29.
- SIRTURO™ product information for healthcare providers. Titusville: Janssen Therapeutics (http://www.sirturo.com/sites/default/files/pdf/SIRTURO-product-guide.pdf, accessed 19 March 2015).

Annex 2. Minimum laboratory requirements for introduction of bedaquiline

LABORATORY REQUIREMENTS
Smear (ZN and/or FM)
Rapid molecular tests (Xpert® and/or LPA)
Culture (solid and/or liquid)
Diagnosis of MDR-TB (at least RR-TB)
EQA system in place
Access to DST for (at least): isoniazid, rifampicin, ofloxacin/levofloxacin, amikacin/kanamycin In some cases, access to DST for moxifloxacin and capreomycin may be requested from a reference laboratory.
Haematology: haemoglobin (Hgb), white blood cell (WBC; differential blood count)*
Biochemistry: serum creatinine, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), bilirubin, lipase, electrolytes (potassium, calcium)*
HIV tests (screening and confirmation), CD4 cell count, HIV viral load
Pregnancy test
Additional tests if required by national treatment protocol (i.e. TSH, lactic acid in case on antiretroviral treatment or linezolid)

* These are the required tests at the implementing site level during the pilot phase of the programme. As more experience is gained with bedaquiline, the country may consider allowing scale-up sites for bedaquiline use without these tests, provided they are able to send samples to and receive results from a designated laboratory in a timely fashion.

Annex 3. Monitoring MDR-TB treatment response

The table below is extracted from the *Companion handbook to the WHO guidelines for the programmatic management of drug resistant tuberculosis* 2014 *(14)*.

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Evaluation by clinician	*During the intensive phase*: Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. Once stable, the patient is seen twice a month or once a month. *During the continuation phase*: Monthly assessments unless there is a medical necessity to see the patient more often. The DOT supporter sees the patient daily between consultations and signals any concerns to the clinician.
Treatment adherence and tolerance	Daily at every DOT encounter by the DOT provider.
Sputum smears and culture	Monitoring smears and culture monthly throughout treatment. (Note: programmes with limited resources may choose to do monthly smears and cultures until conversion and then monthly smears with every other month cultures.)
Weight	At baseline, then every two weeks for first three months and then monthly.
Height	At start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).
Drug susceptibility testing	At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after month four (see Chapter 3 for more information on DST).
Chest radiograph	At baseline, and then every six months.

Annex 4. Monitoring for adverse events during MDR-TB treatment

The table below is extracted from the *Companion handbook to the WHO guidelines for the programmatic management of drug resistant tuberculosis* 2014 *(14)*.

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Serum creatinine	At baseline; then monthly if possible while receiving an injectable agent. Every one to three weeks in HIV infected patients, diabetics and other high-risk patients.
Serum potassium	Monthly while receiving an injectable agent. Every one to three weeks in HIV infected patients, diabetics and other high-risk patients.
Serum magnesium and calcium	Check magnesium and calcium blood levels whenever hypokalaemia is diagnosed. At baseline and then monthly if on bedaquiline or delamanid. Repeat if any electrocardiogram (ECG) abnormalities develop (prolonged QT interval).
Thyroid stimulating hormone (TSH)	Every three months if receiving ethionamide/prothionamide and *p*- aminosalicylic acid (PAS). Every six months if receiving ethionamide/ prothionamide or PAS, but not both together. TSH is sufficient for screening for hypothyroidism and it is not necessary to measure hormone thyroid levels. Monthly monitoring for clinical signs/symptoms of hypothyroidism is also necessary.
Liver serum enzymes (SGOT, SGPT)	Periodic monitoring (every 1–3 months) in patients receiving pyrazinamide for extended periods or for patients at risk for, or with symptoms of hepatitis. For HIV-infected patients monthly monitoring is recommended. For patients on bedaquiline, monitor monthly. For patients with viral hepatitis, monitor every one to two weeks for the first month and then every one to four weeks.
HIV testing	At baseline, and repeat if clinically indicated.
Pregnancy tests	At baseline for women of childbearing age, and repeat if indicated.
Haemoglobin and white blood cell count	If on linezolid, monitor weekly at first, then monthly or as needed based on symptoms; there is little clinical experience with prolonged use of linezolid. For HIV-infected patients on zidovudine, monitor monthly initially and then as needed based on symptoms.
Lipase	Indicated for work-up of abdominal pain to rule out pancreatitis in patients on linezolid, bedaquiline, D4T, ddI or ddc.

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Lactic acid	Indicated for work up of lactic acidosis in patients on linezolid or antiretroviral treatment (ART).
Serum glucose	If receiving gatifloxacin, monitor fasting blood glucose at baseline and monitor monthly. Educate/remind patients on signs and symptoms of hypoglycaemia and hyperglycaemia monthly.
Audiometry (hearing test)	Baseline audiogram and then monthly while on an injectable agent. Ask patients about changes in hearing at every clinic visit and evaluate their ability to participate in normal conversation.
Vision tests	For patients on long-term ethambutol or linezolid perform at least a visual acuity test with Snellen charts and colour vision test at baseline (as a small percentage of the population has colour blindness). Repeat the test for any suspicion of change in acuity or colour vision.
Educational, psychological and social consultation	At baseline by personnel trained in health education, psychological and social issues relevant to TB management; during treatment and repeat as indicated. Refer to social worker, psychologist or psychiatrist when indicated.
ECG	An ECG should be obtained before initiation of treatment with bedaquiline or delamanid, and at least 2, 4, 8, 12, and 24 weeks after starting treatment. Monitoring ECGs should be done monthly if taking other QT prolonging drugs (i.e moxifloxacin, clofazimin).

Measurement of the QT interval. QT prolongation can result in ventricular arrhythmias (torsades de pointes) and sudden death, and it is imperative that ECGs are used to monitor the QT interval regularly during bedaquiline use. The QT interval must be corrected for the heart rate and the adjusted value is referred to as the "QT-corrected" (QTc). The **Fredericia correction method (QTcF)** is preferred.

· A QTcF greater than 440 ms is considered prolonged.

· A QTcFvalue greater than 480 ms (or an increase of greater than 60 ms from baseline) requires electrolyte testing and more frequent ECG monitoring.

· A QTcF interval of more than 500 ms is considered dangerous and discontinuing QT prolonging drugs is indicated.

Low or high serum electrolyte concentrations in the presence of a QT-interval prolongation predisposes to arrhythmias.

Liver function monitoring. Because a higher incidence of liver toxicity was seen in the clinical arm of patients on bedaquiline, liver enzymes should be monitored monthly. If aminotransferase elevations are accompanied by total bilirubin elevation of more than twice the upper limit of normal, or aminotransferase elevations are more than five times the upper limit of normal, bedaquiline needs to be discontinued.

Annex 5. MDR-TB indicators

The tables below are extracted from the *Companion handbook to the WHO guidelines for the programmatic management of drug resistant tuberculosis* 2014 *(14)*.

Detection indicators

- TB patients with positive DST results for isoniazid and rifampicin (or for only rifampicin where Xpert® MTB/RIF alone is available).
- Confirmed MDR-TB cases detected among TB patients tested for susceptibility to isoniazid and rifamipicin (or RR-TB cases detected among TB patients tested only for rifampicin).
- Confirmed MDR-TB cases tested for susceptibility to any fluoroquinolone and any second-line injectable drug.
- Confirmed XDR-TB cases detected among MDR-TB patients tested for susceptibility to any fluoroquinolone and any second-line injectable drug.
- Interval of time between presumption of RR-/MDR-TB and DST results.

Enrolment indicators

- MDR-TB cases (presumptive or confirmed) enrolled for MDR-TB treatment.
- Confirmed RR-TB or MDR-TB cases enrolled for MDR-TB treatment.
- Confirmed XDR-TB cases enrolled for XDR-TB treatment.
- Interval of time between MDR-TB diagnosis and start of MDR-TB treatment.

aDSM indicators

- Coverage: MDR-TB patients on bedaquiline included in aDSM.
- Completeness: MDR-TB patients started on bedaquiline retained in the cohort.
- Serious adverse events: MDR-TB patients included in aDSM with any serious adverse event.
- Bedaquiline-associated adverse reactions: Frequency of bedaquiline-associated serious drug reactions.
- Bedaquiline-associated serious reactions: Time to development of bedaquiline-associated serious drug reactions.

Interim results

- Rifampicin-resistant (RR)-/MDR-TB cases on MDR-TB treatment with negative culture by six months
- RR-/MDR-TB cases on MDR-TB treatment who died by six months
- RR-/MDR-TB cases on MDR-TB treatment who were 'lost to follow-up' by six months
- Patients on MDR-TB treatment found not to have RR-/MDR-TB
- Patients on XDR-TB treatment found not to have XDR-TB.

Treatment for MDR-TB typically takes 20 months or more and final outcomes can thus only be assessed two to three years after enrolment. The programme manager often needs an indication

of how patients are faring before that. This is particularly important when a drug-resistant TB treatment component of a programme is starting. Assessing culture conversion to negative (for confirmed pulmonary cases) in month six and death by six months is widely used as an indicator of treatment response. Information on loss to follow-up by six months is helpful. It is also useful to know how many patients started on second-line drugs for MDR-TB turned out not to have MDR-TB (and likewise for XDR-TB). This evaluates the effectiveness of the treatment algorithm in treating patients who really need second-line regimens and avoiding a potentially toxic regimen in patients who do not.

The period of assessment is three calendar months (one quarter), usually counted from (i) January to end-March, (ii) April to end-June, (iii) July to end-September, and (iv) October to end-December. All patients registered **and** starting treatment during the period of assessment are included in the calculation. In sites testing with Xpert MTB/RIF alone, the first four enrolment indicators can be modified to include all cases with RR-TB started on a MDR-TB regimen. Only laboratory confirmed RR-TB, MDR-TB and XDR-TB cases who have started treatment are counted for reporting of Interim results. When calculating the proportion of cases with negative culture by six months, all patients started on treatment remain in the denominator, including patients who died or were lost to follow-up before six months. If a patient is lost to follow-up and then dies by six months, then the result retained will be *Lost to follow-up*, having been the first outcome met.

Indicators are measured nine months after the end of the quarter of assessment (see box below). This gives sufficient time for culture results at month six to be issued and retrieved. All data can be extracted from the Second-line TB treatment register.

CALCULATION OF INTERIM RESULTS INDICATORS

Interim results indicator 1:* RR-/MDR-TB cases on MDR-TB treatment regimen with negative culture by six months.**

Numerator: Number of confirmed pulmonary RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment with negative results for culture in month six of their treatment.

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

Interim results indicator 2:* RR-/MDR-TB cases on MDR-TB treatment regimen who died by six months.**

Numerator: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who died of any cause by the end of month six of their treatment.

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

Interim results indicator 3:* RR-/MDR-TB cases on MDR-TB treatment regimen who were lost to follow-up by six months.**

Numerator: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who were lost to follow-up by the end of month six of their treatment

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

Interim results indicator 1 only applies to pulmonary cases. To simplify, the denominator for all indicators is all cases started on treatment. The three indicators should include XDR-TB cases started on prescribed treatment with second-line drugs.

Interim results indicator 4:* Patients on MDR-TB treatment regimen found not to have RR-/MDR-TB.**

Definition: Number of patients started on a prescribed MDR-TB treatment regimen during the period of assessment and later found not to have RR-/MDR-TB.

***Interim results indicator 5:** Patients on XDR-TB treatment regimen found not to have XDR-TB.**

Definition: Number of patients started on a prescribed XDR-TB treatment regimen during the period of assessment and later found not to be XDR-TB.

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* In sites testing with Xpert MTB/RIF alone, the indicators also enumerate RR-TB cases started on a second-line MDR-TB treatment who are assigned an interim result, or, in the case of *Interim results indicator 4*, were prescribed a second-line MDR-TB treatment regimen which was not warranted.

Final outcomes

The final outcome is the most important direct measurement of the effectiveness of the MDR-TB control programme. All confirmed MDR-TB patients entered in the treatment register should be assigned one of six mutually exclusive outcomes at the end of their therapy. In sites testing with Xpert® MTB/RIF alone, the indicators need to be modified to also include RR-TB cases started on a MDR-TB treatment regimen. Cases that are not evaluated due to transferring out, treatment still not completed at the time of final assessment or missing information are all grouped together. A patient who "transfers in" does not get enumerated in the cohort of the receiving treatment centre but only in the outcome cohort of the centre where treatment was started. All patients should be assigned the first outcome they experience for the treatment being evaluated. The outcome *Cured* is restricted to bacteriologically-confirmed pulmonary TB cases. The period of assessment is 12 calendar months, usually counted from January to end December, and referred to as an annual cohort. All patients registered *and* starting treatment during this period are included in the calculation. Only laboratory confirmed RR-TB, MDR-TB and XDR-TB cases are counted for cohort reporting of final outcomes.

Indicators are measured 24 months after the end of the year of assessment. This gives sufficient time for most patients to complete their treatment and for the final culture results to be issued and recorded. All data can be extracted from the second-line TB treatment register.

CALCULATION OF OUTCOME INDICATORS

Outcome Indicators 1–6: RR-/MDR-TB cases on MDR-TB treatment regimen with an outcome:

1. Cured
2. Treatment completed
3. Treatment failed
4. Died
5. Lost to follow-up
6. Not evaluated for outcome

Numerator: The number of confirmed RR-/MDR-TB cases registered for MDR-TB treatment during the period of assessment assigned one of the six outcomes.

Denominator: Number of confirmed RR-/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment.

This indicator is expressed as the percentage of persons in each of the mutually exclusive outcomes.

Programmes having the capacity to differentiate XDR-TB from other MDR-TB cases, particularly those where XDR-TB cases represent > 5% of MDR-TB, should report outcomes for non-XDR MDR-TB (including other RR-TB) and XDR-TB cases separately. MDR-TB patients found to have XDR-TB anytime in the course of their second-line TB treatment would be taken out of the non-XDR MDR-TB cohort and enumerated in the XDR-TB treatment cohort.

Outcome indicators in HIV-infected patients should be computed separately for cases with positive HIV status in countries where HIV prevalence is ≥1% in pregnant women or ≥5% in TB patients (30, 31).

Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

OUTCOME	DEFINITION
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: – lack of conversion[b] by the end of the intensive phase,[a] *or* – bacteriological reversion[b] in the continuation phase after conversion[b] to negative, *or* – evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, *or* – adverse drug reactions.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for two 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.)
Treatment success	The sum of *cured* and *treatment completed.*

[a]   For *Treatment failed*, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of intensive phase applied by the programme. If no maximum duration is defined, an eight-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off of eight months after the start of treatment is suggested to determine when the criteria for *Cured, Treatment completed* and *Treatment failed* start to apply.

[b]   The terms "conversion" and "reversion" of culture 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.

Annex 6. Steps required to introduce and sustain aDSM at national level

The implementation of aDSM will require the following eight essential steps:

1. Create a national coordinating mechanism for aDSM

2. Develop a plan for aDSM

3. Define management and supervision roles and responsibilities

4. Create standard data collection materials

5. Train staff on the collection of data

6. Define schedules and routes for data collection and reporting

7. Electronic consolidation of aDSM data

8. Develop capacity for signal detection and causality assessment

Ideally, all eight steps should be in place before patients are enrolled on treatment with new drugs or novel MDR-TB regimens. As this may not always be feasible, two steps are considered essential ahead of any patient enrolment, i.e. i) creating standard data collection materials; and ii) training staff on the collection of data.

Annex 7. Clinician's checklist for eligible patients

To assist in determining the **eligibility** of a patient for assignment to a bedaquiline-containing treatment regimen, see the checklist below and the template proposed for obtaining **informed consent** from the patient before starting bedaquiline therapy *(14)*.

CLINICIAN'S CHECKLIST OF ESSENTIAL PARAMETERS FOR SELECTION OF MDR-TB PATIENTS WITH BEDAQUILINE	
Parameters	**Tick** **Yes or No**
· Patient is at least 18 years old.	☐ YES ☐ NO
· Patient is known or suspected to be diseased with a multiple-resistant strain of tuberculosis and therefore eligible for treatment with second-line anti-TB drugs.	☐ YES ☐ NO
· Additional laboratory data has been obtained on the susceptibility profile of the patient's TB isolate to the following agents: fluoroquinolones (ofloxacin and moxifloxacin), and second-line parenteral agents (kanamycin, amikacin and capreomycin).	☐ YES ☐ NO
· The drug resistance profile of the patient's isolate suggests that the WHO standard recommended regimen for treatment of MDR-TB cannot be provided.	☐ YES ☐ NO
· Clinically significant ventricular arrhythmia is absent.	☐ YES ☐ NO
· Baseline and repeat ECG shows normal QT interval.	☐ YES ☐ NO
· Aminotransferase and total bilirubin within normal limits.	☐ YES ☐ NO
· The patient's serum albumin, potassium, calcium, and magnesium have been obtained at baseline and levels are within normal limits.	☐ YES ☐ NO
· Informed consent for treatment with bedaquiline has been obtained	☐ YES ☐ NO

If the answer is 'yes' to all questions, the patient can be enrolled on treatment with bedaquiline.

If the answer is 'no' to any of the above, further consideration and consultation with the clinical review committee is needed before enrolment in a treatment regimen with bedaquiline.

Annex 8. Instruction to healthcare providers on patient education and informed consent for bedaquiline

These instructions on patient education and informed consent are given as an example. These serve as a broad guide to address to a patient and delivering the main indications on treatment with bedaquiline and potential harms/benefits. these instructions are extracted from the *Companion handbook to the WHO guidelines for the programmatic management of drug resistant tuberculosis 2014 (14).*

Introduction

Briefly state who you are and explain to patients that you are inviting them to accept bedaquiline as part of the drug regimen necessary to treat their disease. Inform patients that they may talk to anyone they feel comfortable talking with about the drug and that they can take time to reflect on whether they want to receive it or not. Assure the patient that if they do not understand some of the words or concepts, that you will take time to explain them as you go along and that they can ask questions now or later.

Proposed text: *I am X, working for the Y Clinic. At Y Clinic, we have a new drug available for the treatment of those forms of tuberculosis that cannot easily be treated with commonly used drugs. You are suffering from a difficult-to-treat form of tuberculosis, which is called drug-resistant TB. I am going to give you information about the drug, bedaquiline, its potential benefits, and also the potential risks associated with its use. This drug has been tested in patients like you, and has been approved for use in TB patients by the drug control authorities in the European Union and the World Health Organization. You do not have to decide today whether or not you would want to receive this new drug. Before you decide, you can talk to anyone you feel comfortable with about the information you have received and how to respond to it.*

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.

Reasons why bedaquiline is being offered to the patient

Explain **in lay terms** why you are offering to add bedaquiline to the treatment regimen. The language used should clarify rather than confuse. Use local and simplified terms. Avoid using terms like pathogenesis, antibiotic, adverse effects, cardiac, hepatic, etc.

Proposed text: *Tuberculosis is a serious disease that can be fatal. There are many TB cases who are especially difficult to treat with the drugs that are currently used; some patients with resistant TB may have limited treatment options. There is a new drug that has become available recently, and that may work better. Bedaquiline has been observed to have side-effects on the heart and liver in particular, and special tests will be offered to you during treatment to check for these.*

Explain how the treatment will be taken by the patient

Briefly state the type of intervention that will be undertaken. This will be expanded upon in the procedures section but it may be helpful and less confusing to the participant if they know from the very beginning that the drug will be taken by mouth for a period of six months, along with several other drugs administered by mouth or by injection.

Proposed text: *You will need to take four tablets of bedaquiline daily for two weeks, and two tablets on Mondays, Wednesdays and Fridays for a further five and a half months thereafter. It would be necessary to take these tablets here at the clinic in the morning. There will be other drugs to take also for a total of 20 months at least. Bedaquiline is best taken with a light meal. It is important to take the medication as prescribed to avoid the further development of resistance to the drugs you are taking.*

Explain to the patient that taking bedaquiline is their choice (it is voluntary)

Indicate clearly that they can choose to receive the drug or not. State what the alternative – in terms of the treatment offered by the clinic – will be, if they decide not to accept bedaquiline as part of their treatment. State, *only if it is applicable,* that they will still receive all the services they usually do whether they choose to take the drug or not. This can be repeated and expanded upon later in the form as well, but it is important to state clearly at the beginning of the form that receiving the drug is voluntary so that the other information can be heard in this context.

Example: *Your choice to receive bedaquiline for treating your disease is entirely voluntary. It is your choice whether to receive it or not. Whether you choose to accept the medication or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to receive bedaquiline, you will be offered the treatment that is routinely offered in this clinic/hospital for drug resistant tuberculosis, and we will tell you more about it later. You may change your mind later and stop receiving bedaquiline even if you agreed earlier.*

Go over the medication guide for patients taking bedaquiline

Go over each section of the medication guide with the patient.

Write in the contact information of one or more persons at the bottom of the medication guide.

Annex 9. Sample information note and informed consent for patient taking bedaquiline

The following information note and informed consent for patient taking bedaquiline is given as an example. It serves as a broad guide to delivering main information on treatment with bedaquiline and obtaining a signed informed consent from the patient. It should be adapted to the local situation and context and translated into appropriate language. (Source: *Companion handbook to the WHO guidelines for the programmatic management of drug resistant tuberculosis 2014 (14)*).

INFORMED CONSENT PART I:
MEDICATION GUIDE FOR PATIENTS TAKING BEDAQUILINE TABLETS

Read this medication guide before you start taking bedaquiline and each time before your monthly visit. This information does not tell your health care provider about your medical treatment or any medical conditions.

What is the most important information i should know about bedaquiline?

Bedaquiline is a drug used to treat multidrug-resistant tuberculosis (MDR-TB) lungs in people with limited treatment options. MDR-TB is a serious disease that can result in death and for which there are few treatment choices. More people treated with bedaquiline cleared TB from their sputum compared to people who did not receive bedaquiline. In one clinical trial, fewer deaths were seen in people who were treated with bedaquiline compared to people who did not receive bedaquiline.

It is important to complete the full course of treatment of bedaquiline and your other TB medicines and not skip doses. Skipping doses may decrease the effectiveness of the treatment and increase the likelihood that your TB disease will not be treatable by bedaquiline or other medicines.

Bedaquiline can cause serious side-effects.

· Heart rhythm problems can happen with bedaquiline.

It is not known if bedaquiline is safe in:

· Children under 18 years of age
· Pregnancy
· In patients with heart, kidney, liver or other health problems.

Before you take bedaquiline, tell your health care provider if:

· You have had an abnormal heart rhythm or other heart problems.
· Anyone in your family has or has had a heart problem called 'congenital long QT syndrome'.
· You have liver or kidney problems or any other medical conditions, including HIV infection.
· You are pregnant or plan to become pregnant. It is not known if bedaquiline will harm your unborn baby.
· You are breastfeeding or plan to breastfeed. It is not known if bedaquiline passes into breast milk. You and your health care provider should decide if you will take bedaquiline or breastfeed.
· You are taking any prescription and non-prescription medicines, vitamins and herbal supplements.

How should I take bedaquiline?

· Bedaquiline must always be taken with other medicines to treat TB. Your health care provider will decide which other medicines you should take with bedaquiline.

· Always take bedaquiline with a light meal.

· Swallow the tablets whole with water.

· Take bedaquiline for a total of 24 weeks (6 months).

   · Week 1 and Week 2: Take 400 mg (4 tablets) once a day, 7 days a week

   · Week 3 to Week 24: Take 200 mg (2 tablets) three times a week. For example, you may take bedaquiline on Monday, Wednesday and Friday of every week.

· You will need to take your other TB medicines for longer than 24 weeks, and at least for 20 months in total (the injectable drug is usually given for up to 8 months).

· Your treatment will be provided under directly observed treatment (DOT), with a patient-centred approach, which means that a health care provider will accompany you during the treatment and that your information, psychological and material needs will be addressed in order to enable your adherence to treatment.

· Do not skip bedaquiline doses. If you skip doses, or do not complete the total 24 weeks of bedaquiline your treatment may not work as well and your TB may be harder to treat.

· If for some reason you miss a dose, inform the person responsible for your treatment right away, they will tell you what to do.

What should I avoid while taking bedaquiline?

· You should not drink alcohol while taking bedaquiline.

· There are some medications that cannot be taken safety with bedaquiline. Make sure to inform your doctor if you are taking medicines or if medicines are recommended to you by a health care practitioner while you are on treatment for TB with bedaquiline.

What are the possible side-effects of bedaquiline?

· Serious heart rhythm changes. Tell your health care provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. Your heart will be monitored periodically with a machine that checks that the heart rhythm is normal.

· Liver problems. Liver toxicity can present in many ways. Tell your doctor of symptoms such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual tiredness, loss of appetite, light coloured stools, dark colored urine, yellowing of your skin or yellowing of the white of your eyes.

· Other side-effects of bedaquiline include nausea, joint pain, headache, an abnormal laboratory test associated with damage to the pancreas, coughing up blood, chest pain, loss of appetite, and/or rash.

It is possible that it may also cause some problems that we are not aware of. However, you will be followed closely for any unwanted effects or any problems. Other medicines to decrease the symptoms of the side-effects or reactions may also be given.

Always tell your health care provider of any side-effects or problems you are having. Sometimes because of side-effects bedaquiline or other drugs may need to be stopped.

What monitoring tests do I need while on bedaquiline?

- You will need the same monitoring test that all patients on MDR-TB treatment need. In addition, you will need heart monitoring, extra blood tests for the liver and your electrolytes. Consult with your health-care provider about the appropriate schedule of all your monitoring tests and regular doctor visits.

General information about the risk versus the benefit of taking bedaquiline

- RISK: It is possible that you will be at greater risk of not feeling well than you would otherwise because of certain side-effects due to the drug. It is possible that adverse side-effects could be serious and even result in death.

- BENEFIT: There is a greater chance that you will be cured of tuberculosis than if you do not take the medicine. You will possibly also become better very much sooner than if you only take the standard medicines for treatment of resistant TB. Also, it is probably less likely that the drugs you are taking will develop resistance if you are taking bedaquiline.

Confidentiality and sharing of information

- Because bedaquiline is a new drug for which we have limited experience, we are collecting information on patients taking it.

- The information that we collect from you will be kept confidential and no one but the clinical staff will be able to see your medical information.

- Any information collected to help us better use the drug in future patients will be unlinked to your name (made anonymous) before we share or analyse it.

Costs

- If you choose to take bedaquiline and cannot afford it, it may be provided free of charge to you. Many programmes will provide bedaquiline free of charge to all patients whether or not they can afford it.

Right to refuse or withdraw

- You do not have to agree to take bedaquiline if you do not wish to do so and refusing to accept the drug as part of your treatment schedule will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic.

- If you agree to take bedaquiline, you may choose to discontinue it at any point for any reason without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Contact person

If you have any questions, you may contact any of the following persons:

Name_____. Title_____. Phone_____.

Name_____. Title_____. Phone_____.

Name_____. Title_____. Phone_____.

Name of responsible physician: _____

Name of clinic/hospital/institution: _____

INFORMED CONSENT PART II: CERTIFICATE OF CONSENT

This section should be written in the first person and have a statement similar to the one in bold below. If the participant is illiterate but gives oral consent, a witness must sign the relevant section below. The person going over the informed consent must sign this form. The certificate of consent should avoid statements that have "I understand…" phrases. The understanding should perhaps be better tested through targeted questions during the reading of the information sheet, or through the questions being asked at the end of the reading of the information sheet, if the patient is reading the information sheet him/herself.

Example: *I have read the provided information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent to receive bedaquiline for treating the drug-resistant tuberculosis disease that I am suffering from.*

Print Name of Patient: _____

Signature of Patient: _____

Date: _____

      Day/month/year

If illiterate, a literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the care providers). Patients who are illiterate should include their thumbprint.

I have witnessed the accurate reading of the consent form to the potential recipient of bedaquiline, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness:_____

Signature of witness: _____

Date: _____

      Day/month/year

Thumbprint of patient

Statement by the person taking consent

I have accurately read out the information sheet to the potential bedaquiline recipient, and to the best of my ability made sure that the patient understands that the following will be done:

1. Special tests will be conducted to verify eligibility for receiving bedaquiline. These will include ECG assessments, blood tests and additional laboratory tests to determine the full drug resistance profile of the patient's infecting isolate;

2. Tests will be repeated at regular intervals, and are necessary to enable proper monitoring of response to treatment, both from an efficacy and a safety point of view; and

3. Bedaquiline will be administered as part of the drug regimen for a period of six months.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print name of person taking the consent: _____

Signature of person taking the consent: _____

Date: _____

              Day/month/year

Annex 10. Sample Clinical Review Committee decision form

1. Patient information

Surname: _____   Name: _____

Date of birth: dd/mmm/yyyy _____

Requesting physician: _____

2. Clinical Review Committee decision on bedaquiline treatment

☐ Bedaquiline treatment approved   ☐ Bedaquiline treatment refused

3. Reason for approval/refusal of bedaquiline treatment

_____

_____

_____

_____

_____

4. Recommended regimen and drug dosage

GROUP	DRUG	DOSE
Group 1	Pyrazinamide	
	Ethambutol	
Injectables (Group 2)	Kanamycin	
	Amikacin	
	Capromycin	
Higher level fluoquinolones (Group 3)	Levofloxacin	
	Moxifloxacin	
Group 4	Ethionamide/prothionamide	
	Cycloserine/terizidone	
	PAS	
Group 5	Bedaquiline	
	Linezolid	
	Clofazimine	
	Amoxicillin/clavulanate	
	Imipenem/cilastatin + clavulanate	

GROUP	DRUG	DOSE
Group 5	Meropenem + clavulanate	
	High dose isoniazid	
	Chlarythromyicin	
	Thioacetazone	

5. Clinical Review Committee composition

Surname: _____   Name: _____

Signature: _____

Surname: _____   Name: _____

Signature: _____

Surname: _____   Name: _____

Signature: _____

Surname: _____   Name: _____

Signature: _____

Surname: _____   Name: _____

Signature: _____

Surname: _____   Name: _____

Signature: _____

6. Place and date

_____

Annex 11. Data collection forms for active TB drug-safety monitoring and management

Data collection for aDSM[1] is a separate process from that used for routine monitoring in PMDT activities. In accordance to the four (4) packages proposed within the aDSM framework, a set of forms should be instituted when adopting either a Core, Intermediate or Advanced package (see *Step 4.6,* page 41).

In the Core Package of aDSM, an initial form listing clinical and laboratory tests to be recorded at baseline and during regular review (e.g. monthly intervals) must be filled (form a). Likewise, a second standard form to alert the NTP when any SAE occurs will need to be developed (form b). For countries adopting Intermediate and Advanced Packages of aDSM, a set of data collection forms will have to be used to record data at baseline and during regular follow-up (forms c and d).

Templates of such forms have been developed and can be adapted to individual programme needs as follows:

Sample data collection forms for countries adopting core aDSM package

a. Clinical and laboratory testing schedule for aDSM

b. Alert for serious adverse events to the national TB programme

Sample data collection forms for countries adopting intermediate / advanced aDSM packages

c. Treatment initiation form – aDSM

d. Treatment review form – aDSM

---

[1] Updated versions of this form may be published in future at
http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/pharmacovigilance/en/

a. Clinical and laboratory testing schedule for aDSM

to be adapted to the treatment regimen and national policy (*ref.1*)

	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
Date																									
Clinical screen																									
Visual acuity																									
Simple hearing test																									
Audiogram																									
Neuro & psychiatric investigations																									
Serum creatinine																									
ALT (SGPT)																									
AST (SGOT)																									
Bilirubin																									
Alkaline phospatase																									
gGT																									
ECG																									
Lipase																									
Amylase																									
Potassium																									
Magnesium																									
Calcium																									
Albumin																									
CBC																									
Blood glucose																									
Thyroid tests: TSH																									

1 *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (WHO/HTM/TB/2014.11). Geneva, World Health Organization, 2014.

Shade cells for the months when the test will not be done.

Notation for marking the cells: 0= screen/test not done   1=screen/test done; result pending   2=screen/test done; no SAE   3=screen/test done; SAE detected

b. Alert for serious adverse events to the TB programme

CONFIDENTIAL – To be sent even upon suspicion of a serious adverse event

| **IS THIS REPORT A NEW EVENT?** | YES ☐ NO ☐ | GIVE DATE WHEN PREVIOUS SAE FORM SENT: ☐☐ ☐☐☐ ☐☐☐☐ DD   MMM   YYYY |

1. PATIENT DETAILS

SURNAME _____ FIRST NAME _____

SEX   MALE ☐   FEMALE ☐   DATE OF BIRTH   ☐☐ ☐☐☐ ☐☐☐☐   DD   MMM   YYYY
age in yrs if DOB unknown

PREGNANCY   YES ☐   NO ☐

ID NUMBER _____ PHONE NO. _____

ADDRESS

2. SUSPECTED and CONCOMITANT MEDICINE(S)

NAME (Brand name or Generic)	Total daily dose	Date started	Date stopped	Continues
				☐
				☐
				☐
				☐
				☐

3. DETAILS OF SERIOUS ADVERSE EVENT

DATE EVENT STARTED _____ DATE EVENT STOPPED _____

DESCRIPTION OF EVENT

WHY IS THE EVENT CONSIDERED SERIOUS?

☐ Death

☐ Life-threatening event (specify: _____)

☐ Hospitalization or prolongation of hospitalization

☐ Persistent or significant disability (specify: _____)

☐ Congenital anomaly

☐ Other (specify: _____)

4. ACTION TAKEN	5. OUTCOME OF SERIOUS ADVERSE EVENT
☐ Medicine withdrawn	☐ Recovered / resolved
☐ Dose increased	☐ Recovering / resolving
☐ Dose reduced	☐ Recovered with sequelae
☐ Dose not changed	☐ Not recovered / not resolved
☐ Unknown	☐ Died
	☐ Unknown

6. REPORTER

NAME _____ POSITION _____

FACILITY/CLINIC _____

ADDRESS

_____

E-MAIL _____ PHONE NO. _____

SIGNATURE   DATE SENT:

☐☐   ☐☐☐   ☐☐☐☐
DD   MMM   YYYY

Explanatory Note

TO BE ADAPTED ACCORDING TO THE LOCAL SITUATION

- This form is intended for the Core Package of active tuberculosis drug-safety monitoring and management (aDSM). For more details please refer to other documents on aDSM. The spontaneous reporting form in use by the national pharmacovigilance authorities may be adapted to provide for the purposes of alerting the TB programme of SAEs and avoiding parallel reporting structures.
- The completed form can be sent electronically, via email or fax to <address> and the responsible authority alerted by phone.
- The report should be sent within <number> hours after it is detected, even upon suspicion of seriousness.
- The report should be sent even if not all details are available and regardless of certainty of association with any particular medicine. The essential details are the identifiers of the patient and the reporter; the name of the suspected medicine(s); and basic details on the serious adverse event.
- If the report relates to a previously notified event indicate this under section 3; if more than one serious adverse event occur in the same individual, send separate forms for each event.
- All health care professionals are encouraged to report. Patients and relatives may also report.
- Upon receipt of the information the responsible authority will review the information and contact the reporter and/or facility for more details. All information, including identity of the patient and reporter, will be handled in strict confidence. Apart from action to protect public health, anonymised statistics from these reports will be used to improve drug-safety.
- When reporting please use DD MMM YYYY format to report dates. In the DESCRIPTION OF EVENT provide a single diagnosis and include anatomical location if applicable. If diagnosis is unknown, describe clinical picture.

c. Treatment initiation form – aDSM

Interview date: dd/mmm/yyyy

PATIENT DETAILS

Patient Name: _____ Patient ID: _____

Date of birth: dd/mmm/yyyy _____ Age: _____ Sex at birth: ☐ male ☐ female

TREATMENT PROVIDER

District: _____ Health Facility & address: _____

Clinician/Team: _____ Patient File number: _____

Interview site: ☐ Health Centre ☐ Hospital Clinic ☐ Phone interview ☐ Home visit ☐ Other

MEDICAL DETAILS

Weight (kg): _____ Height (cm): _____

Indication for treatment: ☐ Pulmonary TB ☐ Extra-pulmonary TB ☐ TB site/s: _____ ☐ MDR-TB ☐ Prophylaxis

Prior exposure to anti-TB medicines: ☐ No ☐ Yes ☐ Unknown

Pregnant: ☐ Yes   Date of LMP: dd/mmm/yyyy _____ *or* estimated current gestation (weeks): _____

☐ Uncertain   If PREGNANT record patient details in PREGNANCY REGISTER for follow-up

☐ No

Breastfeeding an infant: ☐ No ☐ Yes

Injecting Drug Use Within Past Year: ☐ No ☐ Yes ☐ Unknown | Excessive alcohol use in the past year: ☐ No ☐ Yes ☐ Unknown

Tobacco use within the past year ☐ No ☐ Yes ☐ Unknown | Documented HIV infection: ☐ No ☐ Yes ☐ Unknown

CURRENT AND PAST MEDICAL CONDITIONS & EVENTS (List)	Date of onset	Date of recovery	Continues
			☐
			☐
			☐
			☐
			☐
			☐
			☐
			☐
			☐

LABORATORY & OTHER TESTS.
Include laboratory tests taken at any time during the PAST 30 DAYS

Test	Date	Result (units)	Test	Date	Result (units)
Sputum smear			ESR		
Sputum culture			Total WBC		
Drug susceptibility*			Haemoglobin		
Line probe assay			ALT (SGPT)		
Nucleic acid testing			AST (SGOT)		
Tuberculin Test			Creatinine		
HIV Antibody			Creatinine Clearance		
CD4 Count			Glucose		
Chest X Ray		Cavities (Y/N)	Thyroid function (TSH)		
Audiometry			Electrocardiogram		QTc
Visual acuity			Other		
Hepatitis markers			Other		

MEDICINES

Medicines & traditional medicines taken at any time in PAST 30 DAYS	Indication	Dosage	Frequency	Route	Start date	Stop date	Continues
							☐
							☐
							☐
							☐
							☐
							☐
							☐
							☐

* DST to the following drugs may be useful to record on this form or elsewhere in an accessible electronic medical record: isoniazid, rifampicin, kanamycin (and/or amikacin), capreomycin, ofloxacin (or ciprofloxacin), levofloxacin and moxifloxacin

All NEW anti-TB medicines prescribed at this interview	Indication	Dosage	Frequency	Route	Start date	Anticipated Stop date

All other NEW medicines prescribed at this interview	Indication	Dosage	Frequency	Route	Start date	Anticipated Stop date

Name of the Reporter: _____

Please give this form to the aDSM Focal Person

Focal Person: _____ Phone: _____

Date of next appointment: dd/mmm/yyyy _____

Instructions for the completion of the TREATMENT INITIATION FORM

A **Treatment Initiation Form** should be completed at treatment initiation, i.e. the interview at which anti-tuberculosis therapy is commenced and at which the patient is enrolled in the aDSM programme. This form represents a template and the programme may wish to adapt it according to its needs and preferences; it includes all of the essential data elements to be collected for the aDSM of TB drugs as recommended by WHO.

Patient participation

It is important that monitoring begins at the commencement of therapy. Patients may be enrolled if they are beginning treatment with the monitored medicine(s) for the first time (i.e. treatment naïve) or if their regimen is being changed. Patients who have previously been exposed to anti-TB medicines may also be included in the cohort, but monitoring should begin at the commencement of a new course of treatment.

Patients should be informed about the purpose of the monitoring programme and their agreement to participate should be sought prior to enrolment. Patients who are unwilling to participate should not be enrolled in the monitoring programme.

Patient ID
Type of identification to be selected by country.

Tick boxes (✓)
Where there are tick boxes, please answer by placing a tick ✓ in the appropriate box.

PATIENT DETAILS

Patient initials
Please use initials of given name(s) and family name.

Date of birth
If DOB is unknown, record the patient's age (or estimated age, if true age is unknown).

TREATMENT PROVIDER

Patient file number
Record the file number used to identify the patient in your clinic.

MEDICAL DETAILS

Weight & height
Record the patient's current weight and height on the date of the interview.

Pregnant
If this patient is currently pregnant, please record her details in the **Pregnancy Register** to ensure outcome of pregnancy is **followed up**.

Indication for treatment
Please indicate whether the anti-tuberculosis therapy is to be used for the treatment of pulmonary TB, extra-pulmonary TB, MDR-TB or for prophylaxis. More than one box may be ticked.

CURRENT AND PAST MEDICAL CONDITIONS & EVENTS (List)

Indicate any significant concomitant diagnoses, past medical conditions and events. Include the onset date, if known, and either record the date of recovery or, if the condition is ongoing, note that it 'continues' (Record the approximate date if the exact date is unknown).

LABORATORY & OTHER TESTS

Record the results (including *units*) of any laboratory tests taken in the PAST 30 DAYS. Commonly performed tests have been listed; other tests may be recorded in the space provided. The list of tests is indicative but may be reduced or increased depending on the regimen used and resources.

MEDICINES

Medicines & traditional medicines taken at any time in PAST 30 DAYS
Record the details of any prescription or over-the counter medicines and any traditional medicines, herbal remedies or health supplements taken at any time during the **PAST 30 DAYS**. Include the units in the '**Dosage**' column. If a medicine is given as a fixed dose combination (FDC), either as a co-formulation or in a co-blister pack, record the number of dosage forms (DF) given.

All new medicines prescribed at this interview
Please record the details of all medicines prescribed at this interview, for TB or non-TB in the separate tables.

d. Treatment review form – aDSM

Interview date: dd/mmm/yyyy

PATIENT DETAILS

Patient Name: _____ Patient ID: _____

Date of birth: dd/mmm/yyyy _____ Age: _____ Sex at birth: ☐ male ☐ female

TREATMENT PROVIDER

District: _____ Health Facility & address: _____

Clinician/Team: _____ Patient File number: _____

Interview site: ☐ Health Centre ☐ Hospital Clinic ☐ Phone interview ☐ Home visit ☐ Other

MEDICAL DETAILS

Weight (kg): _____ Height (cm): _____

Indication for treatment: ☐ Pulmonary TB ☐ Extra-pulmonary TB ☐ TB site/s:_____ ☐ MDR-TB ☐ Prophylaxis

Prior exposure to anti-TB medicines: ☐ No ☐ Yes ☐ Unknown

Pregnant: ☐ Yes　　Date of LMP: dd/mmm/yyyy _____ *or* estimated current gestation (weeks): _____

　　　　☐ Uncertain　If PREGNANT record patient details in PREGNANCY REGISTER for follow-up

　　　　☐ No

Breastfeeding an infant: ☐ No ☐ Yes

Events	AE MedDRA / WHO-ARTcode*	Record all NEW EVENTS or CHANGES in pre-existing conditions since last interview					
		Date onset	Date resolved	Outcome**	Severity†	Seriousness‡	Rechallenge§

* to be completed by PV centre after data collection (see also Instructions for completion)

OUTCOME**		MAXIMAL SEVERITY†		SERIOUSNESS‡		RECHALLENGE§	
R1	Recovered/ resolved	1	Mild	N	Not serious	1	No rechallenge
R2	Recovering/resolving	2	Moderate	H	Hospitalization (caused or prolonged)	2	Recurrence of event
S	Recovered with sequelae	3	Severe	P	Permanent disability	3	No recurrence
N	Not recovered/not resolved			C	Congenital abnormality	4	Result unknown
D	Died			L	Life threatening		
U	Unknown			D	Death		

Scale used for grading of severity of AEs:

☐ Clinician's judgement ☐ CTCAE grading system ☐ DAIDS AE Grading Table ☐ Other (specify): _____

LABORATORY & OTHER TESTS

Test	Date	Result (units)	Test	Date	Result (units)
HIV Antibody			ALT (SGPT)		
CD4 Count			AST (SGOT)		
ESR			Lactic acid		
Total WBC			Lipase		
Haemoglobin			Chest X-Ray		Cavities (Y/N)
Creatinine			ECG		QTc
Creatinine Clearance			Audiometry		
Glucose			Visual acuity		
Hepatitis markers			Other		
TSH			Other		

MEDICINES

Anti-TB medicines taken since last interview	Dosage	Frequency	Route	Start date	Stop date	Continues	Reason(s) for stopping #	Action**
						☐		
						☐		
						☐		
						☐		
						☐		
						☐		

Other medicines & traditional medicines taken since last interview	Dosage	Frequency	Route	Start date	Stop date	Continues	Reason(s) for stopping #	Action**
						☐		
						☐		
						☐		
						☐		
						☐		
						☐		
						☐		

All NEW medicines (anti-TB & other) prescribed at this interview	Dosage	Frequency	Route	Start date	Expected stop date	Indication

REASON FOR STOPPING#

1   Adverse event
2   Poor adherence
3   Course completed or cured*
4   Planned interruption
5   Planned medication change
6   No longer needed
7   Treatment failure*
8   Pregnancy
9   Drug out of stock
10 Cost
11 Patient decision
12 Died*
13 Lost to follow-up*
14 Other (please specify)

Outcome* (to be completed at the end of current treatment episode)

☐ Cured	☐ Completed	☐ Treatment failed	☐ Died	☐ Loss to follow up	☐ Not evaluated

If the end of the treatment episode, treatment outcome date: dd/mmm/yyyy

*   as per Definitions and reporting framework for tuberculosis – 2013 revision (WHO/HTM/TB/2013.2). Geneva, World Health Organization; 2013.

    Available from: www.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf

Name of the Reporter: _____

Please give this form to the aDSM Focal Person

Focal Person: _____   Phone: _____

Date of next appointment: dd/mmm/yyyy _____

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Instructions for the completion of the TREATMENT REVIEW FORM

A **Treatment Review Form** should be completed each time the patient is interviewed following commencement of treatment with the monitored medicine(s). This form represents a template and the programme may wish to adapt it according to its needs and preferences; it includes all of the essential data elements to be collected for the aDSM as recommended by WHO.

Patient ID

Type of unique patient identification to be selected by country.

Tick boxes (✓)

Where there are tick boxes, please answer by placing a tick ✓ in the appropriate box.

PATIENT DETAILS

Patient initials

Please use initials of given name(s) and family name.

Date of birth

If DOB is unknown, record the patient's age (or estimated age, if true age is unknown).

TREATMENT PROVIDER

Patient file number

Record the file number used to identify the patient in your clinic.

MEDICAL DETAILS

Weight & height

Record the patient's current weight and height on the date of follow-up visit. Height should be recorded for children at treatment review, but is unnecessary for adults.

Indication for treatment

Please indicate whether the anti-tuberculosis therapy is to be used for the treatment of pulmonary TB, extra-pulmonary TB, MDR-TB or for prophylaxis. More than one box may be ticked.

Pregnant

Please indicate whether the patient is pregnant, uncertain or not pregnant. Women who are pregnant should be entered into a pregnancy register to ensure that the outcome of the pregnancy is followed-up.

EVENTS

Please record:
- All **new health events** that have occurred since the patient started the monitored medicine
- This includes any **deterioration or improvement in pre-existing conditions** (or previously recorded events)

For each event, select the appropriate code for **Outcome**, **Severity**, **Seriousness** and **Rechallenge** from the shaded panel**.** If the severity coding used is not "Mild", "Moderate" or "Severe" please adjust accordingly. Indicate the "Scale used for grading of severity of AEs". Choose **Clinician's judgement** if no scale is used to classify the severity of the event other than the health professional's opinion. **Coding of the events (using AE MedDRA or WHO-ART code) is done by the expert in drug-safety monitoring in consultation with the clinician in charge of the patient; it is not necessarily performed by the person completing the questionnaire. A record on the attribution of an event to one or more medications will be made in the database but is not included in the forms.**

LABORATORY & OTHER TESTS

Record the results (including *units*) of any laboratory tests taken since the patient was last interviewed. Commonly performed tests have been listed; other tests may be recorded in the space provided. The list of tests is indicative but may be reduced or increased depending on the regimen used and resources.

MEDICINES

Anti-tuberculosis medicines or regimen taken since last interview
Anti-tuberculosis medicines may be recorded either as individual medicines or as fixed dose combinations (FDC). Include start and stop dates for medicines that were started or stopped during the interval since the patient was last interviewed and indicate which medicines continue to be taken (continues ✔). For medicines that have been stopped, please select the **reason(s) for stopping** from the list of codes provided (more than one code may be used). For Anti-tuberculosis medicines, please also select the appropriate **adherence code**. Note: If a medicine was stopped and later restarted, include separate entries for each course. If the dose was changed, record the medicine again on a new line with the new dose and dates.

Other medicines & traditional medicines taken since last interview
Record the details of other medicines, including over-the-counter medicines and any traditional medicines, herbal remedies or health supplements taken since the last interview.

All new medicines (Anti-tuberculosis & other) prescribed at this interview
Record the details of all new medicines (Anti-tuberculosis and other medicines) prescribed at this interview.

Annex 12. Guidance for public–private mix consideration for the introduction of bedaquiline

Public–private mix encompasses diverse collaborative strategies, such as public–private (between NTP and the private sector), public–public (between NTP and other public sector care providers, such as general hospitals, prisons or military health services, social security organizations), and private–private (between an NGO or a private hospital and the neighbourhood private providers) collaboration. Public–private mix also implies engaging relevant care providers in prevention and management of MDR-TB and in the implementation of TB/HIV collaborative activities.

Scaling up public–private mix initiatives and introduction of bedaquiline in the private sector will require identifying, approving and further supporting private individuals and institutional providers that have the capacity and willingness to manage TB and drug-resistant TB according to recommended guidelines. A range of mechanisms may be used for a formal recognition of participating providers. Most of this work will be led by the health ministry with input from the NTP.

Three processes of assessment *(21)*

i. **Licensure:** is a mandatory process, usually issued by the government authority, setting the minimum standards to ensure an environment with minimum risk to health and safety.

ii. **Accreditation:** is a voluntary process, usually issued by a recognized organization (often NGOs) aimed to verify compliance with published standards (set at a maximum achievable level to stimulate improvement over time)

iii. **Certification:** is a voluntary process generally issued by an authorized body (government or NGO), to demonstrate that the organization has additional services, technology or capacity

The three processes of assessment described above can be used to engage with the private sector depending on the context in the country and the type of new drug/regimen being introduced *(21)*. Once providers have been appropriately accredited, enforcing these standards is crucial.

Other important steps to engage a public–private collaboration supporting bedaquiline include:

1. Supportive dialogue with private providers, leadership of key private hospitals and/or NGOs running health services and industry/product sponsors to discuss introduction strategy in the private sector.

2. Development of a joint strategy for the introduction of bedaquiline through the following activities:

   – Assess the performance of ongoing public–private mix initiatives (close link between procurement and supply systems).
   – Define goals for the introduction (e.g. maximize access or maximize safety or carry out limited use to build evidence).
   – Accept the working model or design a new model of public–private mix engagement with appropriate policy framework and guidance.
   – Define roles to get buy-in of key stakeholders described in the initial dialogue.

3. Development of a plan for implementation in the private sector.

   – Determine a reasonable timeline of activities that take into account required modifications to the current paradigm (particularly in case of assessment or accreditation of providers).
   – Consider procurement implications of the proposed working model and necessary training.
   – Ensure appropriate training is provided, particularly through external assessment of providers.

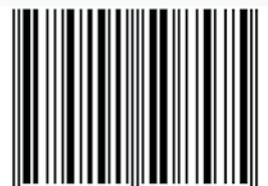| IMPLICATIONS FOR:		DRUG FOR MULTIDRUG-RESISTANCE ADDED TO EXISTING REGIMEN
Private sector provision	Limited private sector	Consider use only in public sector under these circumstances.
	Extensive private sector	Consider first involving providers already collaborating as part of public–private mix initiatives.
		Use a form of external assessment to ensure appropriate use; licensure may be best in this circumstance; close monitoring and addressing any challenges is required to modify guidance and use.
Public sector provision		Closely monitored use and reporting, particularly for drug-safety monitoring likely only at specific centres; clear guidance for usage issues.
Regulatory environment (NRA)		Restricted availability of the drug to the public sector and collaborating private sector providers to ensure appropriate use.
Industry engagement		Early discussions and willingness to distribute through officially sanctioned and restricted channels.
Government/NTP		Engage early with a range of providers and establish clear guidance for private and public sector use.

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