Target regimen profiles for TB treatment

Candidates: rifampicin-susceptible, rifampicin-resistant and pan-TB treatment regimens

WHO Library Cataloguing-in-Publication Data

Target regimen profiles for TB treatment: candidates: rifampicin-susceptible, rifampicin-resistant and pan-TB treatment regimens.

1. Tuberculosis – therapy. 2. Tuberculosis, multidrug-resistant 3. Antitubercular agents.
4. Rifampin – therapeutic use. I. World Health Organization.

ISBN 978 92 4 151133 9 (NLM classification: WF 360)

WHO/HTM/TB/2016.16

CONTENTS

ABBREVIATIONS AND ACRONYMS

ART	antiretroviral therapy
ARV	antiretrovirals
CNS	central nervous system
DDI(s)	drug-drug interaction(s)
DALY	disability-adjusted life year
DOT	directly observed treatment
DST E	drug susceptibility testing
EMA	ethambutol European Medicines Agency
FDA	United States Food and Drug Administration
FDC	fixed-dose combination
GDF	Global Drug Facility
GRADE	grading of recommendations assessment, development and evaluation
H or INH	isoniazid
HDPE	high density polyethylene
HIV	human immunodeficiency virus
M. tuberculosis	Mycobacterium tuberculosis
MDR-TB	multidrug-resistant tuberculosis
OBR	optimized background regimen
P	pyrazinamide
PDP	product development partnership
PK/PD	pharmacokinetics/pharmacodynamics
S	streptomycin
SAE	serious adverse event
SRA	stringent regulatory authority
TAG	technical advisory group
TEAE	treatment-emergent adverse event
TB	tuberculosis
WGS	whole genome sequencing
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

ACKNOWLEDGEMENTS

This document was developed by a team led by Christian Lienhardt, with the assistance of Lice González-Angulo. The core work was produced by the *Task Force on new TB drug policy development* comprising Gavin Churchyard (Chair), Grania Brigden, Frank Cobelens, Geraint Davies, Kelly Dooley, Joel Keravec, Payam Nahid, Norbert Ndjeka, Nguyen Viet Nhung, Michael Rich, Alena Skrahina, and Andrew A. Vernon. Additional contributions were made by Emily Kendall and David Dowdy from the Johns Hopkins University School of Medicine.

The World Health Organisation (WHO) would like to thank the group leads Cathy Bansbach, Payam Nahid and Michael Rich for their important roles in the development of this document.

WHO would like to thank the many contributors to the development of these target regimen profiles, including the participants of the Consensus Meeting for finalization of proposed targets: Koen Andries, Draurio Barreira, Henry Blumberg, Martin Boeree, Esteban Burrone, Marco Cavaleri, Yao Cheng, Daniel Chin, Alicia Chou, Daniela Cirillo, Francesca Conradie, Edward Cox, Charles Daley, Claudia Denkinger, Marc Destito, Keertan Dheda, Thomas Forissier, Lawrence Geiter, Jan Gheuens, Jeffrey Hafkin, Debra Hannah, Myriam Haxaire-Theuwes, Michael Kimerling, Giovanni Battista Migliori, Carol Nacy, Bern-Thomas Nyang'wa, Regina Osih, Patrick Phillips, Rada Savic, Géraldine Sbihi-Bouvier, Marco Schito, Cherise Scott, Sourya Shrestha, Melvin Spigelman, Zaid Tanvir, Wim Vandevelde, Robert Wallis, and Brenda Waning.

WHO/HQ Secretariat: Christian Lienhardt, Lice González-Angulo, Anna Dean, Inés García-Baena, Christopher Gilpin, Malgorzata Grzemska, Dennis Falzon, Ernesto Jaramillo, Avinash Kanchar, Linh Nhat Nguyen, Piero Olliaro, Hazim Timimi, Matteo Zignol, and Lou Maureen Comia. Overall guidance was provided by the Director of the Global TB Programme, Mario Raviglione.

The Bill and Melinda Gates Foundation is also gratefully acknowledged for its support for the development of this document, through grant project number OPP1052577.

ABSTRACT

There is an urgent need for safer, simpler, more efficacious and accessible treatment regimens for all forms of TB. The development of *target product profiles for TB drug regimens* (hereafter referred as *target regimen profiles*) is meant to assist drug regimen developers in identifying important regimen features and aligning these with patient and programmatic needs at country level.

Aimed at the pharmaceutical industry, research institutions, product development partnerships, donors, non-governmental organizations and civil society organizations, these target regimen profiles are based on the idea that TB drug research and development (R&D) is moving towards developing and testing TB regimens rather than individual drugs. The proposed target regimen profiles, which describe prioritized characteristics, take into account the needs of end users, care providers and policy-makers. The novelty of the target profile approach is to have the goal of a treatment regimen in mind very early in the process of drug development, with a desired outcome of shorter, less toxic, and operationally feasible regimens.

In selecting for the appropriate target regimen profiles, it was considered that a rapid drug susceptibility test—such as Xpert MTB/RIF, which allows simultaneous diagnosis of TB and detection of rifampicin resistant strains—would be an ideal triage test for current and novel regimens under routine programmatic conditions. Subsequently, profiles were developed for the treatment of rifampicin-susceptible (RS) and rifampicin-resistant (RR) TB, respectively—the latter being considered a proxy for MDR-TB. In addition, premised on the potential for a regimen of 3-4 entirely new anti-TB drugs for which minimal or no resistance would exist as a result of prior use in the community, a target regimen profile was developed for 'pan-TB treatment'. This regimen would be implemented in a simple and streamlined manner without need for drug-susceptibility testing—or for a separate treatment pathway for patients with at least RR-TB .

The target regimen profiles presented in this document specify the clinical indication of the regimen(s), the goals to be met, the measure of efficacy, the main safety aspects, the target population that will receive the treatment, and the intended end-users. In addition, they outline the most important performance and operational characteristics—with the term "minimal" used to refer to the lowest acceptable output for a characteristic, and "optimal" used to refer to the ideal target for a characteristic. The optimal and minimal characteristics define a range: it is therefore expected that new TB treatment regimens meet at least all of the required minimal characteristics, and, preferably, as many of the optimal characteristics as possible. In addition, certain attributes should be considered as 'priority' (i.e. their minimal targets must be met in order to make a 'go/no-go' decision), but others, deemed less essential, could be considered as potential trade-offs, and are therefore defined as 'desirable'.

The specific attributes and target criteria of each of these three target regimen profiles are presented in this document, together with the rationale for their selection.

1. INTRODUCTION

1.1 BACKGROUND

Treatment of tuberculosis (TB) relies on several bactericidal and sterilising drugs administered in combination for an adequate duration that is long enough to ensure the antimicrobial diversity and synergy of action to achieve durable cure and prevent the selection of drug-resistant mutants *(1, 2)*. Current treatment regimens are, however, unsatisfactory due to low efficacy, high toxicity, long duration and high cost, as in the conventional treatment of multidrug-resistant TB (MDR-TB); or interaction with other drugs, as is the case with rifampicin and some antiretrovirals (ARVs). Some combinations include drugs that have been registered for indications other than TB and are therefore used 'off-label,' such as oxazolidinones, carbapenems, or clofazimine, for the treatment of highly-resistant TB cases *(3, 4)*.

TB, including its drug-resistant forms, continues to be a major health problem worldwide (Figures 1 & 2). New TB drugs and regimens are urgently needed to improve cure rates for people with drug resistant TB (currently around 50% globally) and to shorten the treatment of both drug-susceptible and drug-resistant TB (currently at least six and at least 20 months respectively) *(5, 6)*. For the first time in decades, two new TB drugs, bedaquiline and delamanid, have become available. These are recommended by the World Health Organization (WHO) for the treatment of drug-resistant TB under certain conditions *(7, 8)*. These drugs have, however, been tested for efficacy as add-ons to the conventional (or longer) WHO-recommended treatment regimen for MDR-TB, though their optimal use in combinations that would lead to increased treatment efficacy while improving safety, toxicity and reducing treatment duration remains to be established[1] *(9)*. Other novel compounds are in clinical trials at time of writing, as are some re-purposed drugs, either as part of set treatment regimens or in addition to standard regimens *(10)*.

The development of new, efficacious combination regimens for TB treatment is lengthy and costly. Under the current system, if new drugs were added or substituted into existing regimens one at a time, it would take 20 to 30 years to develop a new regimen of three to four new drugs (5). Developing a regimen without the need to obtain individual drug approvals separately before testing novel combinations would substantially reduce both the duration of the regimen development pathway and the expenditure required to make progress *(11)*. It is therefore highly desirable that combination regimens including promising new drugs with current and/or repurposed drugs be tested early in the clinical development phase. This will aid early identification of optimal combination regimens for the treatment of drug-susceptible and drug-resistant TB that should be tested in phase II and phase III trials. The GTB treatment pipeline has expanded over the last decade, with various innovative candidate drugs and regimens being tested (Figure 3). However, more actions are needed to develop effective, accessible treatment combinations.

Development of shorter, simpler regimens combining new and existing drugs requires detailed information on their respective safety and toxicity *(12, 13)*; their potential for drug-drug interactions (DDIs) *(14)*; their propensity for development of drug resistance while on therapy *(15, 16)*; and their use in specific patient populations such as persons infected with human immunodeficiency virus (HIV), pregnant women, and children. The development of target product profiles allows the identification of desired product attributes or priorities to be considered during the product development process; expanding on this, the determination of target profiles for TB treatment regimens (i.e. target regimen profiles) is expected to assist developers in aligning the characteristics of new TB treatment regimens with programmatic needs at country level.

The elements of any target profile are usually chosen based on expert consensus, but no formal framework exists for identifying and prioritizing the components of TB treatment regimens that could determine their patient- and population-level impact. At a minimum, the target profiles for TB treatment regimens should specify: the clinical indication of the regimen; the goal to be met and the measure of efficacy (e.g. non-relapsing cure); the target population that will receive the treatment; the level of implementation in the healthcare system; and the intended end users. In addition, these targets should outline the most important performance and operational characteristics (with the term "minimal" used to refer to the lowest acceptable output for a characteristic, and "optimal" used to refer to its ideal target), and the likely set of users. The optimal and minimal characteristics define a range: it is therefore expected that the resultant products—TB treatment regimens—will at least meet all of the required minimal characteristics, and as many of the optimal characteristics as possible.

1. The possibility for inclusion of bedaquiline as an element of an all-oral and/or shorter combination treatment of MDR-TB is currently being tested. Working Group on New TB Drugs, 2016. Drug TB Pipeline. Available from: http://www.newtbdrugs.org/pipeline.php

Fig. 1: Estimated TB incidence rates, 2015
Source: *Global TB Report 2016*

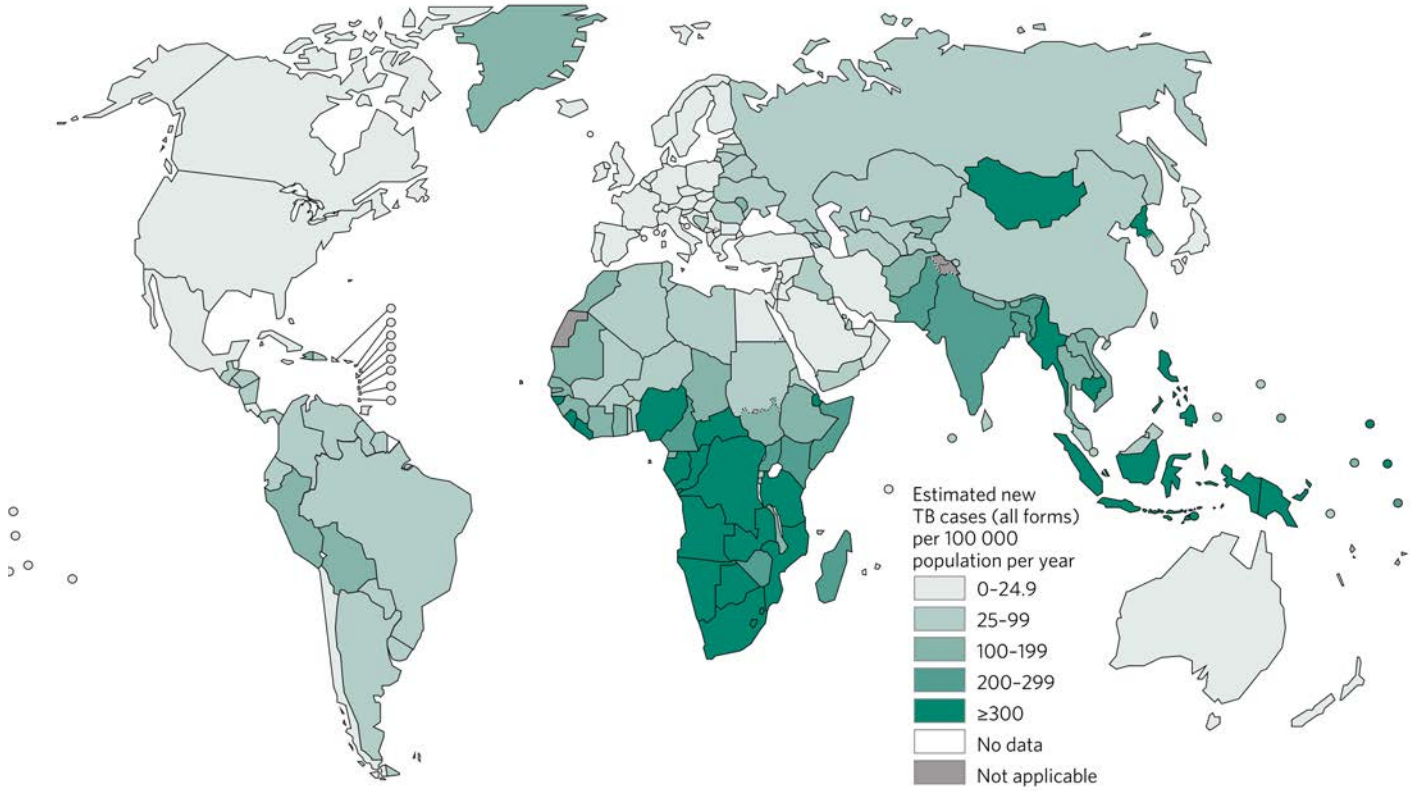
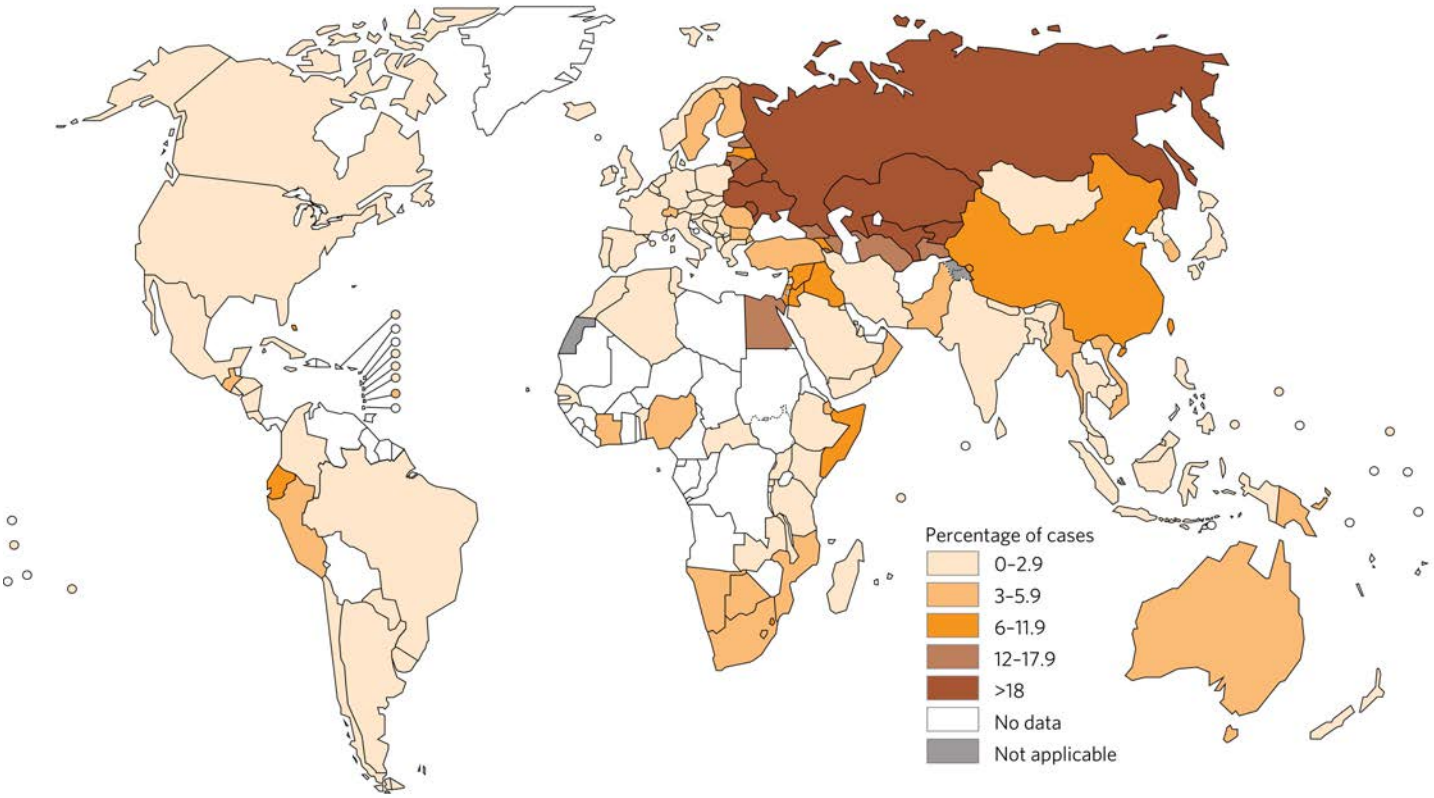


Fig. 2: Percentage of new TB cases with MDR/RR-TB, 2015
Source: *Global TB Report 2016*



The target product profiles for TB treatment presented here have been developed jointly by the WHO Global TB Programme (WHO/GTB) and the *Task Force on new TB drug policy development* (hereafter referred to as the "*WHO Task Force*"), in collaboration with a wide range of stakeholders.

1.2. OBJECTIVE AND TARGET AUDIENCE

The overall objective of the target regimen profiles for TB treatment is to align developers' performance and operational targets for new TB treatment regimens with the needs of end-users. The target audience comprises the pharmaceutical industry, academia, research institutions, product development partnerships, non-governmental and civil society organizations, and donors.

1.3. METHODS

As few tools exist to help prioritize different patient-, programme- and population-specific characteristics that are imperative for establishing drug development targets, the *WHO Task Force* on new TB drug policy development used a stepwise approach to identify specific regimen features that could have an impact not only at a patient level, but also at population level. The activities included a series of expert meetings, an initial stakeholder survey, mathematical modelling, and interviews with a wide range of stakeholders. The initial target regimen profiles incorporated information about as many regimen characteristics as possible.

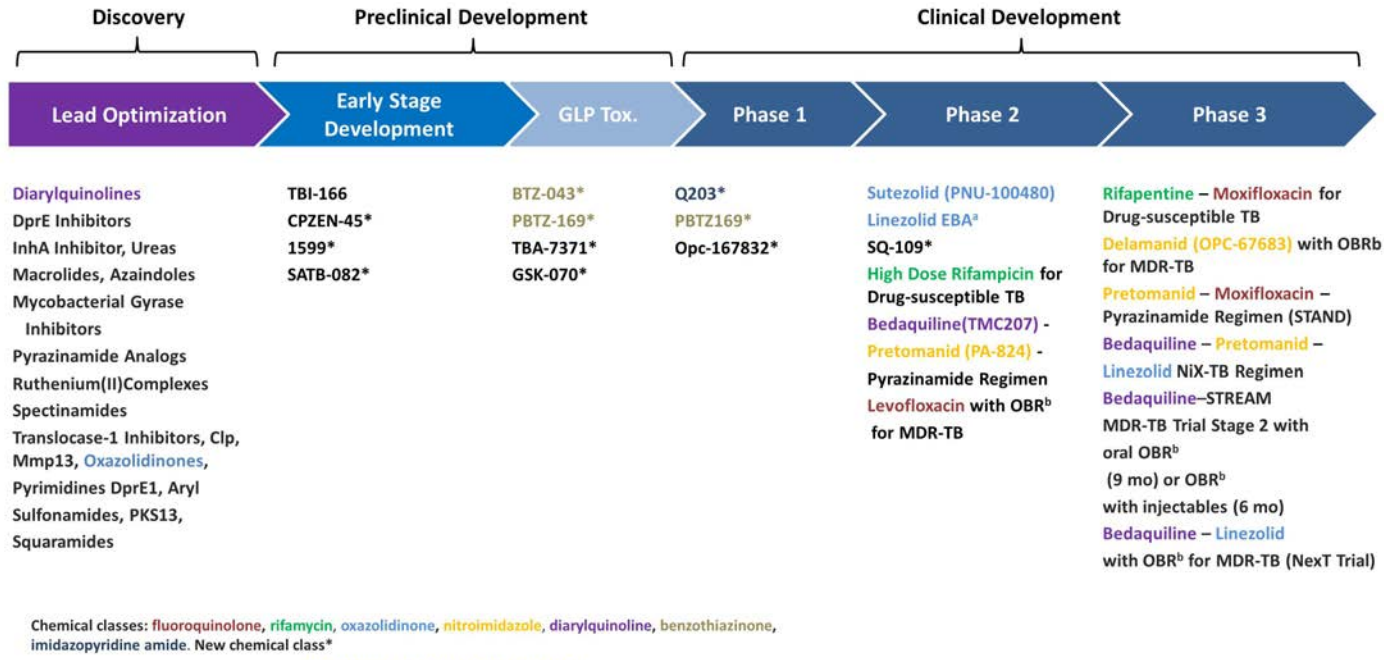
1.3.1. Initial meetings to decide on draft outlines of the potential targets for TB treatment

The process was initiated in October 2015. The *WHO Task Force* analysed the need and context for development of target regimen profiles and decided on a process. A further meeting took place in Cape Town in December 2015 at which the baseline for modelling analyses was discussed. A Technical Advisory Group was then established to develop the initial drafts of the target regimen profiles. It was composed of the members of the WHO Task Force and representatives of Johns Hopkins University, the TB Alliance, and the Bill & Melinda Gates Foundation. The first meeting of this group took place in Geneva in February 2016, and was followed by a series of teleconference calls and consultations with various stakeholders.

1.3.2. The initial stakeholders survey

An initial priority-setting exercise was conducted to specify the priority attributes for the development of the target regimen profiles as identified by a wide audience of stakeholders. It was an Internet-based-survey containing

Fig. 3: Global TB drug pipeline in 2016



Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php
Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.
GLP Tox = Good Laboratory Practice toxicity; EBA = Early Bactericidal Activity; OBR = Optimized Background Regimen.
Source: Stop TB Partnership's Working Group on New TB Drugs, 2016: http://www.newtbdrugs.org

40 core questions in four main categories (efficacy, safety, adherence and operational considerations). Two Likert-type priority scales were used to determine the degree to which specific attributes (variables) were considered essential, and to rank the level of importance of such attributes. Content validity and pre-test and test-retest reliability were used to evaluate comprehensiveness, clarity, and repeatability of the questionnaire.

The survey was distributed among 140 key stakeholders, 84 of whom responded (a 49.2% response rate). Sixty-nine participants fully completed all sections of the survey. Respondents were composed of national TB programme managers (36%); field practitioners/clinicians/laboratory experts (23%); researchers/drug developers (33%); and community and patient organizations (48%).

1.3.3. Mathematical modelling

The major goal of new TB regimen development is to improve TB treatment through shorter, simpler, more tolerable and, in the case of drug-resistant TB, more effective regimens that are more patient-friendly and which can rapidly reduce morbidity and mortality from TB. Individual treatment success rates, disease transmission, antimicrobial resistance, and operational factors may all affect a regimen's ability to fulfil this role.

In order to prioritize different characteristics when constructing and evaluating new regimens, understanding of how those characteristics contribute to a regimen's population-level impact is essential. For this purpose, a mathematical modelling framework was used to estimate the relative impact of different regimen characteristics on population-wide TB incidence and mortality. This entailed the development of a dynamic transmission model of multi-strain TB epidemics in hypothetical populations reflective of different epidemiological situations (e.g. in India, South Africa, the Philippines, and Brazil).

The introduction of novel rifampicin-susceptible or rifampicin-resistant TB regimens was modelled. Six characteristics were identified in consultation with the *WHO Task Force* and external experts, based on their potential to guide drug development and their ease of conceptualization:

1. Efficacy
2. Duration
3. Adherence
4. Medical contraindications
5. Barrier to resistance
6. Baseline prevalence of resistance.

For each characteristic, definitions were laid out of a minimal acceptable value for a new regimen, an optimal target, and an intermediate value, based on literature reviews and expert consultation.

The regimens' impact on TB or rifampicin-resistant TB mortality and incidence after 10 years was evaluated under a standardized regimen scale-up scenario (i.e. assuming that the regimen was scaled up linearly over 3 years to reach 75% of eligible patients in all settings, and that the novel regimen was only initiated after performing drug susceptibility testing (DST) for drugs in the regimen). The primary outcome was the reduction in TB mortality for rifampicin-susceptible and rifampicin-resistant TB, 10 years after regimen introduction, relative to: (i) the standard of care; (ii) a novel regimen meeting only minimal targets; and (iii) a novel regimen meeting all optimal targets. Secondary outcomes included reductions in incidence and in the total number of patient-months on treatment.

1.3.4. Development of draft target regimen profiles for TB treatment

Following the assessment of the modelling data on the relative impact of various regimen characteristics, and after considering a series of interviews with experts and the advice of the Technical Advisory Group, the *WHO Task Force* developed the initial draft target regimen profiles.

The current diagnosis of TB relies on the results of smear microscopy. In case of suspicion of resistance, diagnosis should rely on sputum culture and DST (using either solid or liquid culture media), leading to the determination of "drug-susceptible" or "drug-resistant" TB (the latter including MDR-TB and extensively drug-resistant TB, or XDR-TB). Considering the increasing scale-up of Xpert MTB/RIF in the world today (with 3,763 Xpert machines procured in 116 countries by the end of 2014, and 4.8 million Xpert MTB/RIF test cartridges procured in 2014 alone compared to only 550,000 in 2011), as well as the prospect of portable, battery-powered machines in the near future, the *WHO Task Force* adopted a practical approach to determining potential treatment regimens based on Xpert MTB/RIF. Using Xpert as a "triage test" would rapidly allow the identification of rifampicin-resistant and rifampicin-susceptible TB in a programmatic setting. On this basis, the *WHO Task Force* decided to develop target regimen

profiles for the treatment of rifampicin-susceptible TB and for the treatment of rifampicin-resistant TB, respectively, corresponding to the need at the point of care and/or point of referral, depending on Xpert availability.

In addition, considering that there will be settings in the world where Xpert MTB/RIF remains unavailable or where no other reliable diagnostic test exists at the point of care for rapidly identifying drug resistant strains, it was considered appropriate to devise a target regimen profile for a regimen that could be used empirically so that treatment could begin without delay. Such a novel regimen—a pan-TB regimen—would be simple to implement and use. Furthermore, such a regimen would be based on 3-4 entirely new TB antibiotics (i.e. excluding rifampicin, isoniazid and pyrazinamide) for which minimal or no resistance would exist as a result of prior use in the community (and whichever rapid tests of drug-resistance might be developed or available could act as a complement to further refine the patients' needs given the resistance profile). This would be particularly important in regions with high prevalence of MDR/XDR-TB and low availability of DST, where patients may be treated inappropriately and continue to transmit the disease for extended periods. A pan-TB regimen profile would also provide a bold vision of the future of TB treatment.

Of note, the above distinction acknowledges the fact that rifampicin remains a highly potent (and inexpensive) drug which, due to its unique combination of bactericidal and sterilizing activity, still represents the first intention of treatment for more than 90% of non-drug-resistant TB cases worldwide, and is a major component of TB therapy.

1.3.5. Delphi consultation and consensus meeting

Once draft target regimen profiles were developed, it was considered important to bring the target regimen profiles to a larger stakeholder audience, including further drug developers, clinicians, implementers, and representatives of countries and national TB programmes, before they could be considered finalized. For this purpose, a Delphi-like process was used to facilitate consensus building *(17)*. The target regimen profiles were sent to participants, who were asked to state their level of agreement with each of the proposed characteristics for each of the profiles. Agreement was scored on a Likert scale ranging from 1 to 5 as follows: 1—fully disagree; 2—mostly disagree; 3—neither agree nor disagree; 4—mostly agree; and 5—fully agree. Participants were also asked to provide comments in support of their score (particularly when they did not agree and scored a characteristic at 3 or lower).

In July 2016, a meeting was organised to build further consensus around the three target regimen profiles, the intended use of the regimens, and their performance and operational characteristics. Participants comprised stakeholders from technical and funding agencies; researchers; implementers; representatives from countries and civil society organizations; and representatives from companies working on the development of new drugs or regimens for TB treatment.

Overall, throughout this process, the draft target regimen profiles have been circulated and discussed with a wide range of stakeholders, including researchers, TB drug and regimen developers, representatives from the pharmaceutical industry, product development partnerships, and donors.

2. INSTRUCTIONS FOR USE

The current document is divided into three sections containing information about each target regimen profile: rifampicin-susceptible; rifampicin-resistant; and the pan-TB regimen. Each of these sections provides the reader with background information on the medical need and critical assumptions underlying the development of the target profiles. The regimen-specific target profiles are then described in a series of summary tables detailing the regimens' attributes and relevant appropriate targets.

These summary tables capture the minimal and optimal characteristics of the regimen to be developed. The **minimal** requirements column provides instructions detailing targets that go beyond the current standard of care and which represent an acceptable minimum for global health impact when developing candidate regimens. These criteria provide context for defining clear "go/no-go" decisions to be used throughout the development process. The **optimal** requirements specify performance and use characteristics of an 'ideal' product for which the global health impact should be broader, deeper, and potentially quicker. For both minimal and optimal categories an **annotations** column provides the rationale supporting the targets for each attribute.

Upon consultation with key stakeholders and based on the initial feedback from the priority setting and modelling exercises, various regimen attributes or characteristics were included as proposed targets. However, while preparing the specifications that drug developers should consider, it became clear that certain attributes should be considered as '**priority**' (i.e. their minimal targets must be met in order to make a 'go/no-go' decision), but others, deemed less essential, could be considered as potential trade-offs. This latter type of attribute was defined as '**desirable**'. For example, if a new regimen were to provide more tolerability or efficacy, it could justify a trade off in a desirable area such as the number of drugs in the regimen. Other regimen attributes that could be considered during the drug development process have also been provided.

This document lays out in a simple way the minimal levels of acceptable performance and use characteristics for anti-TB treatment regimens, as well as what the optimal performance could be. It is expected that the formulation of these criteria will provide a baseline for developing candidates well-suited for best treatment of TB.

3. CROSS CUTTING ISSUES

The target regimen profiles detailed in this document present a series of attributes considered essential for novel treatments of TB, such as efficacy of treatment; safety; toxicity; drug-drug interaction(s) (DDIs); potential for acquisition of drug resistance; etc. It must be acknowledged, however, that satisfying all of these characteristics in a single regimen could be difficult to achieve in the short term, and that regimen developers might have to decide on trade-offs. For example, increasing efficacy (cure rates) or safety at the expense of shortening treatment duration; developing a regimen that is simpler and well tolerated in contrast to developing one that is more complex, but which protects patients against the emergence of drug resistance. For these reasons, as explained above, the 'priority' and 'desirable' classifications were created, and for each of these, both minimal and optimal targets were designated. Developers should use their judgement in assessing the relative merits of satisfying key requirements, and should be open to considering that trade-offs may apply within the priority attributes as well—for example, a major advance in one priority attribute, if it were of significant magnitude, would allow additional flexibility with other attributes.

It should be understood that, for an infectious disease such as TB with a large global burden and ongoing person-to-person transmission, the efficacy of new regimens will depend heavily on operational factors that interfere with a regimen's ability to fulfil its role. In addition, the regimen's efficacy will depend closely on various factors related to antimicrobial resistance: the community resistance to existing and repurposed drugs, such as fluoroquinolones; the resistance in the MDR-TB patient population to important existing TB drugs (like pyrazinamide); the development of resistance to new drugs that are being paired with ineffective drugs (existing resistance) during regimen development; and the slow uptake cycle of new drugs. For these reasons, these target regimen profiles should be understood as giving indications on the respective attributes to be considered at the developmental level, but these should not be dissociated from the factors to be considered at implementation level.

In terms of safety, serious adverse events (SAEs) and treatment emergent adverse events (TEAEs) are used to assess the safety of anti-TB drugs *(18)*. Throughout this document, the following definitions for safety events are used:

- A SAE is an adverse event that leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly.

- A TEAE is an event that emerges during treatment having been absent pre-treatment, or which worsens relative to the pre-treatment state.

All drugs used in a studied regimen should meet WHO prequalification or certification from a stringent regulatory authority, or be study drugs tested in a facility with Good Manufacturing Practice certification for quality assurance. It would be suitable for each individual drug component or the regimen as a whole to be approved for use in TB by at least one stringent regulatory authority. If WHO recommends a regimen using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system for evidence review, it is expected that the regimen, or its individual components, should be widely available in quality assured formulations within two years.

In terms of costs, it is expected that a new regimen will reduce non-drug cost aspects (e.g. costs related to monitoring visits, adherence, patient support, safety aspects, etc.), as a result of improved simplicity of use, and that these benefits, in turn, may offset increased drug costs. As the price of medicines is determined by many factors (including production costs, margins to recover development costs, and profit margins), margins depend highly on the volume and speed of product uptake. Nonetheless, in providing guidance as part of these target regimen profiles, the Task Force opined that the price of new medicines could be higher to begin with (with associated higher procurement cost depending on processes and sources), as long as overall cost of care (entire treatment) could be lower taking all variables into account (disability adjusted life years/DALYs, etc.). In addition, it is expected that costs of new medicines will decrease as demand and volume increase. Shorter, more tolerable regimens fulfilling or exceeding the minimal priority attributes are likely to provide cost-savings in implementation, which can offset potentially higher initial drug costs.

Developers following these proposed target regimen profiles should ensure that any resulting products are affordable and accessible in an equitable manner to

patients who need them. This should also consider the components of the End TB strategy to achieve and sustain progress in lessening the burden of TB disease (Figure 4). The following principles will help ensure that the final regimens outlined in this document fulfil these access criteria:

1) Ensure that public financing for research and innovation delivers a public return on investment by linking such financing to public health-driven priority-setting and application of the core principles of affordability, effectiveness, efficiency and equity (as identified in resolutions WHA66.22 and WHA 69.23[2] on the Follow-up of the Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination)[3].

2) Promote and support the development of new partnerships for TB R&D based on open collaborative models, allowing for earlier and easier regimen development. Models should ensure that the costs of TB R&D are delinked from final market prices and apply the core principles listed above. Delinked models which are not market driven allow needs, gaps, and priorities to be based on patient needs for definition of target priority regimen profiles; promote further sharing of research knowledge, intellectual property and data; and allow products to be priced at the lowest sustainable price. An additional benefit of de-linkage is that it facilitates stewardship of the end regimen by removing the need to market the product in order to recoup TB R&D costs within the life of the patent.

Fig. 4: Targets of the End TB strategy

VISION	**A world free of tuberculosis** – zero deaths, disease and suffering due to tuberculosis			
GOAL	**End the global tuberculosis epidemic**			
INDICATORS	**MILESTONES**		**TARGETS**	
	2020	**2025**	**SDG 2030**	**END TB 2035**
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	**90%**	**95%**
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	**80% (<20/100 000)**	**90% (<10/100 000)**
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	**Zero**	**Zero**

Source: The *WHO End TB Strategy*. End TB Strategy factsheet can be found at: http://www.who.int/tb/post2015_TBstrategy.pdf

2. http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_R23-en.pdf
3. http://www.who.int/phi/CEWG_Report_5_April_2012.pdf?ua=1

4. TARGET REGIMEN PROFILE FOR RIFAMPICIN-SUSCEPTIBLE TB

4.1 MEDICAL NEED

Despite the wide availability of a low-cost, six-month duration regimen for the treatment of rifampicin-susceptible TB with an efficacy of more than 90%, improvements are still needed to achieve WHO targets for the "End TB" Strategy—namely, reducing TB deaths by 95% and reducing new cases by 90% between 2015 and 2035, while ensuring that no family is burdened with catastrophic expenses due to TB (Figure 4). The current six-month regimen has several limitations including drug-related adverse events, challenging DDIs (in particular with some anti-retroviral medicines), length, and difficulty in ensuring adherence for the full duration of treatment across all settings. Shorter and simpler regimens would result in better outcomes and lowered risk for acquisition of resistance through improved adherence; faster recovery from illness with a shorter period of lost productivity; shortened period of risk for possible drug-related side effects; and lowered patient and programme costs *(19)*.

An additional improvement on current rifampicin-susceptible TB treatment would be for future regimens to achieve high rates of relapse-free cure even taking into consideration strains that are monoresistant to any drug except rifampicin. For example, isoniazid (INH) monoresistance is a very common, clinically relevant form of resistance worldwide, one for which there is no readily scalable rapid diagnostic available. When treated with current standard regimens, INH monoresistance is associated with a 10% higher risk of failure when compared to patients with drug-susceptible TB *(20)*. Consequently, this target regimen profile for rifampicin-susceptible TB is focused on the development of regimens for patients with active TB caused by strains that are rifampicin-susceptible or monoresistant to any other drug except rifampicin.

4.2 INTENDED USE CASE SCENARIO

The envisioned range of characteristics of a new and optimized TB regimen for rifampicin-susceptible TB are as follows:

- The regimen duration is shortened to 2-4 months, while retaining an efficacy that is *not inferior* to the current standard of care six-month regimen for drug-susceptible TB.

- The TB regimen will be effective against *all forms of drug susceptible TB*, including pulmonary and extrapulmonary TB.

- While the regimen is intended for patients infected with *rifampicin-susceptible M. tuberculosis strains*, it would optimally also be active against strains that are monoresistant to any drug other than rifampicin, such that the only DST needed to include the patient on the regimen would be for rifampicin, through a rapid molecular assay.

- The optimal TB regimen should have an exclusively *oral delivery*, administered preferably once daily, ideally without the need for weight band adjustments, and should be suitable for fixed dose combination formulations. Optimally, intravenous/intramuscular forms should also be available for treatment of severe forms of TB.

- The TB regimen should be *simple to implement* and be readily adoptable by TB programmes without significant new resource needs. This ease of use should extend to national TB programmes, most primary care clinics, and private settings. The new TB regimen should allow for easy implementation in community-based and home-based models of care.

- All drugs in the TB regimen should have *no cold storage requirements* and should have *shelf lives* longer than three, or optimally five, years.

- The need for *clinical monitoring* for efficacy and safety should be minimal.

- The new TB regimen should work in a *wide range of patients* including children, pregnant women, and patients with co-morbidities (HIV, viral hepatitis, diabetes, and others).

- The new TB regimen should have low to no *DDIs*.

- *Adherence to therapy* should be potentially high due to the regimen's good tolerance and low complexity. Minimal support (including the need for directly observed therapy) should be required in order to ensure full patient adherence and achieve target efficacy, thereby minimizing acquisition of drug resistance.

- Drugs included in this target regimen profile should

protect each other against emergence of resistance. In addition, mutants with resistance against the drugs in these proposed targets should not be cross-resistant to drugs used in second line regimens. This last attribute is extremely important in order not to compromise the use of potential new drugs in this target profile or in those proposed for *rifampicin-resistant TB*.

- The projected *cost of the new regimen* (finished product) should be compatible with wide access.

4.3 CRITICAL ASSUMPTIONS

One critical assumption is that a regimen candidate will consist of a combination of drugs that eliminate all populations of bacilli in the patient and thereby assure durable, relapse-free cure. As such, the drugs comprising the TB regimen are likely to need both bactericidal activity and a sterilizing effect, and should effectively target all bacilli populations in various lesion types.

Another critical assumption is that the candidate TB regimen is efficacious in all patients. A regimen that is identified to have high efficacy, adherence, tolerability and safety in a small subset of patient phenotypes will not be considered adequate, even if it meets some of the priority attributes described in this target regimen profile for TB treatment.

4.4. Summary tables of proposed regimen attributes with potential targets for rifampicin-susceptible TB treatment

4.4.1. Priority attributes for rifampicin-susceptible TB treatment regimens

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper and quicker global health impact*	Annotations *For all parameters, included here is the rationale for why this feature is important and/or for the target value*
Indication	The regimen is indicated for patients (regardless of HIV infection status) with active TB caused by rifampicin-susceptible *M. tuberculosis* strains, or in whom there is a low likelihood of resistance to commonly used first line TB drugs.	The regimen is indicated for patients (regardless of HIV infection status) with active TB caused by rifampicin-susceptible *M. tuberculosis* strains, including monoresistance to any drug except rifampicin.	INH-monoresistance is common worldwide. A TB regimen that is equally effective against both rifampicin-susceptible strains and strains that are monoresistant to any drug except rifampicin would be ideal. Operationally, the regimen would be used in patients in whom there is a *low likelihood of resistance*, or in whom susceptibility to rifampicin is confirmed by a rapid molecular test such as Xpert MTB/Rif (without additional susceptibility testing).
Efficacy	A regimen of four months or less with efficacy not inferior to the current standard of care six-month regimen for drug-susceptible TB.	A regimen of two months or less with efficacy not inferior to current standard of care six-month regimen for drug-susceptible TB.	Durable cure is defined as relapse-free cure 12 months after treatment completion. The targets provided take into consideration the efficacy of the current six-month standard regimen for DS-TB under trial conditions (approximately 95%). (Note: "not inferior" is used in place of "non-inferiority," which is a trials design and methodology term).
Safety and Tolerability	Incidence and severity of adverse events no worse than for standard of care. No more than monthly clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes etc.).	Incidence and severity of adverse events better than for standard of care. No active clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes, etc.).	The current standard six-month regimen for TB has known safety issues with each of the component drugs, most notably hepatoxicity *(21)*. In the PaMZ[5] Phase 2B trial, Grade 3 or 4 treatment-emergent adverse events in the HRZE[6] control arm were 25%. Discontinuation due to treatment-emergent adverse events in the HRZE control was 12% *(22)*. In the REMox trial, Grade 3 or 4 AEs in the HRZE arm were approximately 20% overall *(23)*.

[5] PaMZ (pretomanid, moxifloxacin and pyrazinamide) is a novel multi-drug TB treatment currently undergoing clinical testing in the new regimen development paradigm. Further information at: http://www.tballiance.org/portfolio/regimen/pamz

[6] HRZE (Isoniazid + Rifampin + Pyrazinamide + Ethambutol).

4.4.1. Priority attributes for rifampicin-susceptible TB treatment regimens (*cont.*)

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper and quicker global health impact*	Annotations *For all parameters, included here is the rationale for why this feature is important and/or for the target value*
Drug-drug interaction (DDI) and metabolism	Ability to use safely without active laboratory testing or monitoring with: • First-line antiretroviral therapy (ART) regimen(s) • Rifamycins (if a rifamycin is included in the regimen) • Drugs that induce or inhibit P450 liver enzymes • Proarrhythmic drugs that prolong QT/QTc interval.	*No dose adjustment* with other medications and ability to use safely without active laboratory testing or monitoring with: • First-line ART regimens and co-trimoxazole • Rifamycins (if a rifamycin is included in the regimen) • Drugs that induce or inhibit P450 liver enzymes • Proarrhythmic drugs that prolong QT/QTc interval.	ART regimens may include drugs that are substrates of P450 or other metabolizing enzymes or that inhibit or induce P450 enzymes. For the minimal target, dose adjustment of component drug(s) may be needed to manage DDI. Such adjustments would require that dose size/formulations are readily available. For the optimal target, no dose adjustments are needed, including for HIV therapies, allowing for standardization of regimen across populations. Regulatory guidance on QT/QTc prolongation in non-antiarrhythmic drugs is available (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073153.pdf). Regimen developers should be mindful that certain drugs increase the risk of QT/QTc prolongation and, where feasible, regimens combining several of these should be avoided.
Barrier to emergence of drug resistance (propensity to develop resistance, generation of cross-resistance)	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than $1/10^7$ mutations/ bacterium/ generation. New resistance to one or more drugs in the regimen emerges in **less** than 1% of treatment courses when taken as prescribed and when no pre-existing resistance to the drugs in the regimen exists.	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than $1/10^9$ mutations/ bacterium/ generation. Essentially no acquired resistance (<0.01%) when regimen is taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.	Drugs included in this target regimen profile should protect each other against emergence of resistance. In addition, resistance to the drugs included in this proposed target should be non-existent, and mutants with resistance against these drugs should not be cross-resistant to drugs used in 'second line regimens'. This last attribute is extremely important in order not to compromise the use of potential new drugs. The minimal target is based on an acquired resistance rate of 0-2% when five effective drugs are used in the WHO-recommended regimen. The optimal target is based on expert consensus. Frequency of resistance to antibiotics used in MTb *(24)*: Rifampin $2.25x10^{-12}$ Isoniazid $2.56x10^{-8}$ Ethambutol 10^{-7}

4.4.1. Priority attributes for rifampicin-susceptible TB treatment regimens (*cont.*)

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper and quicker global health impact*	Annotations *For all parameters, included here is the rationale for why this feature is important and/or for the target value*
Target Population	All age groups, irrespective of HIV status.	All age groups, irrespective of HIV status.	Pharmacokinetic and safety studies in children will be needed in both minimal and optimal scenarios, but efficacy trials in this population are not necessarily required. TB regimen developers should consider initiating paediatric studies when a drug shows promising efficacy and safety in phase 2A adult trials *(25)*.
Formulation Dosage and Route of Administration	Formulation to be oral for all drugs in regimen, including paediatrics.	Formulation to be oral, fixed dose combination (FDC) and without a need for weight adjustment. Paediatric (oral), and IV formulations must also be available.	FDC is optimal to facilitate implementation across TB programmes, community settings, and private practitioners. IV formulations should be reserved for cases of severe forms of disease, such as central nervous system (CNS) TB or TB sepsis. Alternative routes or formulations offering substantially greater efficacy or convenience may be considered.

4.4.2. Desirable attributes for rifampicin-susceptible TB treatment regimens

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Pill Burden	6 pills per day or fewer.	As FDC, 3 pills per day or fewer.	Additional considerations include but are not limited to the size of pills and the availability of water-dispersible pills.
Dosing frequency	Once or twice daily.	Preferably once a day, and with no specific food requirements.	If a regimen is to be intermittent, it should retain priority attributes while being administered highly intermittently (e.g. once weekly). More frequent dosing (e.g. twice a day) can be considered if it allows for significant reductions in duration of treatment, improvements in safety and tolerability, or other substantial improvements that would offset the challenges associated with dosing more than once daily.
Duration of treatment in extrapulmonary disease	Extension of treatment for extrapulmonary disease comparable to current standard of care.	No extension of treatment needed specifically for extrapulmonary disease, including CNS TB.	
Stability / Shelf Life	Heat, humidity and light stable, with shelf life for all drugs greater than or equal to six months. No cold chain needed.	Heat, humidity and light stable, with shelf life for all drugs greater than or equal to 60 months. No cold chain needed.	Current therapies have at least 24 months of stability.
Target Countries	Global.	Global.	Optimally, directly observed therapy (DOT) will not be necessary for a new regimen that fulfils or exceeds these proposed attributes, and which in addition is not burdening for the patient and/or the system.

4.4.2. Desirable attributes for rifampicin-susceptible TB treatment regimens (*cont.*)

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Product Registration Path	WHO GRADE evidence review for the regimen. Each individual drug component of the regimen OR the new regimen should be approved by at least one stringent regulatory authority (SRA) for use in humans to treat TB.	WHO GRADE evidence review for the regimen. Each individual drug component of the regimen OR the new regimen should be approved by at least one SRA for use in humans to treat TB.	The standard regulatory path for a *regimen* is currently not defined and the strategy might depend on which drugs are included in a regimen. Key sets of regulatory and product documentation must be readily available for any component of the regimen to countries that would perform expedited registration. This would require that new regimens be introduced as a comprehensive package including guidance on use and 'how-to' tools, and an entire set of all regulatory and product documentation required for a standard registration.
Cost of regimen	Projected cost of regimen (finished product) in new regimen should be compatible with wide access.	Projected cost of regimen (finished product) in new regimen should be compatible with wide access.	Access to essential medicines is part of the right to the highest attainable standard of health ("the right to health") and is well founded in international law. Economic factors affecting price, demand and availability of the regimens will depend on many factors, including but not limited to how well the new regimens meet or surpass the attributes as described herein (efficacy, safety, adherence etc.). An improved regimen may provide advantages in other costs to programmes/patients by being shorter in duration, and/or better tolerated, and/or requiring minimal to no monitoring, etc. This would reduce non-drug costs in aspects such as monitoring, visits, handling of adverse events/toxicity, etc.

4.4.3. Additional variables of intetest for rifampicin-susceptible TB treatment regimens

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Special Populations	For women of child bearing potential and pregnant women, there should be a favourable foetal risk profile, based on preclinical data. Inclusion of patients with co-morbidities, including HIV patients on ART.	For women of child bearing potential and pregnant women, human data do not indicate that the component drugs increase the overall risk of structural abnormalities, and the drugs are safe with breastfeeding. Inclusion of patients with co-morbidities, including HIV patients on ART; diabetes; renal disease; alcoholism; illicit drug use; opioid replacement therapy; and viral hepatitis.	WHO recommended first-line ART regimens for TB patients receiving rifampicin-based regimens are those that contain efavirenz (EFV), since interactions with anti-TB drugs are minimal. In several cohort studies, ART with standard-dose efavirenz and two nucleosides was well tolerated and highly efficacious in achieving complete viral suppression among patients receiving concomitant rifampicin-based TB treatment *(26)*.
Population/Segment unlikely to be treated	End-stage renal or hepatic disease.	None.	End-stage renal and liver disease may require significant adjustments in dose and frequency of administration, and may increase the need for clinical and laboratory monitoring. It would be desirable, however, for the optimal TB regimen still to still be usable in patients with severe renal or hepatic disease.
Treatment adherence risks	Regimens should be easy to take and should be able to be administered with minimum support for majority of patients.	Self-administration is feasible in all populations.	To maximize completion of therapy, current TB treatment guidelines recommend the use of a broad range of patient-centred care and case management strategies, including education, incentives, enablers, and DOT (widely used as the standard of practice in many TB programmes). For the minimal target, the majority of patients in this new regimen should be able to complete therapy with minimum support, with only selected populations requiring DOT among other labour- or cost-intensive activities. For the optimal target, all populations should be able to complete therapy via self-administration, without need for DOT or other complex interventions.
Need for DST	A single, rapid molecular rifampicin-susceptibility test.	A single, rapid molecular rifampicin-susceptibility test.	The TB regimen can be used in settings in which there is a low likelihood of rifampicin-resistant TB. Where molecular diagnostic tests are available, a single, rapid molecular rifampicin-susceptibility test will suffice.

5. TARGET REGIMEN PROFILE FOR RIFAMPICIN-RESISTANT TB

5.1 MEDICAL NEED

There is a substantial medical need to develop regimens to treat rifampicin-resistant TB strains (regimens designed to treat rifampicin-resistant TB are referred to as 'MDR-TB regimens' for the purposes of this document). About 480 000 new cases of MDR-TB, which is defined as TB resistant to at least rifampicin and isoniazid, are estimated to occur each year. In 2014, however, only 111 000 MDR-TB patients were reported by countries to have been started on second-line treatment regimens designed to treat MDR-TB *(27)*. The conformity of these regimens to those recommended by WHO and the quality of medicines used is commonly unknown; additionally, an alarming concern is that only about half the patients treated globally are reported to finish treatment successfully *(27)*.

While there is an urgent need to scale up treatment programmes, efforts to do this are severely hampered by financial, political, logistical and technical obstacles *(28)*. Perhaps the biggest barrier to scale-up stems from the poor characteristics of currently recommended conventional MDR-TB regimens. With current drugs, MDR-TB treatment is lengthy, complex, ineffective, poorly tolerated, toxic (with significant serious adverse events) and expensive. The current conventional WHO-recommended regimen for treating MDR-TB typically has a total duration of 20 months and requires at least five medicines to be given concomitantly, including an injectable agent given daily for 6-8 months. In a meta-analysis of individual patient data from over 9000 patients receiving treatment for pulmonary MDR-TB worldwide, treatment success was reported in only 54% of them, while 23% were lost to follow up, 15% died, and treatment failed in 8% *(29)*. In addition, MDR-TB is very costly to treat and manage. A conventional standard 24-month treatment course can cost between 1,000 and 4,400 United States dollars (USD) per patient, even when drugs are procured through the Global Drug Facility (GDF) *(30)*. Additionally, direct costs such as clinical management, laboratory tests and hospitalization can be up to 14 times higher than the cost of the regimen itself, and increase as resistance patterns expand *(31)*.

Treatment of MDR-TB is further complicated by the emergence of resistance to a number of current second-line drugs (such as fluoroquinolones) and the second-line injectable agents (aminoglycosides, capreomycin). Resistance to these as well as to rifampicin and INH defines extensively drug resistant TB, or XDR-TB *(32)*.

There are currently 23 different agents on the market to treat MDR-TB (Table 1). Drugs used in the present WHO-recommended MDR regimen are very toxic (as demonstrated in the five-country report by Nathanson et al *(33)*), which contributes to low cure rates and high treatment default rates (Table 2).

The development of new regimens for MDR-TB coincides with the larger global approach to containment of antimicrobial resistance (AMR). The 2001 WHO global strategy for the containment of AMR provides a framework for slowing the emergence and reducing the spread of new AMR, with one of its key components being to foster innovation in new drugs and vaccines *(34)*. The targeted development of new regimens for MDR-TB is directly aligned with the framework for containing AMR, and especially to the targets outlined in the variables 'barriers to resistance' and 'treatment adherence risks'. Regimen development and subsequent use of new regimens should always occur under the principles of good antimicrobial stewardship *(35, 36)*. Antimicrobial stewardship is defined as:

> *...the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance. (37, 38)*

Accurate and available diagnostics, including DST, are crucial elements in tailored, effective MDR-TB regimens. As new anti-TB drugs such as bedaquiline and delamanid are introduced, resistance to these drugs will inevitably emerge, and new diagnostics will be needed to test for that resistance. Rapid molecular tests like Xpert MTB/RIF have already been developed and are being deployed worldwide to test for rifampicin resistance. Whole genome sequencing (WGS) is also showing promise in its ability to reveal the genetic basis of resistance in new TB drugs *(39)*; the development of WGS as a diagnostic tool could prove enormously helpful in designing novel drugs and regimens. As new regimens are developed, emphasis should be placed on also developing the appropriate diagnostics, ideally for use at point of care and appropriate for all contexts in which TB is present.

Table 1: Medicines recommended fo the treatment of rifampicin-resistant and multidrug-resistant TB[1]

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)[3]	Am Cm Km (S)
C. Other core second-line agents		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide Ethambutol High-dose isoniazid	Z E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	p-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)

[1]This regrouping is intended to guide the design of conventional regimens; for shorter regimens lasting 9-12 months the composition is usually standardised
[2]Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations)
[3]Refer to the text for the conditions under which streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistant TB (XDR-TB)
[4]Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin
[5]HIV-status must be tested and confirmed to be negative before thioacetazone is started

Note: List extracted from WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. October 2016 revision *(40)*

The conventional or longer treatment proposed by WHO is the result of expert opinion based on observational studies *(1)* rather than the result of properly planned and conducted randomized controlled trials, and there has been no head-to-head comparison of any kind of one MDR regimen (consisting of a specific drug regimen) versus another *(5, 9, 41)*. As a consequence, the available evidence to inform clinicians on the optimal use of current anti-TB drugs in a regimen is generally of low or very low quality.

The two new TB drugs, bedaquiline (approved in 2013 by the FDA and in 2014 by the EMA) *(42, 43)* and delamanid (approved in 2014 by the EMA) *(44)* have been recommended by WHO for use in MDR-TB under strict conditions (45, 46). They show real potential to improve MDR regimens, but the only available evidence is on their use on top of the conventional WHO-recommended regimen. Some new drugs currently in the drug development pipeline (e.g. PA-824, SQ109, and sutezolid) show promise for use in MDR regimens (Figure 3). In addition, some existing drugs not yet licensed for the treatment of MDR-TB (such as linezolid, clofazimine, and fluoroquinolones) are already being used to treat it.

An additional argument for the urgent need for new treatment regimens for MDR-TB is that the complexity and lack of efficacy of present regimens mean they are predisposed to the development of additional resistance (47) and will limit future treatment options for both patients and populations. A delay in improving MDR regimens will result in circulating strains that may only be susceptible to the new TB drugs. This, in turn, could accelerate amplification of resistance to the new TB drugs if regimens are used with an insufficient number of companion drugs to treat highly resistant strains.

Lastly, there is an urgent need to lower the cost of MDR regimens. It is expected that a new, optimally designed (shorter, safer and more efficacious) regimen will add significant value to the current standard of care and lower costs, as it would require less supervision, patient support, intramuscular injections and monitoring. Furthermore, and perhaps of greatest value, a more effective and user friendly MDR regimen is likely to be much easier to scale up, allowing a significant increase in the number of patients with MDR-TB who are receiving effective regimens. There is plenty of room to prove a new MDR regimen to be superior in cost effectiveness when compared to the 20-month standard WHO MDR regimen, as the 20-month regimen was considered cost effective even despite its low cure rate and significant side effects *(48)*.

5.2. INTENDED USE CASE SCENARIO

As mentioned earlier (see introduction), a practical approach is taken that posits that expanded scale-up and access to Xpert MTB/RIF under programmatic conditions will allow categorisation of patients at diagnosis as either susceptible or resistant to rifampicin. Thus, the regimen for rifampicin-resistant TB is intended for patients infected with rifampicin-resistant or MDR strains, whether or not those strains are resistant to the other oral first-line drugs isoniazid, pyrazinamide and ethambutol, or to key second-line drug groups including the fluoroquinolones and injectable agents (XDR-TB).

The intended use case scenario for rifampicin-resistant TB is thus built on the practical basis that the only DST needed to include the patient on the regimen is for rifampicin. With time, it is expected that cheap, rapid, point of care DST for other drugs would expand a similar strategy to further refine the patients' needs, allowing more detailed insight into the resistance profile of the strains responsible for their disease.
In the intended use case scenario, the preferred (optimal) rifampicin-resistant TB regimen should:

- Contain four or fewer effective drugs, each from a different drug class;

- Be used in patients of all ages diagnosed with rifampicin-resistant TB (i.e. suitable in children and adults);

- Be adaptable, affordable and available for patients in low and middle income countries;

- Have medicines that may be prescribed in decentralized settings;

- Have an exclusively oral delivery and simple dosing schedule (preferably once daily dosing with no food restrictions as a minimal in the optimal case; additional desirable dosing scheduling characteristics include the ability to dose intermittently, or to put the regimen drugs in a fixed-dose combination);

- Have parenteral formulations of medicines in the regimen for when oral administration is not possible;

- Be effective against pulmonary and extrapulmonary rifampicin-resistant TB, including meningitis;

- Include drugs that have no cold storage requirements and have shelf lives longer than three years;

- Include monitoring for efficacy through monthly smears and cultures;

- Require no active safety monitoring such as blood tests, electrocardiograms or audiometry, except when indicated by clinical events;

Table 2: Rates of adverse events in the WHO-recommended MDR-TB regimen

Event	*Number affected (%) (n = 818 patients)*
Nausea/vomiting	268 (32.8)
Diarrhea	173 (21.1)
Arthralgia	134 (16.4)
Dizziness/vertigo	117 (14.3)
Hearing disturbances	98 (12.0)
Headache	96 (11.7)
Sleep disturbances	95 (11.6)
Electrolyte disturbances	94 (11.5)
Abdominal pain	88 (10.8)
Anorexia	75 (9.2)
Gastritis	70 (8.6)
Peripheral neuropathy	65 (7.9)
Depression	51 (6.2)
Tinnitus	42 (5.1)
Allergic reaction	42 (5.1)
Rash	38 (4.6)
Visual disturbances	36 (4.4)
Seizures	33 (4.0)
Hypothyroidism	29 (3.5)
Psychosis	28 (3.4)
Hepatitis	18 (2.2)
Renal failure/nephrotoxicity	9 (1.1)
Arrhythmias	Not determined
QT prolongation	Not determined

- Work in a wide range of patients with co-morbidities, including HIV, and have minimal or no DDIs. Specifically, with:
    - ART
    - Drugs metabolized by P450 liver enzymes
    - Proarythmic QT prolonging drugs;

- Be simple to implement and include in the operational setting where drug susceptible TB is treated. This includes countrywide national TB programmes along with most primary care clinics and private settings that have capacity to manage drug susceptible TB. The new MDR regimen should allow for easy implementation in community-based and home-based models of care. In addition the new MDR-TB regimens should be as easy, or easier, to implement as drug-susceptible TB regimens for new TB patients;

- Allow for easy administration and high patient acceptance, to ensure good adherence to therapy. DOT or other acceptable digital technology equivalent *(49)* is expected to be part of early implementation of the regimen until operational research can support the use of self-administration;

- Have an overall duration that is in the order of the current drug-susceptible TB treatment—i.e. six months or preferably much less;

- Result in low patient support costs related to ancillary support of monitoring and management of adverse effects, DOT, social and economic patient support, health care staff, etc., on par with the standard of care of the six month first-line regimen.

5.3 CRITICAL ASSUMPTIONS

A critical assumption is that the candidate regimen will consist of a minimum combination of drugs that target all possible populations of bacilli in the patient (i.e. bacilli that are proliferating in local acidic conditions as well as bacilli that are in states of brief sporadic metabolism or replication). These drugs will also have a clear sterilizing effect, enabling a non-relapsing cure within a few months of start of treatment. It is expected that an optimal rifampicin-resistant TB regimen will function like the six-month rifampicin-based regimen for drug-susceptible TB, and rifampicin-resistant TB patients will respond whether or not they have already received a TB treatment.

An additional assumption is that as the efficacy of drugs included in the regimens increases, the total number of drugs that comprises a regimen can decrease. This should minimize the probability of DDIs or drug toxicities and increase the ability to co-formulate the individual drugs into fixed dose combinations. It is also assumed that the new regimen candidates will be readily accepted by national TB programmes, because they will be easier to implement and will fit readily into structures already in place to manage TB.

Strategies to lower regimen costs should be considered from the onset of regimen studies, and the access to medicine principles should be followed. Once a new regimen is established as superior in terms of safety or efficacy, then stakeholders should work to bring down the cost of the regimen by working on costs of individual drugs, as well increasing the demand for the new regimen. Finally, it is assumed that within a few years of release, the production for supply of the drugs in the new MDR regimen could be rapidly scaled up to match demand, with corresponding decreases in price.

5.4. Summary tables of proposed regimen attributes with potential targets for rifampicin-resistant TB treatment

5.4.1. Priority attributes for rifampicin-resistant TB treatment regimens

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Indication	The *rifampicin-resistant TB* regimen is indicated for patients infected with rifampicin-resistant strains (including MDR-TB). Indication may be contingent upon additional resistance to existing first or second line drugs, and supported by appropriate DST.	The *rifampicin-resistant TB* regimen is indicated for all patients infected with *rifampicin-resistant TB* strains, with usage consistent with principles of good antibiotic stewardship.	Drug susceptibility for the minimal target would be assessed via individual DST at the start of therapy, or through information determined via drug resistance surveys. For both the minimal and optimal cases, DST to the drugs in the regimen will have to be established. Resistance will inevitably emerge for any regimen, and DST may be needed at the start of treatment to diagnose the resistance pattern to determine whether a particular regimen is indicated. Furthermore, DST will be needed for monitoring amplification of resistance in an individual patient, and monitoring resistance prevalence in a population.
Efficacy (Probability of durable cure)	Efficacy (bacteriologic cure without relapse in at least one-year follow up, among patients who are not lost to follow up) should be not inferior to the WHO recommended standard of care for MDR-TB *(29)*.	Efficacy should be greater than 90%.	Suggested definitions of favourable and unfavourable outcomes can be found in a paper by Furin et al *(50)*. At present the standard of care consists of the shorter MDR-TB treatment regimen under specific conditions of eligibility, and the longer WHO-recommended regimen for those not fulfilling eligibility criteria for the shorter MDR-TB regimen. The optimal case is based on estimated efficacy observed in a study on a short MDR regimen in Bangladesh *(51)*, and regimens for drug-susceptible TB.

5.4.1. Priority attributes for rifampicin-resistant TB treatment regimens (*cont.*)

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Safety	Serious adverse events (SAEs) no more than 5%, and treatment discontinuation due to treatment emergent adverse events (TEAEs) no more than 2.5%. The QT prolongation and proarrhythmic effects of the regimen would not put the patient at a moderate or high risk of arrhythmias or sudden death.	SAEs are no more than 2%, and treatment discontinuation due to TEAEs no more than 2%. The regimen would have no or insignificant QT prolongation or proarrhythmic effects.	Consensus from stakeholders is that a new MDR regimen must significantly improve on the high rates of toxicity (e.g. renal failure and hearing loss) associated with the current standard of care MDR regimen. The SAE and TEAE cutoffs were informed by the range of adverse events seen in a number of pivotal TB trials *(5, 41, 51-53)* and set by expert opinion and stakeholder consensus. For the minimal case, safety in respect to QT prolongation, a regimen should not put the patient at risk to the degree that a stringent regulatory authority would be unlikely to approve the regimen. The optimal target assumes that post-market surveillance demonstrates significant confidence that there are no rare serious side effects of the medicine.
Duration of treatment	6-12 months.	Less than or equal to six months.	The minimal should significantly improve on the duration of the conventional 20-month MDR regimen. The recent WHO recommendation that a shorter MDR-TB regimen of 9-12 months may be used instead of a conventional regimen (typically 20 months or more) informed the minimal target in terms of duration. The optimal target was set to be equal to or less than the length of treatment of the WHO-recommended drug-susceptible TB regimen of six months. Three recent "duration shortening TB trials" demonstrated the challenges in shortening the first-line therapy to less than six months. All three trials were unsuccessful in demonstrating non-inferiority, demonstrating that the optimal target of six months or less for *rifampicin-resistant TB* is ambitious. A regimen providing a sustainable cure with a duration of six months or less is likely to have radically different pharmacokinetic/ pharmacodynamic properties influencing drug efficacy.

5.4.1. Priority attributes for rifampicin-resistant TB treatment regimens (*cont.*)

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Drug-drug interactions and metabolism	Ability to adjust dosing or perform safe monitoring for DDIs with: • At least one first-line ART regimen • Drugs that induce or inhibit P450 liver enzymes • Proarrhythmic QT prolonging drugs.	No dose adjustment with other medications and ability to use safely without active laboratory monitoring with: • ART regimens and co-trimoxizole • Drugs that induce or inhibit P450 liver enzymes • Proarrhythmic QT prolonging drugs.	ART regimens may include drugs that are substrates of P450 or other metabolizing enzymes (e.g. dolutegravir, UGT1A1 and CYP3A) or which inhibit or induce P450 enzymes (e.g. efavirenz, CYP2B6; ritonavir, CYP3A). The minimal target allows for mitigation of DDI through dose adjustment of the TB or the HIV drug(s), provided dose size/ formulations are available to achieve this. For the optimal target no dose adjustments are required regardless of HIV status or concomitant drugs, allowing for standardization of the regimen across populations. Regulatory guidance on QT/QTc prolongation in non-antiarrhythmic drugs is available (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073153.pdf). Regimen developers should be mindful that certain drugs increase the risk of QT/QTc prolongation and, where feasible, regimens combining several of these should be avoided.
Clinical monitoring for drug toxicity	Active drug safety monitoring may consist of regular laboratory tests (e.g. liver function test and complete blood counts).	No active drug safety monitoring that consists of laboratory tests is needed for the monitoring of therapy. No ECG monitoring of QT interval required.	No renal monitoring, electrolyte monitoring or audiometry for minimal case scenario. This assumes any new *rifampicin-resistant TB* regimen would be free of nephrotoxic and ototoxic drugs.
Barrier to emergence of drug resistance (propensity to develop resistance, generation of cross-resistance)	New resistance to one or more drugs in the regimen emerges in fewer than 2% of treatment courses when taken as prescribed and when no pre-existing resistance to the drugs in the regimen exists.	Essentially no acquired resistance (<0.1%) when regimen is taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.	The minimal target is based on an acquired resistance rate of 0-2% when five effective drugs are used in the WHO-recommended regimen *(47)*. The optimal target is based on expert consensus.
Target Population	Adolescents (age 12-19) and adults.	All age groups, irrespective of severity of disease, pulmonary or extrapulmonary status, or HIV status.	Pharmacokinetic and safety studies in children are compulsory, but efficacy trials in this population are not necessarily required in early stages of regimen development.

5.4.2. Desirable attributes for rifampicin-resistant TB treatment regimens

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point.*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value.*
Number of component drugs	Six or fewer.	Four or fewer.	The minimal requirement is based on the current short MDR-TB regimen being an effective seven-drug regimen. The optimal requirement is based on the drug-susceptible regimen being an effective four-drug regimen.
Formulation Dosage and Route of Administration	Formulation to be oral for all drugs in regimen, including paediatric.	Formulation to be oral. FDC formulations available (desirable to have no weight adjustment for adults). Paediatric (oral), and IV formulations must also be available.	FDC is optimal in order to facilitate implementation across TB programmes, community settings, private practitioners, etc. IV formulations should be reserved for cases of severe forms of disease, such as CNS TB or TB sepsis. Alternative routes or formulations may be considered that offer substantially greater efficacy or convenience.
Pill burden	Fewer than 10 pills a day for a 55kg adult patient.	Not more than four pills a day for adults. Potential for one pill daily (using fixed dose combinations with three to four medications).	The minimal target is based on WHO-recommended regimen.
Dosing (incl. schedule)	Twice daily and manageable food restrictions.	Once daily or intermittent. (Preference for once weekly or once monthly as the intermittency.)	
Stability / Shelf life	Three years for all drugs in the regimen. No cold chain requirements.	Five years for all drugs in the regimen. No cold chain requirements.	

5.4.2. Desirable attributes for rifampicin-resistant TB treatment regimens (*cont.*)

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point.*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value.*
Target Countries	Global.	Global.	Regimens must work in TB high burden countries and countries with limited resources.
Primary Target Delivery Channel	For use in national TB programmes through decentralized care (hospitalization not required).	For use in national TB programmes, primary care health care facilities, and in the private sector through decentralized care (hospitalization not required).	
Cost of regimens	Projected cost of new regimen (finished product) should be compatible with wide access.	Projected cost of new regimen (finished product) should be compatible with wide access.	Access to essential medicines is part of the right to the highest attainable standard of health ("the right to health") and is well-founded in international law. Economic factors affecting price, demand and availability of the regimens will depend on many factors, including but not limited to how well the new regimens meet or surpass the attributes described herein (efficacy, safety, adherence etc.). An improved regimen may provide advantages in other costs to programmes/patients by being shorter in duration, and/or better tolerated, and/or requiring minimal to no monitoring, etc. This would reduce non-drug costs for aspects such as monitoring, visits, handling of adverse events/toxicity etc.

5.4.3. Additional variables of intetest for rifampicin-resistant TB treatment regimens

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Special Populations	Adults and women of childbearing potential. Increased acceptable risk (benefits outweigh the risk in most cases) for pregnant women, paediatrics, and those with significant renal or hepatic disease. Inclusions of patients with co-morbidities including: HIV, diabetes, alcoholism and viral hepatitis.	Adults, paediatrics, women of childbearing potential, pregnant women. Ability to use the regimen in patients with significant renal or hepatic disease. Inclusions of patients with co-morbidities including: HIV, diabetes, alcoholism, viral hepatitis and opiate addiction.	
Population/Segment unlikely to be treated	Patients with severe end-stage renal or hepatic disease.	None.	End-stage renal and liver disease may require significant adjustments in dose and frequency of administration, and may increase the need for clinical and laboratory monitoring. It would be desirable, however, for the optimal TB regimen still to be usable in patients with severe renal or hepatic disease.
Treatment adherence risks (robustness to non-adherence)	Can be self-administered in most populations. High barrier to resistance; generation of cross-resistance less than current standard of care regimen.	Can be self-administered in most populations. High barrier to resistance; generation of cross-resistance less than current standard of care regimen.	

6. TARGET REGIMEN PROFILE FOR PAN-TB TREATMENT

6.1 MEDICAL NEED

TB treatment would be revolutionized by a highly effective, safe, well-tolerated 3-4 drug oral regimen that could be administered to any patient with active TB. These drugs would need to be simple to administer, ideally once daily, and would have minimal DDIs with each other and with other drugs that are often co-administered, such as antiretrovirals. These novel drugs, for which minimal prior natural or man-made resistance would be known to exist, could be prescribed without knowledge of the patient's drug resistance profile. Availability of one set of drugs that would treat all patients with pulmonary TB would be expected to greatly reduce the complexity of programmatic treatment, and potentially increase the effectiveness of delivery systems.

Currently, several compounds with novel mechanisms of action or improved pharmacologic profiles are entering clinical development, and it is expected that combination of these agents with each other or with existing agents will form the foundation of a pan-TB regimen that would treat all current forms of TB (including rifampicin-susceptible and rifampicin-resistant TB, and forms with additional resistances to current first-line and second line drugs). Rifampicin, isoniazid, and pyrazinamide would therefore be excluded from the pan-TB regimen.

According to WHO, rapid drug susceptibility testing (i.e. Xpert MTB/RIF) of rifampicin is recommended in adults and children over conventional testing or no testing of people with presumptive TB (in resource limited settings, priority should be given to patients with presumptive MDR-TB). In patients with confirmed rifampicin resistance, the availability of reliable and rapid tests for fluoroquinolones and second-line injectable drugs (in the absence of other rapid DST) would be valuable in helping decide within a few days which patients would be eligible for the new shorter MDR-TB regimens, and what modifications to conventional MDR-TB regimens would be necessary based on resistance detected *(40)*. Nonetheless, it is recognised that, in settings where laboratory-based DST to fluoroquinolones or injectable agents is not available, treatment decisions would need to be guided by the likelihood of resistance to these medicines, informed by the patient's clinical history and recent representative surveillance data. In such settings and for clinical situations in which urgent empirical treatment for TB is needed, a pan-TB regimen would be particularly useful. For example, in settings where rifampicin resistance is common and rifampicin DST is not yet scaled up, patients with rifampicin-resistant TB may currently be underdiagnosed and inappropriately treated, and so may continue to transmit disease.

A pan-TB regimen would also offer benefits over current standard of care to patients with rifampicin-susceptible TB disease, and at a minimum would confer no new disadvantage compared to current standard therapy. The development of a regimen that is no worse than standard of care for rifampicin-susceptible TB with respect to safety and tolerability, that can be used with ART, and which can be given to all patients without the need for formal rifampicin DST (the minimum profile) would have particular value in these settings.

Lastly, an affordable regimen with improved safety and shorter duration compared to the current standard of care, as described in the optimal scenario, would be preferred worldwide over the use of separate rifampicin-susceptible and rifampicin-resistant regimens, and would eliminate the delay to treatment that can occur following diagnosis of TB.

6.2 INTENDED USE CASE SCENARIO

6.2.1 Assumptions

The intended use case assumes that this simple, novel regimen is simultaneously studied and approved for use in both rifampicin-susceptible and rifampicin-resistant TB patients with bacilli strains susceptible to the new drugs (defined as new chemical entities or drugs that have not been used extensively in the treatment of TB). The novel regimen would be used empirically so that treatment could begin without delay. This would be particularly important in areas with high prevalence of MDR-TB and low availability of DST, where patients may currently be treated inappropriately and may continue to transmit disease for extended periods.

Availability and use of TB diagnostics and treatment resources differ considerably between and within countries, and include private health providers as well as nationally supported TB treatment programmes. Looking forward five years, this heterogeneity is likely to remain. This use case assumes the patient presents to, or has been referred to, a national TB treatment clinic/provider where diagnostic testing (for primary or reflex testing) and new drug regimens are available.

The use case also assumes that resistance has not yet developed to the new drugs to any significant level, or to drugs that would confer cross-resistance to the new drugs, and that emergence of resistance to the components of the new regimen will be slow (measured with surveillance and DST).

6.3. Summary tables of proposed regimen attributes with potential targets for pan-TB treatment

Goal: An oral regimen composed of three or four novel antibiotics that will efficiently cure all patients with active TB, regardless of pre-existing resistance to rifampicin, while minimizing the emergence of drug resistance.

6.3.1. Priority attributes for pan-TB treatment regimens

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point.*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value.*
Indication	Drug regimen indicated as first-line treatment for pulmonary TB without the requirement for determining rifampicin resistance.	Drug regimen indicated as first-line treatment for pulmonary TB without the requirement for determining rifampicin resistance.	Clinical trials in extrapulmonary disease are not anticipated, although regimen may be adopted for this use.
Target Population	Adults and children, irrespective of HIV status.	Adults and children, irrespective of HIV status.	Pharmacokinetic and safety studies in children will be needed in both minimal and optimal scenarios, but efficacy trials in this population will not necessarily be required.
Efficacy	Not inferior to *rifampicin-susceptible TB* standard of care in a six-month regimen.	Not inferior to *rifampicin-susceptible TB* standard of care in regimen of four months or less.	Efficacy of current HRZE regimen is reported to be as high as ~95% in clinical trial conditions.
Safety and Tolerability	Incidence and severity of adverse events no worse than for standard of care. No more than monthly clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes etc.).	Incidence and severity of adverse events better than for standard of care. No active clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes, etc.). No ECG monitoring of QT interval required.	The current standard six-month regimen for TB has known safety issues with each of the component drugs, most notably hepatoxicity *(21)*. In the PaMZ Phase 2B trial, Grade 3 or 4 treatment-emergent adverse events in the HRZE control arm were 25%. Discontinuation due to treatment-emergent adverse events in the HRZE control was 12% *(22)*. In the REMox trial, Grade 3 or 4 AEs in the HRZE arm were approximately 20% overall *(23)*.

6.3.1. Priority attributes for pan-TB treatment regimens (*cont.*)

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point.*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value.*
Drug-Drug Interactions and Metabolism	• Ability to adjust dosing or perform safe monitoring for DDIs with: o At least one first-line ART regimen o Drugs that induce or inhibit P450 liver enzymes o Proarrhythmic QT prolonging drugs.	• No dose adjustment with other medications. • Ability to use safely, without monitoring through active laboratory tests, with: o ART regimens and co-trimoxizole o Drugs that induce or inhibit P450 liver enzymes o Proarrhythmic QT prolonging drugs.	ART regimens may include drugs that are substrates of P450 or other metabolizing enzymes (e.g. dolutegravir, UGT1A1 and CYP3A) or which inhibit or induce P450 enzymes (e.g. efavirenz, CYP2B6; ritonavir, CYP3A). The minimal target allows for mitigation of DDI through dose adjustment of the TB or the HIV drug(s), provided dose size/formulations are available to achieve this. For the optimal target, no dose adjustments are required, regardless of HIV status or companion drugs, allowing for standardization of the regimen across populations.
Barrier to emergence of drug resistance (propensity to develop resistance, generation of cross-resistance)	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than $1/10^7$ mutations/ bacterium/ generation. New resistance to one or more drugs in the regimen emerges in fewer than 2% of treatment courses when taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than $1/10^9$ mutations/ bacterium/ generation. Essentially no acquired resistance (<0.1%) when regimen is taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.	To provide a high barrier to resistance, the frequency of spontaneous resistance to the regimen must be lower than the bacterial burden in the patient. Moreover, resistance rates should be balanced such that one component is not more vulnerable than the others. The minimal target is based on an acquired resistance rate of 0-2% when five effective drugs are used in the WHO-recommended regimen *(47)*. The optimal target is based on expert consensus.

6.3.2. Desirable attributes for pan-TB treatment regimens

Variable	Minimal *The minimal target should be considered as a potential go/no go decision point*	Optimal *The optimal target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Formulation Dosage and Route of Administration	Oral, once daily. Containing ≤4 novel antibacterial compounds; ≤ 1 solid oral dosage form/ drug/ day. All components of regimen given no more than once daily for up to six months. Individual solid oral dosage form for each component of the regimen packaged in blister packs and HDPE (high density polyethylene) bottles.	Oral, once daily, no special weight banding. Containing ≤3 novel antibacterial compounds; two of three or all components of the regimen in a fixed dose combination no larger than a prenatal vitamin oral tablet (i.e. size 00 capsule). All components of regimen given no more than once daily for up to four months. Packaged in blister packs and HDPE bottles.	Oral, once daily is preferable. However, if duration of treatment can be substantially reduced, a twice-daily administration may be acceptable provided that a missed dose does not increase resistance or decrease efficacy. To optimize compliance, ease of use, delivery and stocking, a fixed dose combination product is desired. FDC is optimal to facilitate implementation across TB programmes, community settings, and private practitioners. Blister packs and HDPE bottles are needed to serve different regions and health care settings. Consider scored tablets for adolescents. To meet regulatory requirements to demonstrate safety in children, a paediatric granule formulation or powdered/ reconstituted suspension or dispersible tablet used with ≤ 60mL of liquid should be available.
Stability / Shelf Life	Stable for ≥ 3 years in climate zones 3 and 4 at 30°C / 75%RH.	Stable > 5 years in climate zones 3 and 4 at 30°C / 75% RH.	
Target Countries	Global.	Global.	Regions with high prevalence of rifampicin-resistant TB and low availability of DST may be prioritized.

REFERENCES

1. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update (http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf, accessed 15 March 2015). 2011.

2. Hughes J, Isaakidis P, Andries A, Mansoor H, Cox V, Meintjes G, et al. Linezolid for multidrug-resistant tuberculosis in HIV-infected and -uninfected patients. Eur Respir J. 2015;46(1):271-4.

3. Tiberi S, Payen MC, Sotgiu G, D'Ambrosio L, Alarcon Guizado V, Alffenaar JW, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016;47(4):1235-43.

4. Lienhardt C, Raviglione M, Spigelman M, Hafner R, Jaramillo E, Hoelscher M, et al. New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future. J Infect Dis. 2012;205 Suppl 2:S241-9.

5. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J. 2013;41(6):1393-400.

6. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012;366(23):2151-60.

7. Pym AS, Diacon AH, Tang SJ, Conradie F, Danilovits M, Chuchottaworn C, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J. 2016;47(2):564-74.

8. Zumla A, Chakaya J, Centis R, D'Ambrosio L, Mwaba P, Bates M, et al. Tuberculosis treatment and management--an update on treatment regimens, trials, new drugs, and adjunct therapies. Lancet Respir Med. 2015;3(3):220-34.

9. Nunn AJ, Rusen ID, Van Deun A, Torrea G, Phillips PP, Chiang CY, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials. 2014;15:353.

10. Working Group on New TB Drugs. Drug pipeline 2016 [Available from: http://www.newtbdrugs.org/pipeline.php.

11. Ramachandran G, Swaminathan S. Safety and tolerability profile of second-line anti-tuberculosis medications. Drug safety. 2015;38(3):253-69.

12. Semvua HH, Kibiki GS, Kisanga ER, Boeree MJ, Burger DM, Aarnoutse R. Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource-limited settings. Therapeutic drug monitoring. 2015;37(1):22-32.

13. Gao J, Ma Y, Du J, Zhu G, Tan S, Fu Y, et al. Later emergence of acquired drug resistance and its effect on treatment outcome in patients treated with Standard Short-Course Chemotherapy for tuberculosis. BMC Pulm Med. 2016;16:26.

14. Cegielski JP, Dalton T, Yagui M, Wattanaamornkiet W, Volchenkov GV, Via LE, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. Clinical Infectious Diseases. 2014;59(8):1049-63.

15. Vasakova M. Challenges of antituberculosis treatment in patients with difficult clinical conditions. The clinical respiratory journal. 2015;9(2):143-52.

16. Food, Administration D. Guidance for industry and review staff: target product profile-a strategic development process tool. Rockville, MD. 2007.

17. Helmer-Hirschberg O. Analysis of the future: The delphi method. 1967.

18. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - ICH Harmonized Tripartite Guideline. Post-approval safety data management: Definitions and standards for expedited reporting (e2d). 2003.

19. Gospodarevskaya E, Tulloch O, Bunga C, Ferdous S, Jonas A, Islam S, et al. Patient costs during tuberculosis treatment in Bangladesh and Tanzania: the potential of shorter regimens. Int J Tuberc Lung Dis. 2014;18(7):810-7.

20. Menzies D, Benedetti A, Paydar A, Royce S, Madhukar P, Burman W, et al. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. PLoS Med. 2009;6(9):e1000150.

21. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf. 2006;5(2):231-49.

22. Dawson R, Diacon AH, Everitt D, van Niekerk C, Donald PR, Burger DA, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. Lancet. 2015;385(9979):1738-47.

23. Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med. 2014;371(17):1577-87.

24. David HL. Probability distribution of drug-resistant mutants in unselected populations of Mycobacterium tuberculosis. Appl Microbiol. 1970;20(5):810-4.

25. Nachman S, Ahmed A, Amanullah F, Becerra MC, Botgros R, Brigden G, et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. The Lancet Infectious Diseases. 2015;15(6):711-20.

26. World Health Organization (WHO). The use of antiretroviral drugs for treating and preventing HIV infection. Geneva: WHO. 2013.

27. World Health Organization. Global tuberculosis report 2015 Geneva: 2015 (WHO/HTM/TB/2015.22 http://www.who.int/tb/publications/global_report/en/, accessed 12 November 2015). 2015.

28. Brigden G, Nyang'wa B-T, du Cros P, Varaine F, Hughes J, Rich M, et al. Principles for designing future regimens for multidrug-resistant tuberculosis. Bulletin of the World Health Organization. 2014;92(1):68-74.

29. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300.

30. Médecins Sans Frontières (MSF). DR-TB Drugs Under the Microscope: 4th edition. 2016.

31. Marks SM, Flood J, Seaworth B, Hirsch-Moverman Y, Armstrong L, Mase S, et al. Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005-2007. Emerg Infect Dis. 2014;20(5):812-21.

32. World Health Organization (WHO). Drug-resistant TB: XDR-TB FAQ. 2006.

33. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis. 2004;8(11):1382-4.

34. Organization WH. WHO global strategy for containment of antimicrobial resistance. 2001.

35. U.S. Food and Drug Administration. Guidance for Industry. Antibacterial therapies for patients with unmet medical need for the treatment of serious bacterial diseases. (Accessible at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM359184.pdf). 2013.

36. File TM, Jr., Srinivasan A, Bartlett JG. Antimicrobial stewardship: importance for patient and public health. Clin Infect Dis. 2014;59 Suppl 3:S93-6.

37. Gerding DN. The search for good antimicrobial stewardship. The Joint Commission Journal on Quality and Patient Safety. 2001;27(8):403-4.

38. Doron S, Davidson LE, editors. Antimicrobial stewardship. Mayo Clinic Proceedings; 2011: Elsevier.

39. Köser CU, Javid B, Liddell K, Ellington MJ, Feuerriegel S, Niemann S, et al. Drug-resistance mechanisms and tuberculosis drugs. Lancet. 2015;385(9965):305.

40. World Health Organization (WHO). WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. WHO, Geneva 2016. 2016.

41. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371(8):723-32.

42. United States Food and Drug Administration. FDA news release. 31 December 2012 (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm accessed on 15 March 2015). 2012.

43. European Medicines Agency (EMA). European Medicines Agency recommends approval of a new medicine for multidrug-resistant tuberculosis. 2013.

44. European Medicines Agency - Committee for Medicinal Products for Human Use (CHMP). Assessment report, Deltyba, Procedure No.: EMEA/H/C/002552. 2013.

45. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf, accessed 10 September 2015).

46. World Health Organization (WHO). The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. 2014.

47. Cegielski JP, Kurbatova E, van der Walt M, Brand J, Ershova J, Tupasi T, et al. Multidrug-resistant tuberculosis treatment outcomes in relation to treatment and initial versus aquired scond-line drug resistance. Clin Infect Dis. 2015.

48. Suárez PG, Floyd K, Portocarrero J, Alarcón E, Rapiti E, Ramos G, et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. The Lancet. 2002;359(9322):1980-9.

49. Story A, Garfein RS, Hayward A, Rusovich V, Dadu A, Soltan V, et al. Monitoring Therapy Compliance of Tuberculosis Patients by using Video-Enabled Electronic Devices. Emerg Infect Dis. 2016;22(3):538-40.

50. Furin J, Alirol E, Allen E, Fielding K, Merle C, Abubakar I, et al. Drug-resistant tuberculosis clinical trials: proposed core research definitions in adults. Int J Tuberc Lung Dis. 2016;20(3):290-4.

51. Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014;18(10):1180-7.

52. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet. 2004;364(9441):1244-51.

53. Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. New England Journal of Medicine. 2014;371(17):1588-98.

9 789241 511339