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

Implementation plan

World Health Organization
APRIL 2015
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<tbody>
<tr>
<td>CD4 cell</td>
<td>T-helper cells</td>
</tr>
<tr>
<td>CEM</td>
<td>cohort event monitoring</td>
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<td>DOTS</td>
<td>directly observed treatment, short-course</td>
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<td>DRS</td>
<td>Drug Resistance Survey</td>
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<tr>
<td>DST</td>
<td>drug susceptibility testing</td>
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<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>EMA</td>
<td>European Medicine Agency</td>
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<tr>
<td>EQA</td>
<td>external quality assurance</td>
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<td>FM</td>
<td>fluorescent microscopy</td>
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<td>GDF</td>
<td>Global Drug Facility</td>
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<tr>
<td>Global Fund</td>
<td>Global Fund to fight AIDS, Tuberculosis and Malaria</td>
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<tr>
<td>Hgb</td>
<td>haemoglobin</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>IDA</td>
<td>International Dispensary Association</td>
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<td>ISTC</td>
<td>International Standards for Tuberculosis Care</td>
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<tr>
<td>LPA</td>
<td>line-probe assays</td>
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<tr>
<td>MDR-TB</td>
<td>multidrug-resistant TB</td>
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<tr>
<td>ms</td>
<td>milliseconds</td>
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<tr>
<td>NGO</td>
<td>nongovernmental organization</td>
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<td>NPVC</td>
<td>national pharmacovigilance centre</td>
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<tr>
<td>NRA</td>
<td>National Regulatory Authority</td>
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<tr>
<td>NTP</td>
<td>national TB programme</td>
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<tr>
<td>PAS</td>
<td>para-aminosalicylic acid</td>
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<tr>
<td>PCSM</td>
<td>procurement and supply chain management</td>
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<tr>
<td>PMDT</td>
<td>programmatic management of drug-resistant TB</td>
</tr>
<tr>
<td>QT interval</td>
<td>start of Q wave to the end of the T wave</td>
</tr>
<tr>
<td>QTc</td>
<td>QT-corrected</td>
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<tr>
<td>QtcF</td>
<td>Fredericia correction method</td>
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<tr>
<td>RR-TB</td>
<td>rifampicin-resistant TB</td>
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<tr>
<td>SGOT</td>
<td>serum glutamic oxaloacetic transaminase</td>
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<tr>
<td>SGPT</td>
<td>serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SNRL</td>
<td>Supra-National Reference Laboratory</td>
</tr>
<tr>
<td>STROBE</td>
<td>Strengthening the Reporting of Observational Studies in Epidemiology</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
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<tr>
<td>USFDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>WBC</td>
<td>white blood cell</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>XDR-TB</td>
<td>extensively drug-resistant TB</td>
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<tr>
<td>Xpert®</td>
<td>assay for <em>M. tuberculosis</em></td>
</tr>
<tr>
<td>MTB/RIF</td>
<td>and rifampicin resistance mutations</td>
</tr>
<tr>
<td>ZN</td>
<td>Ziehl–Neelsen</td>
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**WHO**

**FINAL PRE-FORMATTED VERSION APRIL, 2015**
Definitions

**Adverse drug reaction**: response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans.

**Adverse events**: any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.

**Event**: any new clinical experience that occurs after commencing treatment with a medicine regardless of its severity or seriousness and without judgement on its causality. Events include pregnancy, lactation exposure, etc. Favourable events may be recorded as an indication of an unexpected therapeutic effect.

**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.

**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, the two most important first-line drugs to treat drug-susceptible TB.

**New drug**: novel drug for TB and/or drug-resistant TB that is being evaluated in Phase II and/or III trials.

**New regimen**: novel drug combination for treatment of drug-susceptible or drug-resistant TB, including new or repurposed drugs.

**Pharmacovigilance**: the science and activities relating to the detection, assessment, understanding and prevention of adverse drug reactions or any other drug-related problem.

**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 detected using phenotypic or genotypic methods, 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.

**Serious adverse event**: any event occurring during treatment that leads to hospitalization or prolongation of hospitalization, a persistent significant disability, a congenital anomaly, a life-threatening condition, or death.

**Signal**: reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously.
**Note**: 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.
1. Why an implementation plan?

Introduction

The emergence of drug-resistant tuberculosis (TB) is a major threat to global TB care and control. In 2013, the World Health Organization (WHO) estimated that 480,000 people developed multidrug-resistant TB (MDR-TB), of which 210,000 died. 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. In the 2010 cohort of detected cases, only 48% were successfully treated, as a result of high frequency of death (15%) and loss to follow-up (28%), commonly associated with adverse drug reactions, among other factors. Ninety-two 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 9.6% of MDR-TB cases have XDR-TB. Treatment options for XDR-TB patients are even more limited and 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.

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 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 pharmacovigilance and conduct more complex necessary 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 to: (i) develop ad hoc policy recommendations for TB treatment with new drugs; and (ii) 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 has been 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.

The present implementation plan is directed at: (i) assisting countries in establishing proper infrastructure, and (ii) carrying out adequate activities to ensure that patients and communities in need get access to bedaquiline and are treated in a way that maximizes the benefits for patients and the programme.

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* (7). The drug is given daily for two weeks and then thrice weekly for a total of six months (8). 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 standard therapy for MDR-TB using a surrogate marker of treatment efficacy (9). Primary adverse events 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 (10). The drug was approved under an accelerated procedure by the USFDA in December 2012 (11) and conditionally approved by the EMA in February 2014 (12).

In June 2013, the WHO issued interim policy guidance on the use of bedaquiline in the treatment of MDR-TB (13). 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 Phase III trial, become available. The WHO document specifies the essential conditions for the use of bedaquiline and is targeted at national TB programmes (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 (13).
Further to this guidance, an instructional document on ‘How-to use bedaquiline?’ has been developed, that is available 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) (14).

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. 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).

2. 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).

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

4. Adherence to principles of designing a WHO-recommended MDR-TB regimen typically composed of at least pyrazinamide and four second-line drugs 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 a fluoroquinolone and/or the 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).

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

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 the Expanded Access Programme in South Africa showed 83% treatment success rate 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).
Objective of the implementation plan

The aim of the 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. It provides a logical and comprehensive framework, adaptable to a large diversity of country and programme settings.

Target audience for the implementation plan

The implementation plan is targeted at 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 WHO Companion handbook for PMDT (14).
2. Establishing the implementation plan

The implementation plan includes a 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.

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.

<table>
<thead>
<tr>
<th>STEP 1.</th>
<th>Recommended activities to establish the framework for the introduction of bedaquiline at country level</th>
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<tbody>
<tr>
<td>a.</td>
<td>Assess the national context</td>
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<tr>
<td>b.</td>
<td>Contact relevant units/departments at the health ministry</td>
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<tr>
<td>c.</td>
<td>Identify implementing partners</td>
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<td>d.</td>
<td>Create a national implementation Task Force</td>
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<td>e.</td>
<td>Coordinate with the National Regulatory Authority</td>
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<td>f.</td>
<td>Establish a dialogue with pharmaceutical companies</td>
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<td>g.</td>
<td>Ensure appropriate procurement system for bedaquiline</td>
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<td>h.</td>
<td>Organize sensitization workshops</td>
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a. 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. 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, 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).
• 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) (17)
• Results from a recent TB prevalence survey at national or subnational level (if available) and related programme implications.
• TB/HIV co-infection 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).

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*); case holding strategy (such as enablers, psychosocial support, adherence measurement), including retrieval of patients lost to follow-up.

Pharmacovigilance (existing pharmacovigilance system in place).

* 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 cases, a radiologist, a microbiologist, specialist from drug management, monitoring and evaluation, and surgeons.
b. **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 “experimental” or “too costly”. Smooth introduction of the drug would require contact with relevant units/departments at health ministry level, such as planning, finance, hospital and pharmaceutical 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 the introduction of bedaquiline and the steps necessary to start using the drug in the country.

c. **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.

d. **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 the implementer 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.

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**BOX 2. What NTP/countries should know BEFORE introduction of bedaquiline**

**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 DRS (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, enrolment on cotrimoxazole preventive therapy and antiretroviral treatment of coinfected patients.

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

**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.*
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 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:

- benefits, risks and costs of the drug;
- health system’s capacity to finance, manage and appropriately use bedaquiline;
- drug management system’s capacity to ensure timely procurement, quality assurance, inventory control and sustainable access to bedaquiline; and
- 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 organizations, ethical committees, technical partners, major private sector healthcare provider groups)
- donors
- civil society (such as patient support groups, NGOs)
- international stakeholders/technical partners.

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 (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.

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 guidance on new drug/regimen, 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, development of a national pharmacovigilance implementation plan, 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 the supportive 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.

e. **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 drug(s). 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 pharmacovigilance as needed.

Registration, inclusion in the Essential Medicines List, regular procurement and distribution, prevention of inappropriate marketing, responsible prescription as well as pharmacovigilance must apply **not only to bedaquiline but also to all the accompanying drugs included in the drug-resistant TB regimen**. While the initial application for adding bedaquiline to the Essential Medicines List was denied, the WHO has resubmitted it for approval and expects a positive response.

f. **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 pharmacovigilance; and
- ensure assessment of resistance to the new drug(s).

g. **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 (PCSM) 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, quarantine storage, etc.)
- Distribution to selected centres
- Buffer level (stock pile).
It is advisable to enter into a dialogue with the Global Drug Facility (GDF)* 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 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.

<table>
<thead>
<tr>
<th>Standard procurement process through the GDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Complete drug requirements are calculated using GDF-approved tools.</td>
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<tr>
<td>2. The calculations and the signed Technical Agreement are sent to the GDF.</td>
</tr>
<tr>
<td>3. GDF generates an order in the GDF Order Management System.</td>
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<tr>
<td>4. GDF requests its procurement agent (the IDA) to provide a price quote.</td>
</tr>
<tr>
<td>5. GDF shares the price quote with the country.</td>
</tr>
<tr>
<td>6. The country approves the price quote and transfers funds to IDA.</td>
</tr>
<tr>
<td>7. Upon receipt of funds by the IDA, the order is placed with the suppliers.</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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.

**h. 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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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.*

This second step describes 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 assess where improvements may be needed for bedaquiline introduction and scale-up.

**STEP 2.**
**Recommended activities for meeting the minimal requirements for introduction of bedaquiline**

a. Laboratory capacity  
b. Drug resistance surveillance  
c. Clinical Review Committee  
d. Case management  
e. Recording and reporting system  
f. Monitoring and evaluation  
g. Pharmacovigilance  
h. Budget  
i. Technical assistance  
j. Drug supply system  
k. Checklist for country preparedness and planning

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

**a. 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 appropriate, specific actions may be needed to upgrade the laboratory capacity with reference to available models.* This would need to be appropriately resourced 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 smear 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 laboratory.

- **General laboratory:** availability of the following tests through 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 (T-helper cell) count, HIV viral load).

**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 Supra-National Reference Laboratory (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 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 in different scenarios of new drug/regimen introduction are detailed in Annex 2.**

**b. Drug resistance survey**

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, DRS 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 be 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.

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.

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Country level/programme approach: population-representative drug resistance survey. 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.

c. Clinical Review Committee

At country level, the implementation of bedaquiline requires strict monitoring and supervision and 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, M/XDR-TB, and other personnel with relevant experience (i.e. pharmacists, nurses, social workers). The Committee should have in place a chairperson and secretary and 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 bedaquiline and the suggested treatment regimen composition (Annex 11). All evaluated cases should be recorded in a dedicated register according to standard operating procedures of the Clinical Review Committee.

Treating physicians are requested to update the Committee regularly about the treatment response and/or adverse effects experienced by the patients, and consult the Committee for any decision on treatment change or interruption, as well as on treatment completion.

d. 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 Annex 4 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 side-effects 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.

e. 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 definition 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).

f. 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. It may therefore 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 when evaluating the use of bedaquiline at the national level.

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.

g. Pharmacovigilance

The occurrence of adverse events during anti-TB treatment can contribute to additional morbidity, treatment interruption before completion, treatment failure, emergence of drug-resistance, reduced quality of life, or death. 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 safety monitoring even stronger. Furthermore, the complete safety profile of bedaquiline has not yet been developed. Thus active pharmacovigilance is needed to help identify any rare adverse drug reactions that may be associated with the use of bedaquiline.

Pharmacovigilance (PV) is defined as the “science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem” (24). It is a fundamental activity to inform the management of patient safety measures in health care. PV is a public health surveillance activity. In essence, pharmacovigilance means keeping track of any problems that may occur in patients receiving a new drug. The aims of pharmacovigilance are 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.

Three methods of pharmacovigilance are classically described (24):

i. **Spontaneous reporting** is the most common form of PV is spontaneous (also called voluntary) which involves a health-care worker - or even the patient - reporting a drug-related reaction. The effectiveness of such systems very much depends on the patient volunteering this information (people have different thresholds when they decide to approach formal careers for reporting), on health-care workers’ competence to recognise an event, and their motivation to report it. Episodes of suspected adverse drug reactions linked to the use of drugs are reported voluntarily by health care workers or patients to the designated body responsible for pharmacovigilance within the country (i.e. the national pharmacovigilance centre (NPVC)).

ii. **Targeted spontaneous reporting** uses a methodology that monitors and records all or a specific set of safety concerns in a defined population of treated patients, e.g. drug-resistant TB patients on treatment.

iii. **Active PV** is a more systematic and proactive form of safety surveillance. In active PV, events are elicited as part of patient monitoring using a set of questions and an array of laboratory/clinical tests at defined periods of time, before, during and after treatment. The records from active PV make it possible to determine the exact number of patients monitored and exposures to a drug; they also enumerate the events related to an exposure, in a similar way to what one would do in a longitudinal epidemiological study. **Cohort event monitoring** (CEM) is one of the standard methods of active PV which is used to monitor adverse events in patients who receive a particular medication or treatment regimen. Patients are followed up prospectively in groups and all adverse events are registered during treatment and usually for a given time after its end. The CEM method is the form of active PV which has been best defined and used in different settings, both well resourced and low income. Beyond its role as part of a risk management plan, CEM can provide useful insights into the patterns of utilization and the adoption of a new drug in clinical practice (e.g. acceptability by clinicians and patients).

When introducing bedaquiline, a plan for implementing active pharmacovigilance is essential to record in a reliable way the evidence of adverse drug reactions or drug–drug interactions and use this information to inform policy decisions, clinical guidelines and treatment recommendations. Because it provides the most complete and comprehensive data of the three methods listed above, and in accordance with WHO interim guidance recommendation, CEM is the recommended approach to active pharmacovigilance for introduction of bedaquiline (14, 25). This recommendation was supported by the independent experts who reviewed the information.
available on safety of bedaquiline in the Guideline Development Group meeting held in 2013. Bedaquiline is still relatively new and only a limited number of patients have been treated with the drug. Its conditional marketing approval by stringent drug regulatory authorities ahead of the completion of Phase 3 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. All reasonable measures are thus needed to ensure that patient safety is monitored alongside the effectiveness of the treatment. In this situation, spontaneous reporting is not expected to represent an appropriate level of care and active PV techniques, such as CEM, was considered necessary to improve the early and systematic detection of harms. Conversely, it is also important to collect safety data accurately in order to ensure that any adverse event is properly investigated and no hasty conclusions 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.

CEM remains an observational type of study of a cohort (group) of patients who are taking a particular medication or regimen. It is intended to be done under programmatic conditions, without any randomization of study subjects to intervention and to control/comparison arms. Operational research on other aspects of care can be built alongside CEM, such as a comparator cohort of patients receiving standard care to be monitored concurrently. The Phase 3 trials for bedaquiline, which will randomize patients to control and intervention arms, will still be needed to look closer at the efficacy and safety of this drug.

The CEM design requires recording ALL clinical events – not just suspected or known adverse drug reactions. It involves active and systematic requests for reports of any event occurring while drugs are being prescribed and provides a method that facilitates reporting. The detection and reporting of serious adverse events is a priority and a necessity for monitoring. All deaths are to be reported. All efforts should be made to ascertain the immediate and contributing causes of death and determine if death could be linked to TB or TB treatment. This may require recovering information from vital registration coding. Reporting of other adverse events 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. For CEM, a non-severe event may be the early manifestation of a more consequential process (eg a dose-dependent effect). Such events should be captured on the data collection forms. To reduce on workload it is usually left optional to the projects to enter this information on the CEM database.

CEM is important when patients are treated with a medicine for which the drug safety profile is as yet incomplete. 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 individual patient. A national programme also should strive to capture data in the private sector and public-private partnerships.

Many countries implementing PMDT have a form of spontaneous (or passive) reporting of suspected adverse drug reactions already in place. Here clinicians already assess patients clinically for adverse drug reactions on a regular basis, both at initiation and during follow-up visits. They do not, however, report them on a national level and in a standardized way. The presence or absence of these clinical findings is often recorded in medical records, and this aspect of pharmacovigilance is part of routine clinical care in most settings. At the present stage, using bedaquiline will require monitoring for possible adverse drug reactions in a more standardized and systematic fashion. The
change in establishing and using an active PV system is that it requires an *active search of adverse events* through regular queries to patients and formal *recording* of these events on standard forms and *reporting* of these events to a central PV focal point.

As part of readiness planning for bedaquiline introduction, it is necessary to **assess what pharmacovigilance experience exists in the country** (14, 24, 25). While most countries may not have existing programmes specifically for pharmacovigilance in TB, they may have a pharmacovigilance centre in place or pharmacovigilance for other diseases (i.e. malaria, HIV) possibly via programmes at universities or pharmacy schools. The assessment of the existing pharmacovigilance at country level should include the following questions:

- Is a functional spontaneous pharmacovigilance system present at country level to report adverse drug reactions? If yes, what are its functions, roles and responsibilities? Is it restricted to specific drugs?
- How is pharmacovigilance organized (from periphery to central level)?
- Which system exists for adverse drug reactions or adverse events reporting? Do TB treatment centres already have experience in collecting data on drug safety (e.g. participated in clinical trials for TB or other conditions)?
- What is the pharmacovigilance data collection system (recording/reporting form and/or electronic database)?
- Is there a centralized collection of adverse drug reactions data with flow of data from periphery to central level? Is there a clear responsibility for the analysis of these data at the national pharmacovigilance centre?
- Are there linkages between the NTP and the national pharmacovigilance centre?
- Is the national pharmacovigilance centre collaborating with, or a member of, the WHO Programme for International Drug Monitoring?

It is important that measures are taken to ensure that essential CEM elements are in place in order that the key safety data are collected for all patients started on regimens containing a new drug such as bedaquiline, namely a broad agreement between the national TB programme and the national PV centre on the process to implement the CEM project for TB drugs; preparation for the collection of data (e.g. forms); and staff properly trained to collect the data. Capacity for CEM could be built over the following months.

### h. Budget

Adequate financial resources should be allocated to ensure successful and sustainable implementation of bedaquiline introduction 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 (new drug, 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, 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, pharmacovigilance, etc.).
• Costs of implementation (e.g. human resources, technical and management assistance, training, laboratory reagents and consumables costs, pharmacovigilance, 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 (26).

i. Technical assistance

The introduction process requires a multidisciplinary approach and 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 competencies and resources available. Issues such as laboratory or health system strengthening, staff training, pharmacovigilance, drug resistance survey at country level and others 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.

j. 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 PSCM 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 to guarantee regular drug supply and distribution.
• Absence of stockout for one year (= 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 and what steps were taken to solve stockout 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.

k. 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. Pharmacovigilance
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.

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

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.
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<tr>
<th>Domain</th>
<th>Minimal requirements for country implementation of bedaquiline</th>
<th>In place/available</th>
<th>To be strengthened</th>
<th>To be set-up/established</th>
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<tbody>
<tr>
<td><strong>Health and regulatory environment</strong></td>
<td>Background information on health system infrastructure</td>
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<td>Background information on NTP infrastructure</td>
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<td>Background information on PMDT in the country</td>
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<td>TB burden indicators</td>
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<td></td>
<td>NTP performance indicators</td>
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<td></td>
<td>Background information on TB case management at country level</td>
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<td></td>
<td>Background information on national drug regulatory process</td>
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<tr>
<td><strong>Laboratory capacity</strong></td>
<td><strong>At country level</strong></td>
<td>Background information on general laboratory infrastructure</td>
<td></td>
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<td></td>
<td>Background information on TB laboratory infrastructure</td>
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<td></td>
<td>WHO/ISTC standards for TB diagnosis</td>
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<td></td>
<td>Decentralized access to rapid molecular tests</td>
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<td></td>
<td>Reference laboratory with sufficient capacity for culture</td>
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<td></td>
<td>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)</td>
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<td></td>
<td>Quality assurance system through an established link with a SNRL</td>
<td></td>
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<tr>
<td></td>
<td><strong>At implementing site level</strong></td>
<td>Sputum smear microscopy or other WHO-accepted initial diagnostic test</td>
<td></td>
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<tr>
<td></td>
<td>Rapid molecular tests: Xpert(^®) MTB/RIF and/or LPA technology</td>
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<td></td>
<td>Culture (solid and/or liquid)</td>
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<tr>
<td></td>
<td>Access to DST to first- and second-line drugs (as per national treatment protocol)(^a)</td>
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<tr>
<td></td>
<td>Haematology (white blood count, haemoglobin, platelet count)</td>
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<td></td>
<td>Biochemistry (kidney function tests, liver functions tests, pancreatic function tests, electrolytes)</td>
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<td></td>
<td>HIV test, CD4 cells count, HIV viral load</td>
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<td></td>
<td>Pregnancy test</td>
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<td></td>
<td>Other tests as per treatment protocol (e.g. thyroid stimulating hormone (TSH), lactic acid, serum glucose)</td>
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<tr>
<td><strong>Drug procurement and supply chain management</strong></td>
<td>Adequate PSCM system in place to guarantee regular drug supply and distribution</td>
<td></td>
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<tr>
<td></td>
<td>Absence of stockouts for one year</td>
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<tr>
<td><strong>Case management</strong></td>
<td><strong>At country level</strong></td>
<td>WHO/ISTC standards for treatment</td>
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<td></td>
<td>Clinical Review Committee (e.g. MDR-TB Consilium)</td>
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<td></td>
<td>Appropriate case holding strategy</td>
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<td></td>
<td><strong>At implementing site level</strong></td>
<td>Chest radiographs</td>
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<td></td>
<td>ECG and access to continuous ECG monitoring</td>
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<tr>
<td></td>
<td>Audiology(^a)</td>
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<td></td>
<td>Visual acuity tests(^a)</td>
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<td></td>
<td>Psychosocial evaluation</td>
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<td>Ancillary drugs</td>
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<td></td>
<td>Measures to maximize treatment adherence and adequate patient support systems in place</td>
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<td></td>
<td>Access to psychiatric evaluation if needed(^a)</td>
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<tr>
<td>Monitoring and evaluation</td>
<td>Access to neurologic evaluation if needed&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>Access to bronchoscopy if needed&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>Access to surgery and histopathology if needed&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>Access to ultrasound if needed&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>Recording and reporting in line with revised WHO recommendations (27,28)</td>
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<td></td>
<td>Electronic recording and reporting system</td>
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<td></td>
<td>Minimum indicators routinely generated</td>
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<td></td>
<td>Regular supervision plan (minimum 2 rounds/year) to each implementing site</td>
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<td></td>
<td>Regular cohort data analysis</td>
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<tr>
<td></td>
<td>Drug resistance survey in the past 2–3 years</td>
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<tr>
<td></td>
<td>Plan to repeat drug resistance survey 3–5 years after new drug/regimen introduction</td>
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<tr>
<td><strong>Pharmacovigilance</strong></td>
<td>Background information on pharmacovigilance system at country level</td>
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<tr>
<td></td>
<td>Minimal requirements in place (14, 25)</td>
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<td>Availability of a system for active pharmacovigilance, e.g. cohort event monitoring</td>
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<tr>
<td><strong>Financial resources and country support</strong></td>
<td>Background information on NTP budget</td>
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<tr>
<td></td>
<td>Budget for introduction of new drug/regimen developed</td>
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<tr>
<td></td>
<td>Funds for new drug/regimen introduction secured</td>
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<td></td>
<td>Technical assistance partners identified</td>
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<td></td>
<td>Plan for technical assistance developed</td>
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</table>

<sup>a</sup> 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 of 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 set eligibility criteria.
- A lack of staff experience in handling bedaquiline and managing side-effects 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 on 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 (i.e. TB dedicated ward, ambulatory, laboratory, staff).
- WHO recommended revised recording and reporting system (27).
- Access to quality assured TB drugs through an efficient procurement system in place.
- Active pharmacovigilance 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 (i.e. urban vs rural, HIV-infected) can take place.

The modality of treatment administration (hospital- or outpatient-based) should be also considered, based on 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 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 side-effects and drug–drug interactions. If, per country policy, bedaquiline has to be administered in hospital, appropriate infrastructure (TB ward bed capacity, isolation rooms, infection control measures, etc.) needs to be assessed prior to selecting the specific implementing sites.

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.

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 to a larger scale (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.

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 TB programme 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.

At initial stage, and depending on the type of drug/regimen, it is recommended to introduce the new drug/regimen in centres accredited by government authorities only, as misuse or occurrence of adverse events 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 be planned in the second phase, after initial introduction of the new drug/regimen in government facilities and the preliminary monitoring of implementation.
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 in the box below.

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

- a. Rationale for the introduction of bedaquiline at country level
- b. Development or update of national clinical guidelines
- c. Development of plans for laboratory needs
- d. Recording and reporting
- e. Monitoring and evaluation
- f. Pharmacovigilance
- g. Ethical aspects
- h. Calculation of drug needs
- i. Training of managers and staff
- j. Human resources development plan
- k. Timeline development
- l. Budget development
- m. Obtaining consensus from donor agencies

#### a. 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.

#### b. 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 not be treated with the drug, following interim guidance issued by the WHO.
- Optimal use of bedaquiline should describe preferred methods for bedaquiline administration, the type of companion drugs, 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 give guidance on patient management. These strategies should follow WHO recommendations as detailed in the *WHO Companion handbook for PMDT* (14).
- 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 strategy for enhancing and monitoring adherence to treatment, including patient psychosocial/economic support, and other aspects of patient-centred care should be in place.

Guidance for the clinical use of bedaquiline can be found in the WHO Companion handbook for PMDT (14) – Chapter 11.

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). This should also include the development of practical clinical tools (such as flipcharts, leaflets, hand book) with bedaquiline indications and contraindications, companion drugs to be chosen in different scenarios and their dosage, patient monitoring information, side-effects and their management.

c. 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.

d. Recording and reporting

All patients receiving bedaquiline should be assembled in a cohort with specific collection of data. Recording the outcome of treatment for the cohort should follow the routine recording and reporting system used at country level, according to WHO recommended MDR-TB treatment cards and registers (see WHO documents: Revised TB recording and reporting forms and registers – version 2006 (27) 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 (28).

e. 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>
<thead>
<tr>
<th>Table 2. Suggested indicators for monitoring and evaluation</th>
<th>Suggested frequency of</th>
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<tbody>
<tr>
<td>Indicator</td>
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### Monitoring

<table>
<thead>
<tr>
<th>Metric</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Number of national implementation Task Force meetings</td>
<td>Annually</td>
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<tr>
<td>Number of Technical Working Group meetings</td>
<td>Twice a year</td>
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<tr>
<td>Number of sites with patients receiving bedaquiline</td>
<td>Yearly</td>
</tr>
<tr>
<td>Number of providers trained on bedaquiline</td>
<td>Quarterly</td>
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<tr>
<td>Number of patients screened for bedaquiline</td>
<td>Quarterly</td>
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<tr>
<td>Percentage of eligible patients receiving bedaquiline</td>
<td>Quarterly</td>
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<tr>
<td>Number of patients receiving bedaquiline</td>
<td>Quarterly</td>
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<tr>
<td>MDR-TB patients on bedaquiline included in CEM</td>
<td>Quarterly</td>
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<tr>
<td>MDR-TB patients on bedaquiline retained in the cohort for event</td>
<td>Yearly</td>
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<tr>
<td>monitoring</td>
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<tr>
<td>MDR-TB patients included in CEM with any serious adverse event</td>
<td>Quarterly</td>
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<tr>
<td>Frequency of bedaquiline-associated adverse drug reactions</td>
<td>Quarterly</td>
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<tr>
<td>Time to development of bedaquiline-associated adverse drug reactions</td>
<td>Quarterly</td>
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<tr>
<td>Buffer stock of bedaquiline</td>
<td>Quarterly</td>
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<tr>
<td>Buffer stock of companion drugs</td>
<td>Quarterly</td>
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<tr>
<td>Number of technical assistance missions</td>
<td>Twice a year</td>
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<tr>
<td>Number of support/supervisory visits to pilot sites</td>
<td>Twice a year</td>
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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.

### Pharmacovigilance

As mentioned previously, the introduction of bedaquiline requires the establishment of an active pharmacovigilance system to monitor the occurrence of adverse events and collect information on the safety profile of bedaquiline (13). Details of implementation of active pharmacovigilance through the establishment of CEM for introduction of bedaquiline can be found in the following documents:

- Sample data collection forms for cohort event monitoring ([http://www.who.int/entity/tb/challenges/sample_data_collection_forms_for_cem_to_antibiotics_27march.pdf](http://www.who.int/entity/tb/challenges/sample_data_collection_forms_for_cem_to_antibiotics_27march.pdf)) (32)
- Active pharmacovigilance for new TB drugs and regimens: an implementation plan for cohort event monitoring for introduction of bedaquiline at country level (29) - (hereafter called Pharmacovigilance implementation plan).

Annex 6 shows how the 9 key steps for the establishment of CEM could be addressed ahead of the start of patient recruitment, building 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 that is required to mount and maintain CEM but the TB monitoring approach is a clear advantage that TB programmes have over other disease programmes when implementing CEM. As mentioned previously (see Step 2, section g in this chapter), it is important to ensure that essential CEM elements are in place before the enrolling patients on bedaquiline: i) a broad agreement between the national TB programme and the national PV
centre on the process to implement the CEM project for TB drugs; ii) preparation for the collection of data (e.g. forms); and iii) staff properly trained to collect the data.

g. 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. The use of bedaquiline, however, requires additional specifications to be duly acknowledged (Annex 10).

h. 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 of the numbers of tablets are 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 stocks should be planned in the drug calculations and buffer stock should also be ordered according to standard practice for second-line drugs taking into account spillage, breakage or other types of loss of medication.

i. Training of managers and staff
The NTP, in collaboration with the treatment centres, should identify: (i) where bedaquiline will be introduced, and (ii) where the 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 staff for the NPVC on the principles of CEM 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.

j. 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 a new drug/regimen according to the type of activities to be undertaken.
**k. 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 activities (listed below). (Many of these activities can be done in parallel to speed-up the preparatory phase of the introduction.)

- 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 the pharmacovigilance 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 new drug/regimen 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.

**l. 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 costs of bedaquiline implementation will be covered throughout the implementation period.

**m. Obtaining consensus from donor agencies**

Multiple donors are supporting the introduction of bedaquiline globally, including the Global Fund, United States Agency for International Development, 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 pharmacovigilance). 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 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 implemented in settings with robust PMDT programmes, established and maintained according to WHO guidelines.

### STEP 4

**Recommended activities for meeting the minimal requirements for introduction of bedaquiline**

- a. Identify patients eligible for treatment with bedaquiline
- b. Informed consent
- c. Clinical Review Committee consultation
- d. Treatment initiation
- e. Monitoring treatment response
- f. Pharmacovigilance: detection, management and reporting of adverse events
- g. Individual drug resistance monitoring

### a. 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.** *Persons 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.

Following 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 containing four second-line drugs in addition to pyrazinamide, according to WHO recommendations, 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 accept the medication 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.

• **Geriatric use (patients above 65 years of age).** Clinical studies of bedaquiline did not include sufficient numbers 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 antiretroviral 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-sensitive TB or drug-resistant TB cases in which another satisfactory regimen is available.**

### b. 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 told. 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.

A written informed consent should be sought from each patient starting 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.

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

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 10* for a sample informed consent form).

### c. Clinical Review Committee consultation

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, but in addition for patients being considered for bedaquiline, the following information should be included (see Annex 11):

- Clinical Review Committee decision on bedaquiline treatment (approval/refusal).
- 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.

d. Treatment initiation

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, 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 generally lasts for about 20 months.

Table 3. Length of treatment for bedaquiline-containing regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Suggested duration of treatment in months when bedaquiline is added to the standard WHO regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline (oral)</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>Second-line injectable drug</td>
<td>1 2 3 4 5 6 7 8</td>
</tr>
<tr>
<td>Other oral anti-TB drugs</td>
<td>1 2 3 4 5 6 7 8 9 10 1 2 3 4 5 6 7 8 1 2 3 4 5 6 7 8 9 1 2 0</td>
</tr>
</tbody>
</table>

*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 (14).

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 and should be taken with a light meal (bedaquiline is better absorbed with food).*

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 week three 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).†

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 (14) for further details).

At the time of treatment initiation and during follow-up visits, relevant patient details, comorbidities, laboratory test results and adverse events need to be collected. PMDT forms already in use should be adapted to incorporate additional data fields required for pharmacovigilance (see Meeting report of the inter-regional workshop on pharmacovigilance for TB (30) for the minimum CEM data collection elements; Sample CEM data collection forms (32), and Pharmacovigilance implementation plan (particularly Annex 1 - 3) (29). Patients on bedaquiline should be flagged as such and pharmacovigilance data preferably entered in the “routine recording and reporting system”. Thus, additional data fields related to pharmacovigilance need to be included both in the paper and electronic recording and reporting systems.†

e. Monitoring 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 patient is hospitalized; weekly if on 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).
- 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 adverse events, including creatinine, electrolytes, thyroid function, liver function, complete blood count, audiometry, visual acuity and ECGs. The timing of these routine assessments is described in Annex 4.
- Chest radiograph: baseline, then every six months.

* 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).
† The Pharmacovigilance implementation plan provides a list of essential data elements and a data dictionary to facilitate incorporation of pharmacovigilance data fields in a standardized manner across countries.
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 expected amount per patient.
- **Sputum culture conversion**: occurrence and date.
- **Patient survival**: has the patient died? If yes, all efforts should be made to ascertain the immediate and contributing causes of death and determine if it was linked or not to TB treatment. The International Classification of Diseases coding of the cause of death should always be recorded. As death is by definition considered a serious adverse event, all legal requirements on reporting of serious adverse events should be obeyed. More details can be found in the *Pharmacovigilance implementation plan (29)*.
- **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).

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

- **Enrolment indicators**
  - MDR-TB patients declared eligible for treatment with bedaquiline by the Clinical Review Committee that 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 serious adverse events.
  - Proportion of patients on bedaquiline who changed treatment regimen due to adverse events.
  - 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 (14)* and the *Pharmacovigilance implementation plan (29)*.

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 MDR-TB eligible patients started on bedaquiline in year 1, 2 and 3, respectively.
- Number of pharmacovigilance reports collected.
• Number of supportive supervision visits performed (at least two supervision rounds/year to each implementing site are recommended).
• Number of drug stockouts and reasons.

f. Pharmacovigilance: detection, assessment and reporting adverse events

Special attention should be paid to ensure that adverse events – in particular hepatic and cardiac events – are detected early and promptly managed. Patients receiving bedaquiline are to be monitored closely throughout their treatment, and adverse events promptly recorded and reported through active pharmacovigilance, preferably using the CEM method (see chapter 2, Step 2.g above). Adverse events monitoring should take place within the context of PMDT. The recommended adverse event monitoring schedule for patients with MDR-TB should be used.

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

Adverse event monitoring. For adverse event 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 (five-and-a-half 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 adverse events during MDR-TB treatment.

A detailed monitoring schedule is provided in the Pharmacovigilance implementation plan (Annex 1).

Adverse event management. For each adverse event, 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 of the event; and
• to report the event in the routine electronic reporting and recording system.

Adverse event recording and reporting. Data on adverse events 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 adverse event). 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)).

When reporting the event, it is essential that patient and event data be accurately identified and all due information reported. For details on data that should be recorded, refer to 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 (30).

ALL events (such as new event, change in a pre-existing condition, abnormal change in laboratory tests, admission to hospital with date and cause, observation of pregnancy of any duration, accidents, death with date and cause, possible drug interactions) must be reported. Filled forms should be transmitted to the national or regional pharmacovigilance centre, according to each country’s policy. At the national level, a pharmacovigilance committee (consisting of experts from
both the NPVC and NTP) will conduct a formal causality assessment. This would help assess the potential relationship between reported adverse events and drugs taken by the patient. If there is ample experience with CEM and resources are available in the NPVC, it is preferred that the national pharmacovigilance committee operates as a subgroup under the guidance of the NPVC. If the national pharmacovigilance committee starts under the guidance of the Technical Working Group, at a later point in time, the committee for TB drugs should become an independent entity under the responsibility of the NPVC. Thus, the ultimate goal is for the NPVC to become the leading agency in organization of pharmacovigilance for new TB drugs/regimens.

**Bedaquiline safety** should be monitored through the following indicators:

- MDR-TB patients on bedaquiline included in cohort event monitoring
- MDR-TB patients started on bedaquiline retained in the cohort for event monitoring
- Serious adverse events: MDR-TB patients included in CEM with any serious adverse events.
- Frequency of bedaquiline-associated adverse drug reactions.
- Time for development of bedaquiline-associated adverse drug reactions.

**g. Individual drug resistance monitoring**

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 during treatment for testing to bedaquiline. In addition, the repeat DST for first- and second-line drugs (including bedaquiline) should be done on the last positive culture isolate. Should laboratory capacity for susceptibility testing to selected drugs not be available at country level, the strains should be sent to the SNRL for testing.
Step 5: Generating evidence for scale-up

As countries start to implement bedaquiline for 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, and new pharmacovigilance requirements. 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 be very useful to inform eventual wide-scale expansion and assist other countries intending to embark on the same process as they introduce bedaquiline (and other new TB drugs/regimens). In addition, countries will need to decide what information they require to collect to determine if the introduction of bedaquiline was “successful” in their setting.

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) serious adverse events (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 is 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 persons with adverse events in the two groups, and if the adverse 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 cohort event monitoring;
- percentage of MDR-TB patients started on bedaquiline retained in the cohort for event monitoring; 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 pharmacovigilance system development. Programmes should monitor the costs of implementation of the drug to have a realistic sense of budget planning and resource allocation. 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 pharmacovigilance in MDR-TB treatment.

Data for both outcome and process indicators that are most likely to be valuable should have the following features:
They come from treatment centres with reliable access to good quality drugs and monitoring facilities run by staff with good proficiency in clinical care.

They are collected using a quality-assured methodology for the variables and the organization of data, respecting ethical norms and standards for data management.

They represent a series with relatively large numbers of patients of a diverse age and gender profile.

They are 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 (31).

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

<table>
<thead>
<tr>
<th>Key action steps</th>
<th>Step</th>
<th>Domain</th>
<th>Responsible body</th>
<th>Activities</th>
</tr>
</thead>
</table>
| Before/during implementation | Step 1 | Establish the framework for bedaquiline introduction | National level (health ministry, NTP, implementation Task Force) | a. Assess the national context  
b. Contact relevant units/departments at the health ministry  
c. Identify implementing partners  
d. Create a national Implementation Task Force and Technical Working Group  
e. Coordinate with the National Regulatory Authority  
f. Establish a dialogue with pharmaceutical companies  
g. Establish appropriate procurement system for bedaquiline  
h. Organize sensitization workshops |
| | Step 2 | Meet the minimal requirements (see checklist) | National level (health ministry, NTP, implementation Task Force) | a. Laboratory capacity  
b. Drug resistance surveillance  
c. Clinical Review Committee  
d. Case management  
e. Recording and reporting system  
f. Monitoring and evaluation  
g. Pharmacovigilance  
h. Budget  
i. Technical assistance  
j. Drug supply system  
k. Checklist for country preparedness and planning |
<p>| | 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 | | a. Rationale for introduction of bedaquiline at country level |</p>
<table>
<thead>
<tr>
<th>Step 4</th>
<th>Implement bedaquiline use</th>
<th>NTP, implementation Task Force, Technical Working Group, pilot/implementing site level staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Identify patients eligible for treatment with bedaquiline</td>
<td></td>
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<tr>
<td>b. Informed consent</td>
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<td>g. Individual drug resistance monitoring</td>
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<tr>
<th>Step 5</th>
<th>Generating evidence for further scale-up</th>
<th>National level (NTP, implementation Task Force, Technical Working Group)</th>
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</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>
Annex 1. Reference documents on new TB drugs

WHO website
2. Tuberculosis and Pharmacovigilance. (http://www.who.int/tb/challenges/pharmacovigilance/en/)

Working Group on new TB drugs of the Stop TB Partnership

New drugs and regimens framework

Pharmacovigilance
Main publications on bedaquiline


### Annex 2. Minimum laboratory requirements for introduction of bedaquiline

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

* 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.

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

<table>
<thead>
<tr>
<th>Monitoring and evaluation</th>
<th>Recommended frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical evaluation</strong></td>
<td><em>During the intensive phase:</em> 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 on a monthly basis.</td>
</tr>
<tr>
<td></td>
<td><em>During the continuation phase:</em> Monthly assessment 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.</td>
</tr>
<tr>
<td><strong>Treatment adherence and tolerance.</strong></td>
<td>Daily, at every DOT encounter by the DOT provider.</td>
</tr>
<tr>
<td><strong>Sputum smears and culture</strong></td>
<td>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.)</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>At baseline, then every two weeks for first 3 months and then monthly</td>
</tr>
<tr>
<td><strong>Height</strong></td>
<td>At start of treatment for all (to be able to assess BMI throughout treatment), monthly for children (to assess growth).</td>
</tr>
<tr>
<td><strong>Drug susceptibility testing</strong></td>
<td>At baseline for first and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after month 4.</td>
</tr>
<tr>
<td><strong>Chest radiograph</strong></td>
<td>At baseline, and then every six months.</td>
</tr>
</tbody>
</table>
Annex 4. Monitoring for adverse events during MDR-TB treatment

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

<table>
<thead>
<tr>
<th>Monitoring and evaluation</th>
<th>Recommended frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>At baseline, then monthly if possible while receiving an injectable agent. Every 1–3 weeks in HIV-infected patients, diabetics and other high-risk patients.</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>Monthly while receiving an injectable agent. Every 1–3 weeks in HIV-infected patients, diabetics and other high-risk patients.</td>
</tr>
<tr>
<td>Serum magnesium and calcium</td>
<td>Check magnesium and calcium blood levels whenever hypokalaemia is diagnosed. At baseline and then monthly if on bedaquiline. Repeat if any ECG abnormalities develop (prolonged QT interval).</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH)</td>
<td>Every three months if receiving ethionamide/prothionamide and para-aminosalicylic acid (PAS). Every six months if receiving ethionamide/prothionamide or PAS. Note that the combination ethionamide+PAS or prothionamide+PAS should not be provided together. TSH is sufficient for hypothyroidism screening and is not necessary to measure hormone thyroid levels. Monthly monitoring for clinical signs/symptoms of hypothyroidism is also necessary.</td>
</tr>
<tr>
<td>Liver serum enzymes (SGOT, SGPT)</td>
<td>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 monthly monitoring is recommended. For patients on bedaquiline measure monthly. For patients with viral hepatitis, monitor every 1–2 weeks for the first month and then every 1–4 weeks.</td>
</tr>
<tr>
<td>HIV testing</td>
<td>At baseline, and repeat if clinically indicated.</td>
</tr>
<tr>
<td>Pregnancy tests</td>
<td>At baseline for women of childbearing age, and repeat if indicated.</td>
</tr>
<tr>
<td>Haemoglobin and white blood count</td>
<td>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.</td>
</tr>
<tr>
<td>Lipase</td>
<td>Indicated for abdominal pain to rule out pancreatitis in patients on linezolid, bedaquiline, D4T, ddI or ddc. Baseline lipase is recommended for patient on bedaquiline.</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>Indicated for lactic acidosis in patients on linezolid or antiretroviral treatment.</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>If receiving gatifloxacin, measure fasting blood glucose at baseline and monthly. Educate and remind patient about signs and symptoms of hypoglycaemia and hyperglycaemia monthly.</td>
</tr>
<tr>
<td>Audiometry (hearing test)</td>
<td>Baseline and then monthly audiograms while on an injectable agent. Ask patient about changes in hearing at every clinic visit and evaluate their ability to participate in normal conversation.</td>
</tr>
<tr>
<td>Vision tests</td>
<td>For patients on long-term ethambutol or linezolid perform a colour vision test at baseline (as a small percentage of the population has colour blindness). Repeat test for any suspicion of change in colour vision.</td>
</tr>
<tr>
<td>Educational, psychosocial and social consultation</td>
<td>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.</td>
</tr>
<tr>
<td>ECG</td>
<td>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).</td>
</tr>
</tbody>
</table>
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 QTcF value 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 rifampicin (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 on MDR-TB treatment.
- Confirmed RR-TB or MDR-TB cases enrolled on MDR-TB treatment.
- Confirmed XDR-TB cases enrolled on XDR-TB treatment.
- Interval of time between MDR-TB diagnosis and start of MDR-TB treatment.

CEM indicators
- Coverage: MDR-TB patients on bedaquiline included in CEM.
- Completeness: MDR-TB patients started on bedaquiline retained in the cohort for event monitoring.
- Serious adverse events: MDR-TB patients included in CEM with any serious adverse event.
- Bedaquiline-associated adverse reactions: Frequency of bedaquiline-associated adverse drug reactions.
- Bedaquiline-associated adverse reactions: Time to development of bedaquiline-associated adverse 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 where '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 the start of enrolment. The programme manager often needs an indication of how patients are faring well before that. This is particularly important for a new drug/regimen being introduced for a drug-resistant TB treatment programme. Assessing culture conversion to negative (for confirmed pulmonary cases) in month six or death by six month is widely used as an indicator of treatment response. Information on 'lost to follow-up' by six months is also very helpful.

The period of assessment is three calendar months (one quarter), and is usually counted as: (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 persons who have started treatment are counted for reporting of interim results. When calculating the proportion of culture conversions at six months, all patients started on treatment are entered in the denominator, including patients who died or were lost to follow-up before six months. If a patient whose sputum became negative early on 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. 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**

*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.

The first indicator would only apply 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.

**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

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*In sites testing with Xpert® MTB/RIF alone, the indicators enumerate also 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.*
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**

**Outcome Indicators for RR-/MDR-TB cases on MDR-TB treatment regimen:**

- Cured
- Treatment completed
- Treatment failed
- Died
- Lost to follow-up
- Not evaluated for outcome.

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

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 at any time during 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.
### Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>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.</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>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.</td>
</tr>
<tr>
<td>Treatment failed</td>
<td>Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:</td>
</tr>
<tr>
<td></td>
<td>- lack of conversion(^a) by the end of the intensive phase, (^a) or</td>
</tr>
<tr>
<td></td>
<td>- bacteriological reversion(^b) in the continuation phase after conversion(^b) to negative, (or)</td>
</tr>
<tr>
<td></td>
<td>- evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, (or)</td>
</tr>
<tr>
<td></td>
<td>- adverse drug reactions.</td>
</tr>
<tr>
<td>Died</td>
<td>A patient who dies for any reason during the course of treatment.</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>A patient whose treatment was interrupted for two consecutive months or more.</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>A patient for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown.)</td>
</tr>
<tr>
<td>Treatment success</td>
<td>The sum of cured and treatment completed.</td>
</tr>
</tbody>
</table>

\(^a\) 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 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 as used here are defined as follows:

**Conversion (to negative)**: culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

**Reversion (to positive)**: culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.
Annex 6. Pharmacovigilance: Steps required to introduce and sustain a CEM component at national level

The implementation of CEM requires the following nine essential steps (14):

1. Constitution of a CEM committee at national level with a secretariat to manage its work.

2. Proper implementation, management and supervision of the pharmacovigilance programme. This should preferably be built into the management and supervision of the PMDT programme but will demand extra resources for planning, supervision, data entry, analysis and sharing of results.

3. The development of a CEM protocol that clearly defines the activities and the standard operating procedures, including the plan for data analysis and communication.

4. The design and production of forms for data collection. These consist primarily of treatment initiation and treatment review forms to register baseline and follow-up patient data (see Sample data collection forms for CEM for TB (32)). Instructions for the completion of these two forms, including definitions of terms and specifying what, how, when and the duration to report each event or other necessary data elements are detailed in the CEM protocol.

5. Ethical approval must be applied to the CEM protocol and activities, in accordance with local requirements. Pharmacovigilance activities should be considered as a standard for patient care and seen as another facet of public health surveillance not dissimilar from the way many countries operate for routine surveillance of TB drug resistance based on diagnostic testing.

6. A training programme for the staff involved at all levels of healthcare.

7. The start and maintenance of data collection during the period of patient monitoring.

8. The creation of an electronic database or the adaptation of an existing one to ensure proper safekeeping of data. A electronic database that is kept up-to-date with data reported by the various units undertaking the CEM, and captures sporadic reports, is indispensable for the analysis of data and will facilitate the sharing of data between centres.

9. As part of the data analysis there needs to be an assessment of relationship and causality between events and exposures, and the identification of signals (see sections G–L in the pharmacovigilance handbook (24)).
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).

<table>
<thead>
<tr>
<th>Clinician’s checklist of essential parameters for selection of MDR-TB patients with bedaquiline</th>
<th>Tick Yes or No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the patient have an absolute contraindication to bedaquiline (refuses to consent, significant cardiac disease, history of an allergic reaction).</td>
<td>☐ Y ☐ N</td>
</tr>
<tr>
<td>Patient is known or suspected to have a multidrug-resistant strain of tuberculosis and therefore eligible for treatment with second-line anti-TB drugs.</td>
<td>☐ Y ☐ N</td>
</tr>
<tr>
<td>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).</td>
<td>☐ Y ☐ N</td>
</tr>
<tr>
<td>The drug resistance profile of the patient’s isolate (and/or patient treatment history) suggests that the WHO standard recommended regimen for treatment of MDR-TB cannot be provided.</td>
<td>☐ Y ☐ N</td>
</tr>
<tr>
<td>Clinically significant ventricular arrhythmia is absent.</td>
<td>☐ Y ☐ N</td>
</tr>
<tr>
<td>Drugs already included in the regimen not known to prolong the QTcF interval.</td>
<td>☐ Y ☐ N</td>
</tr>
<tr>
<td>Baseline and repeat ECG shows normal QTcF interval (≤440 ms).</td>
<td>☐ Y ☐ N</td>
</tr>
<tr>
<td>Aminotransferases less than three times the upper limit of normal and total bilirubin less than two times the upper limit of normal.</td>
<td>☐ Y ☐ N</td>
</tr>
<tr>
<td>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.</td>
<td>☐ Y ☐ N</td>
</tr>
<tr>
<td>Informed consent for treatment with bedaquiline has been obtained.</td>
<td>☐ Y ☐ N</td>
</tr>
</tbody>
</table>

**IF THE ANSWER TO THE FIRST QUESTION IS ‘NO’ AND TO ALL THE OTHERS IS ‘YES’, THE PATIENT CAN BE ENROLLED FOR TREATMENT WITH BEDAQUILINE.**

**IF THE ANSWER TO ANY OF THE ABOVE EXCEPT NUMBER 1 IS ‘NO’, FURTHER CONSIDERATION AND REVIEW IS NEEDED BEFORE ENROLMENT FOR TREATMENT WITH BEDAQUILINE.**
Annex 8. Instruction to healthcare providers on patient education and informed consent for bedaquiline (14)

**Instruction to healthcare providers on patient education and informed consent for bedaquiline**

**Introduction**

Briefly state who you are and explain to patients that you are inviting them to accept bedaquiline as part of the drug regimen 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 participant 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 (TB) that cannot easily be treated with commonly used drugs. You are suffering from a difficult-to-treat form of TB, 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 recently been approved for use in TB patients by drug control authorities in the USA and by the World Health Organization. It is however still undergoing studies to examine its safety and its effectiveness. 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, or the doctor or the staff.

**Reason why bedaquiline is being offered to the patient**

Explain in lay terms why you are offering to add bedaquiline to the treatment regimen. Use local and simplified terms. Avoid using technical terms such as pathogenesis, antibiotic, adverse effects, cardiac, hepatic.

*Proposed text: Tuberculosis (TB) is a serious disease that can be fatal. There are many TB cases that are especially difficult to treat with the drugs that are currently used to help people with TB. Some patients with resistant TB may have limited treatment options. There is a new drug which 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 how the drug will be taken. This will be expanded upon in the information sheet that will be given to the patient again, but it may be helpful and less confusing to the participant if they know from the very beginning that the drug will be taken orally for six months, along with several other drugs administered orally 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 under directly observed therapy at home/clinic/hospital. There will be other drugs to take also; and these are taken for a total of 20 months at least. Bedaquiline should be taken with a light meal. It is important to take the medication as prescribed to avoid further development of drug resistance to the drugs that 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 is in terms of the treatment offered by the programme; and what it would 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.

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 (TB), and we will tell you more about it later. You may change your mind later and stop receiving bedaquiline even if you agreed earlier. Please let your doctor or nurse know beforehand if you wish to stop the drug.

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 person at the bottom of the Medication Guide.
Annex 9. Sample information note for patient taking bedaquiline (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 replace talking to your healthcare 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) of the 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.

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.
- In one clinical trial, more deaths were seen in people who were treated with bedaquiline compared to people who did not receive bedaquiline.
- Heart rhythm problems can happen with bedaquiline.

It is not known if bedaquiline is safe:
- for children under 18 years;
- during pregnancy;
- in forms of TB that are not drug-resistant TB or not TB of the lungs; and
- in patients with heart, kidney, liver or other health problems.

Before consenting to take bedaquiline, inform your healthcare provider if the following apply:
- 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 healthcare provider should take a decision if you will take bedaquiline or breastfeed.
- You are taking any prescription and nonprescription medicines, vitamins and herbal supplements.

How should I take bedaquiline?
- Bedaquiline must always be taken with other medicines to treat TB. Your healthcare provider will decide which other medicines you should take with bedaquiline.
- Always take bedaquiline with a light meal (not heavy in fat).
- 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 each day, 7 days a week.
  - Week 3 to Week 24: Take 200 mg (2 tablets) a day thrice a week. For example, you may take bedaquiline on monday, wednesday and friday 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, short course (DOTS), which means that a healthcare provider will accompany you during the treatment (observe you swallow the medications and provide support around your 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 and they will tell you what to do.

What should I avoid while taking bedaquiline?
- You should not drink alcohol while taking bedaquiline.

What are the possible side-effects of bedaquiline?
- Serious heart rhythm changes. Tell your healthcare 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 for heart rhythm.
- Liver problems (hepatotoxicity). Liver toxicity can present in many ways. Inform your doctor about symptoms, such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual tiredness, loss of appetite, light coloured bowels, dark coloured urine, yellowing of your skin or yellowing of the white of your eyes.
- Other side-effects of bedaquiline may 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 observed closely for any unwanted effects or any problems. Other medicines may be administered to decrease the symptoms of the side-effects or reactions.

Always tell your healthcare 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. Talk to your healthcare provider regarding the 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 than you would otherwise be due to certain side-effects of the drug. It is possible that a side-effect could be serious and even result in death.
- BENEFIT: There is a greater chance that you will be cured of TB than if you did not take the medicine. You health will possibly improve much sooner than if you only took the standard medicines for treatment of drug-resistant TB. Also, it is less likely that the drugs you are currently taking will develop resistance if you are also 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 to ensure better use of the drug for patients will be unlinked to your name (made anonymous) before we share it or analyse the information.

**Costs**

- If you choose to take bedaquiline and cannot afford it, it will 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. 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 also at any point stop doing so 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: _______________________________________

*Adapted from USFDA approved Medication Guide Sirturo™. New Jersey: Janssen Therapeutics; 2013.*
Annex 10. Sample informed consent form for patients taking bedaquiline (14)

### 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 respective 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 himself/herself.

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 that I am suffering from.

<table>
<thead>
<tr>
<th>Print Name of Patient:</th>
<th>__________________________________________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature of Patient:</td>
<td>__________________________________________________________</td>
</tr>
<tr>
<td>Date:</td>
<td>__________________________________________________________</td>
</tr>
</tbody>
</table>

If 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 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.

<table>
<thead>
<tr>
<th>Print name of witness:</th>
<th>_____________________________ AND Thumbprint of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature of witness:</td>
<td>__________________________________________________________</td>
</tr>
<tr>
<td>Date:</td>
<td>__________________________________________________________</td>
</tr>
<tr>
<td></td>
<td>(day/month/year)</td>
</tr>
</tbody>
</table>

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 the following:

1. Special tests were conducted to determine if he/she can receive bedaquiline. These tests show that he/she is eligible for the medication and that he/she has no conditions that would contraindicate its use. Tests will be repeated at regular intervals, as they are necessary to enable proper monitoring of response to treatment, both from an efficacy and a safety point of view; and

2. Bedaquiline will be administered as part of the drug regimen for a period of six months; then the treatment will continue without bedaquiline.

I confirm that the participant/patient was given an opportunity to ask questions about the study, and all
the questions asked by the participant/patient have been answered appropriately to the best of my ability. I confirm that the individual has not been coerced into giving consent and that 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 ___________________________
Annex 11. Sample Clinical Review Committee decision form

1. Patient information
   - Surname ___________________________ Name ____________________________
   - Date of birth _______________________________________
   - 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

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Pyrazinamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td></td>
</tr>
<tr>
<td>Injectable</td>
<td>Kanamycin</td>
<td></td>
</tr>
<tr>
<td>(Group 2)</td>
<td>Amikacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capromycin</td>
<td></td>
</tr>
<tr>
<td>Higher level fluoroquinolones</td>
<td>Levofoxacin</td>
<td></td>
</tr>
<tr>
<td>(Group 3)</td>
<td>Moxifloxacin</td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>Ethionamide/prothionamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycloserine/terizidone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PAS</td>
<td></td>
</tr>
<tr>
<td>Group 5</td>
<td>Bedaquiline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amoxicillin/clavulanate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imipenem/cilastatin + clavulanate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meropenem + clavulanate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High dose isoniazid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlarythromycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thioacetazone</td>
<td></td>
</tr>
</tbody>
</table>

5. Clinical Review Committee composition
   a. Surname, name and signature
   b. Surname, name and signature
   c. Surname, name and signature
   d. Surname, name and signature
   e. Surname, name and signature

6. Place and date _______________________________________________

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 lead by the health ministry with input from the NTP.

Three processes of assessment

1. **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.
2. **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).
3. **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. Once providers have been appropriately accredited, enforcing these standards is crucial.

Other important steps to be taken to support public–private mix of 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:
   a. Assess the performance of ongoing public–private mix initiatives (close link between procurement and supply systems).
   b. Define goals of the introduction (e.g. maximize access or maximize safety or carry out limited use to build evidence).
   c. Accept the working model or design a new model of public–private mix engagement with appropriate policy framework and guidance.
   d. 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.
   a. 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).
   b. Consider procurement implications of the proposed working model and necessary training.
c. Ensure appropriate training is provided, particularly through external assessment of providers.

<table>
<thead>
<tr>
<th>Implications for:</th>
<th>Drug for multidrug-resistance added to existing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private sector provision</td>
<td>Consider use only in public sector under these circumstances.</td>
</tr>
<tr>
<td>Limited private sector</td>
<td>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.</td>
</tr>
<tr>
<td>Extensive private sector</td>
<td>Closely monitored use and reporting, particularly for pharmacovigilance; likely only at specific centres; clear guidance for usage issues.</td>
</tr>
<tr>
<td>Public sector provision</td>
<td>Restricted availability of the drug to the public sector and collaborating private sector providers to ensure appropriate use.</td>
</tr>
<tr>
<td>Regulatory environment (NRA)</td>
<td>Early discussions and willingness to distribute through officially sanctioned and restricted channels.</td>
</tr>
<tr>
<td>Industry engagement</td>
<td>Engage early with a range of providers and establish clear guidance for private and public sector use.</td>
</tr>
</tbody>
</table>
References


29. Active pharmacovigilance for new TB drugs and regimens: an implementation plan for cohort event monitoring for introduction of bedaquiline at country level.

