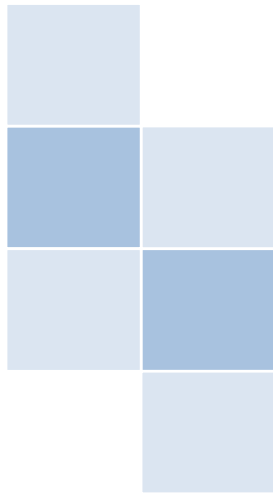# Target Regimen Profiles for TB Treatment

Candidates: Rifampicin-susceptible, Rifampicin-resistant and Pan-TB treatment regimens

World Health Organization

THE
END TB
STRATEGY

Target Regimen Profiles for TB Treatment

Candidates: Rifampicin-susceptible, Rifampicin-resistant and Pan-TB treatment regimens

Contents

Abbreviations

ART	antiretroviral therapy
ARV	antiretrovirals
CNS	central nervous system
DDI	drug-drug interaction (s)
DALY	disability-adjusted life year
DOT	Directly Observed Treatment
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FDC	fixed-dose combination tablets
GDF	Global Drug Facility
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
MDR-TB	multidrug-resistant tuberculosis
OBR	optimized background regimen
PDP	product development partnership
PK/PD	pharmacokinetics/pharmacodynamics
PMDT	programmatic management of drug-resistant tuberculosis
SAE	serious adverse event
SRA	stringent regulatory authority
TAG	technical advisory group
TEAE	treatment-emergent adverse event
TB	tuberculosis
TPP	Target Product Profile
TRP(s)	Target Regimen Profile (s) for TB treatment
WGS	whole genome sequencing
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Acknowledgements

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- TRPs) intends to assist drug regimen developers towards important features and align these with patient and programmatic needs at country level. The proposed TRPs, which are based on prioritized characteristics, encompass the needs of end-users, care providers and policy-makers to have shorter, less toxic, and operationally feasible regimens.

The novelty of the TRP approach is to have the goal of a treatment regimen in mind very early in the process of drug development. Based on the idea that TB drug research and development (R&D) is moving towards developing and testing TB regimens rather than individual drugs, a set of targets is needed based on prioritized characteristics and representing the needs of end users. Aimed at the pharmaceutical industry, research institutions, product development partnerships, donors, non-governmental organizations (NGOs) and civil society organizations (CSOs), TRPs align targets and specifications for developers with the view of achieving shorter, less toxic, operationally feasible and cheaper regimens.

Since Xpert MTB/RIF test is being promoted, scaled-up and increasingly used in most countries where TB is a major problem, it is expected that it will be most widely used in the near future to diagnose TB and give indication on whether the bacilli are rifampicin-resistant or not. For this reason– and based on Xpert availability –TRPs have been developed for rifampicin-susceptible and rifampicin-resistant treatment regimens. However, in countries where Xpert MTB/RIF is not yet scaled-up or in hard-to-reach areas, a third TRP would be required for a drug regimen that can be used in any situation, ie a 'pan-TB' regimen, based solely on new drugs, in order to be able to kill all bacilli, regardless of resistance type. The specific attributes and target criteria of these 3 TRPs are presented in this document.

1. Introduction

1.1. Background

Treatment of tuberculosis relies on several bactericidal and sterilising drugs administered in combination for an adequate duration of time to ensure diversity and synergy of action needed to achieve durable cure and prevent the selection of drug-resistant mutants (1, 2). Current treatment regimens are, however, unsatisfactory, due to low efficacy, toxicity, duration and cost – as in the conventional treatment of MDR-TB – or interaction with other drugs – as is the case with rifampicin and some antiretrovirals (ARVs). Further, 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). 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 6 and 20 months, respectively) (5, 6). For the first time in decades, two new TB drugs have recently become available – bedaquiline and delamanid - and are recommended by the World Health Organization (WHO) for the treatment of drug-resistant TB under certain conditions (7, 8). However, these drugs have been tested for efficacy as add-on to conventional WHO recommended treatment in MDR-TB, and their optimal use in combinations that would lead to increased treatment efficacy while improving safety, toxicity and reducing treatment duration still remains to be established[1] (9). Other novel compounds are in clinical trials currently, as well as some re-purposed drugs, either as part of set treatment regimens or in addition to standard regimens (10).

The development of new TB drugs is lengthy and costly. Currently, for the development of efficacious combination regimens, if new drugs are added to 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 for treatment of tuberculosis (5). Developing a novel regimen without going through intermediary steps to obtain individual drug approvals separately and only then beginning to test novel combinations and regimens would substantially reduce the duration of the regimen development pathway as well as the expenditures needed to make significant progress in the field (11). It is therefore highly desirable that combination regimens including one or several promising new drugs with current and/or repurposed drugs be tested early in the clinical development phase so as to identify early optimal combination regimens for the treatment of DS and DR-TB that should be tested in Phase II and III trials.

Development of shorter and simpler regimens combining new and existing drugs requires detailed information on their respective safety and toxicity (12, 13), as well as on their potential for drug-drug interactions (14), their propensity for development of drug resistance while on therapy (15, 16) and their use in specific patient populations (such as persons with HIV/AIDS, pregnant women and children). The development of **Target Product Profiles (TPPs)** is being proposed to allow the identification of desired product attributes or priorities to be considered during the product development process. Expanding on this, the determination of TPPs for TB *treatment regimens* is expected to guide the development process towards important treatment regimen characteristics and is intended to assist regimen developers to align the performance and operational characteristics of new TB treatment regimens to the programmatic needs at country level. TPP elements are usually chosen based on *expert consensus*, but no formal framework exists for identifying and prioritizing the components of future TB treatment regimens that could most likely determine their patient- and population-level impact. At a minimum, the TPPs for TB treatment regimens should specify the clinical indication of the regimen, the goal to be met and 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, TPPs should outline the *most important performance*

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[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

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), and the likely set of users. The optimal and minimal characteristics define a range: it is therefore expected that products (TB treatment regimens) meet at least all of the required minimal characteristics, but preferably they would meet as many of the optimal characteristics as possible.

Considering the need for safer, simpler, more efficacious and accessible **treatment regimens** (i.e., combination therapy rather than individual drugs) for all forms of TB, TPPs for TB treatment - referred hereafter as ***Target Regimen Profiles for TB treatment (TRPs)*** – are being developed in a synergistic effort by the WHO/GTB and the WHO Task Force on New TB Drug Policy Development, in collaboration with the contribution of a large array of stakeholders.

1.2.   Objective and Target audience

The overall objective of the *Target Regimen Profiles for TB treatment* is to align the targets and specifications that developers should meet for the performance and operational characteristics of new TB treatment regimens with the needs of end-users. The target audience is composed of pharmaceutical industry, academia, research institutions, product development partnerships, NGOs, CSOs and donors.

1.3.   Methods

The WHO Task Force on New TB Drug Policy Development drafted the initial Target Regimen Profiles for TB treatment based on a series of activities, including a series of working expert meetings, an initial stakeholder survey, mathematical modelling, and the interview of a wide range of stakeholders. The initial TRPs were detailed and incorporated information about as many characteristics as possible.

1.3.1.   *Initial meetings to decide on draft outlines of the potential TRPs*

The process was initiated at a meeting of the WHO Task Force on Development of Policies for the introduction of new TB drugs in October 2015. The Task Force analysed the need and context for the development of TPPs and decided on a process including the various steps described below. A further meeting took place in Cape Town in December 2015 at which the baseline for modelling analyses was discussed. A Technical Advisory Group (TAG) was established to develop the initial drafts of the TPPs. It was composed of the members of the WHO Task Force, and representatives of the John Hopkins University, the TB Alliance, and the Bill & Melinda Gates Foundation. The TAG initially met in Geneva in February 2016, which was followed by a series of teleconference calls and consultations with various stakeholders.

1.3.2.   *The initial stakeholder's survey:*

An initial priority-setting exercise was conducted to identify the priority attributes the wide audience of stakeholders would value for the development of the TPPs. It was an Internet-based survey, containing 40 core questions distributed in four (4) main sessions (efficacy; safety; adherence; and operational considerations). Two Likert-type priority scales were used to determine how essential specific attributes (variables) were, and also to rank the level of importance of such attributes. Content validity, pre-test and test-retest reliability were used in order to evaluate comprehensiveness, clarity, and repeatability of the questionnaire.

The survey was distributed among 140 key stakeholders. Eighty-four stakeholders responded the survey (49.2% response rate), and 69 participants fully completing 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 the treatment of TB through shorter, simpler, more tolerable—and, in the case of drug-resistant TB, more effective—regimens that are more patient-friendly and can rapidly reduce the morbidity and mortality from TB with the hope of reducing transmission to control the epidemics. Individual treatment success rates, disease transmission, antimicrobial resistance, and operational factors may all affect a regimen's ability to fulfill this role. In order to appropriately prioritize different characteristics when constructing and evaluating new regimens, one should understand how those characteristics contribute to a regimen's population-level impact. Few tools currently exist to help prioritize different drug development targets from this epidemiologic perspective. Therefore, mathematical modelling was used to estimate the relative impact of various 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 the epidemiological situations (e.g. in India, South Africa, the Philippines, and Brazil). The introduction of various novel rifampicin-susceptible or rifampicin-resistant TB regimens was modelled. These regimens differed on six characteristics, identified in consultation with the WHO Task Force and external experts: (1) efficacy, (2) duration, (3) adherence, (4) medical contraindications, (5) barrier to resistance, and (6) baseline prevalence of resistance. These characteristics were chosen based on potential to guide drug development and ease of conceptualization, understanding that this list is not comprehensive. For each characteristic, a minimum acceptable value for a new regimen, an optimistic target, and an intermediate value were defined, based on literature review and expert consultation. 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 (rifampicin-susceptible and rifampicin-resistant TB, respectively) mortality, 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 total number of patient-months on treatment.

1.3.4. Development of draft TRPs

On the basis of a series of interviews with various experts, and the assessment of the modelling data on the relative impact of various regimen characteristics, and with the advice of a Technical Advisory Group, the WHO Task Force has developed initial draft TRPs with the view to guide the development process toward essential regimen characteristics.

The current diagnosis of TB relies on the results of smear microscopy, and, in case of suspicion of resistance, 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 the MDR and XDR-TB forms). Considering the increasing and sustainable scale-up of Xpert MTB/RIF in the world today (with currently 3763 Xpert machines being procured in 116 countries by the end of 2014, and 4.8 million Xpert MTB/RIF test cartridges being procured in 2014 alone compared to 550000 in 2011), and the prospects of availability of ambulatory battery-processed machines in the near future, the Task Force decided to adopt a very practical approach to the determination of the potential treatment

regimens based on Xpert MTB/RIF as a 'triage test' under wide programmatic conditions. On this basis, the diagnosis of TB is immediately linked with the information of whether the patient has a rifampicin-susceptible or rifampicin-resistant form of the disease. For that reason, the Task Force decided to develop TRPs for the treatment of *rifampicin-susceptible TB* (Rif-S) and for the treatment of *rifampicin-resistant TB* (Rif-R), as 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 the above diagnostic tool will remain unavailable and/or that no other reliable diagnostic test will exist at the point-of-care for the identification of drug-resistance, the Technical Advisory Group considered it appropriate to devise a TRP for '*pan-TB treatment*', that would be used empirically so that treatment may begin without delay. Such a novel pan-TB treatment would be simple to implement and use and be based on 3-4 entirely new TB antibiotics (i.e. excluding rifampicin, isoniazid, pyrazinamide) for which minimal or no resistance would exist as a result of prior use in the community.[2] 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 disease for extended periods. It was also thought that such a 'pan-TB' TRP could give a bold vision of where TB treatment could go in the future.

Of note, the above classification takes into consideration the fact that rifampicin remains a highly potent (and inexpensive) drug that is representing the first intention of treatment for more than 90% of TB worldwide (non DR), due to its unique combination of bactericidal and sterilizing activities, making it still a major component of TB therapy.

These draft TRPs 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 (PDPs) (e.g. Global TB Alliance), as well as donors.

1.3.5. Delphi consultation and consensus meeting

In addition to the consultative process that was carried out during the preparation of the TRPs, it was considered important to bring these to a larger stakeholder audience, including further drug developers, clinicians, implementers and representatives of countries and national TB programmes, before they were finalized. To this aim, a Delphi-like process was used to facilitate consensus building (17). The shortened TRPs was sent to all invited participants with invitation to provide a statement on how much they agree with each of the proposed characteristics for each of the TRPs. Agreement was scored on a Likert scale ranging from 1 to 5 (1-fully disagree, 2-mostly disagree, 3-don't agree or disagree, 4-mostly agree, 5-fully agree). Individuals were asked to provide comments in support of their score (particularly when they will not agree with a statement - that is, when they score a characteristic at 3 or lower).

A consensus-gathering meeting was organized in July 2016 by the WHO/Global TB Programme. The meeting built further consensus around the three high priority TRPs, the intended use of the regimens and their performance and operational characteristics. Participants will be 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.

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[2] Then, whichever rapid tests of drug-resistance might be developed/available, they would suitably come as a complement to further refine the patients' needs given the resistance profile.

2. Instructions for use

The current document is divided in three (3) sections containing information about each Target Regimen Profile, i.e. rifampicin-susceptible; rifampicin-resistant; and 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 that list the detail of the various attributes of the regimens with relevant appropriate targets.

These summary tables capture the minimum and optimistic characteristics for the candidate regimen to be developed. The minimum requirements column provides instructions detailing the minimal targets that go beyond the current standard of care and 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 optimistic requirements include a set of performance and use characteristics of an 'ideal' product for which the global health impact should be broader and deeper, and potentially quicker. For each of these, an 'Annotations' column provides the rationale supporting the minimum and optimistic targets for each attribute.

In developing the tables, it appeared that certain attributes should be considered as 'priority' (minimum must be met in view of a 'go/no-go' decision), whereas others could be considered for potential trade-offs (i.e. 'nice to have', but not part of the go/no go decision, as reaching these targets should be coming in addition to meeting those for priority attributes); these are defined as 'desirable'. For example, if a regimen were designed that had significant improvements in tolerability or efficacy, it may justify a trade off in another area, such as number of drugs in the regimen.

Additional variables of interest are provided, that should be considered during the drug-development process.

This document lays out in a simple way the lowest level of acceptable performance and use characteristics for anti-TB treatment regimens. It is expected that the formulation of these criteria provides a baseline for developing candidates well suited for implementation for optimal treatment of TB.

3. Common areas of understanding / Cross-cutting issues

The TRPs detailed below present a series of attributes that are considered essential for novel treatments of TB, such as efficacy of treatment, safety, toxicity, drug-drug interactions, potential of acquisition of drug resistance, costs, etc. It must be acknowledged, however, that satisfying all of these characteristics in a single regimen might be difficult to achieve in the short term, and regimen developers might have to face trade-offs: for example, increasing efficacy (cure rates) or safety *vs.* shortening treatment duration, or making regimens simple and well tolerated *vs.* making them more complex and robust to emergence of drug resistance. For these reasons, the various attributes listed below have been classified as either "priority" or "desirable" and for each of these, both minimum or optimal targets have been indicated. In any case, developers should exert their judgement in the assessment of the relative merits of satisfying key requirements, and be open to consider that trade-offs may apply to within the priority attributes as well, for example in case of a major advance in one priority attribute of a magnitude significant enough to allow additional flexibility on other priority attributes.

It should be understood that, for an infectious disease such as TB with large global burden and ongoing person-to-person transmission, the efficacy of the new regimens will depend heavily on operational factors that also affect a regimen's ability to fulfil its role. It will also depend closely on

background antimicrobial resistance, especially the community resistance to existing repurposed drugs (such as fluoroquinolones), or the resistance in the MDR TB patient population to important existing TB drugs (like PZA), or 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 TRPs 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' and 'treatment emergent adverse events' are used in criteria to assess the safety of anti-TB drugs (18). Throughout this document, we use the following definitions: a serious adverse event (SAE) is an adverse event which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. A treatment emergent adverse event (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 study regimen should meet either WHO prequalification or certification from a stringent regulatory authority or be study drugs that are tested in a facility with Good Manufacturing Practice certification for quality assurance. It would be suitable that each individual drug component *or* the regimen as a whole be approved for use in TB by at least one stringent regulatory authority. If a regimen is recommended by the WHO using GRADE evidence review, it is expected that the regimen, or its individual components, 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 costs aspects (e.g. monitoring visits, adherence, patient support, safety aspects, etc.) thereby improving simplicity of use, and these benefits may offset increased drug costs. The Task Force considered that the price of medicines is determined by many factors, including production costs, margin to recover the development costs, and profit margin. Both margins highly depend on the volumes and the speed of product uptake. Nonetheless, in providing guidance as part of these TRPs, the Task Force opinion was that the price of new medicines could be higher at the beginning (and also cost of their procurement depending on the processes and sources), as long as overall cost of care (entire treatment) can be lower given all variables – eg DALYs, etc. In addition, it is expected that, as demand and volume increase, costs of new medicines would decrease. Shorter, more tolerable regimens meeting or exceeding the minimal priority attributes are likely to provide cost-savings in implementation, which can offset potential initially high drug costs.

The proposed TRPs should also include specific provisions to ensure that any resulting products are affordable and accessible in an equitable manner to patients who need them. The following principles will help ensure that the final regimens as outlined in this document fulfil these access criteria:

1) Ensure that public financing for research and innovation delivers a public return on the investment by linking such financing to public health-driven priority-setting and application of the core principles of affordability, effectiveness, efficiency and equity (identified in resolutions WHA66.22 and WHA 69.23[3] on the Follow-up of the Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG).[4]

2) Promote and support the development of new partnerships for R&D based on open collaborative models, allowing for earlier and easier regimen development. Models should ensure that the costs of research and development 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 target priority regimen profiles definition; promote

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

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 to recoup R&D costs within the life of the patent.

4. Target Regimen Profile for Rifampicin-Susceptible TB

4.1. Medical need

Despite the wide availability of a 90+% efficacious, low-cost, regimen of 6 months duration for the treatment of rifampicin susceptible tuberculosis (Rif-S-TB), improvements are still needed if we are to achieve the World Health Organization targets for the "End TB" Strategy - namely, reducing TB deaths by 95% and new cases by 90% between 2015 and 2035, in conjunction with ensuring that no family is burdened with catastrophic expenses due to TB. The current 6-month regimen has several limitations including drug-related adverse events, challenging drug-drug interactions (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 lowering risk for acquisition of resistance through improved adherence, recovering from illness faster with shorter period of lost productivity, shortening the period at risk for possible drug-related side effects, and lowering patient and program costs (19). Lastly, a key improvement on current Rif-S-TB regimens would be for future regimens to also have activity against strains that are monoresistant to any drug except rifampicin. For example, INH monoresistance is a very common, clinically relevant form of resistance worldwide - one for which there is not a readily scalable rapid diagnostic available. When treated with current standard regimens, INH monoresistance is associated with a 10% higher risk of failure, as compared to patients with pan-susceptible TB (20). A major advance for future RS-TB regimens would be to achieve high rates of relapse-free cure even taking into consideration strains that are monoresistant to any drug except rifampicin. Consequently, this TRP 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:

- The regimen duration is shortened to 2-4 months, while retaining an efficacy that is *not inferior* to the current standard of care 6-month regimen for drug-susceptible TB;

- The regimen is intended for patients infected with *rifampicin-susceptible M.Tb strains* but, optimally, would also be active against strains that are monoresistant to any drug other than rifampicin, such that the only drug susceptibility test (DST) needed to include the patient on the regimen is 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 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 will be effective against *all forms of DS-TB*, including pulmonary and extrapulmonary TB.

- The TB regimen should be simple to implement and be readily adopted by TB programmes without significant new resource needs. This includes 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 have shelf lives longer than three, or optimally five, years.

- The need for clinical monitoring for efficacy and safety is 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, others), and have low to no drug-drug interactions.

- Adherence to therapy is potentially high due to good tolerance and low complexity of the regimen. Subsequently, minimal support (including the need for directly observed therapy) is required to ensure full patient adherence and achieve target efficacy, as well as minimizing acquisition of drug resistance.

- Drugs included in this TRP should protect each other against emergence of resistance. In addition, mutants with resistance against the drugs of this TRP 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 TRP as well as in the TRP for rif-resistant TB.

- Projected cost of regimen (finished product) in new regimen should be compatible with wide access

4.3. Critical Assumptions

A 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 will likely need to have both bactericidal activity and a sterilizing effect, and will 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 TRP.

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

4.4.1. Priority attributes for rifampicin-susceptible TB treatment regimens

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimistic *The optimistic 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 TB 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 and 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 4 month or shorter regimen with efficacy not inferior to the current standard of care 6 month regimen for drug-susceptible TB.	A 2 month or shorter regimen with efficacy not inferior to the current standard of care 6 month regimen for drug-susceptible TB.	Durable cure is defined as relapse-free cure 12 months after end of treatment completion. The targets provided take into consideration the efficacy of the current 6-month standard regimen for DS-TB under trial conditions (approximately 95%). (Note: the term "not inferior" is intentionally 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 6 month regimen for tuberculosis has known safety issues with each of the component drugs, most notably hepatotoxicity (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).

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimistic *The optimistic 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 safely use without active laboratory testing or monitoring with: ● First-line 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 safely use without active laboratory tests 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 minimum 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 optimistic 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, regimen 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 $1/10$ exp7 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 $1/10$ exp9 mutations/bacterium/generation Essentially no acquired resistance (<0.01%) when regimen taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.	Drugs included in this TRP should protect each other against emergence of resistance. In addition, resistance to the drugs included in this TRP 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 minimum target is based on **an acquired** resistance rate of 0-2% when five effective drugs are used in the WHO-recommended regimen. The optimistic target is based on experts' consensus. Frequency of resistance to antibiotics used in MTb (24): Rifampin $\quad$ 2.25x10-12 Isoniazid $\quad$ 2.56x10-8 Ethambutol $\quad$ **10-7**

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimistic *The optimistic 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 minimum and optimistic 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, FDC and without a need for weight adjustment. Paediatric (oral), and IV formulations must also be available.	Fixed Drug Combination (FDC) is optimal to facilitate implementation across TB programmes, community settings, and private practitioners. I.V. formulations should be reserved in cases of severe forms of disease, such as 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	Minimum *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimistic *The optimistic 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 or less pills per day	As FDC, 3 or less pills per day	Additional considerations include the size of pills, the availability of water-dispersible pills, among others.
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 (i.e., once weekly). More frequent dosing (i.e., 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 more than once daily dosing.
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 greater than or equal to 36 month shelf life for all drugs. No cold chain needed.	Heat, humidity and light stable, with greater than or equal to 60 month shelf life for all drugs. No cold chain needed.	Current therapies have at least 24 months of stability.
Target Countries	Global	Global	Optimally, DOT will not be necessary and such an infrastructure will not need to be developed where it is currently absent.

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimistic *The optimistic 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 products documentation must be readily available for any component of the regimen to countries which would do the 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 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 programs/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 interest for rifampicin- susceptible TB treatment regimens

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point*	Optimistic *The optimistic 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, a favourable fetal risk profile, based on preclinical data

Inclusions 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. Inclusions of patients with co-morbidities including: HIV patients on HAART, diabetes, renal disease, alcoholism, illicit drug use, opioid replacement therapy, and viral hepatitis | The 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, as well as increase the need for clinical and laboratory monitoring. It would be desirable, however, for the optimal TB regimen, 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 directly observed therapy (DOT) - widely used as the standard of practice in many tuberculosis programmes. For the minimum target, the majority of patients 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 of 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 drug regimens to treat rifampicin-resistant TB strains (regimens designed to treat rifampicin-resistant TB are referred to as "MDR regimens" for the purpose of this document). About 480,000 new multidrug-resistant tuberculosis (MDR-TB; defined as tuberculosis resistant to at least rifampicin and isoniazid) cases are estimated to occur each year. However, in 2014, 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, and only about one half of patients treated globally is reported to finish treatment successfully (27).

While there is an urgent need to scale up treatment programmes, it is being severely hampered by financial, political, logistical and technical obstacles (28). Perhaps the biggest barrier to the scale-up stems from the poor characteristics of the currently recommended conventional MDR regimens. With current drugs, MDR treatment is lengthy, complex, ineffective, poorly tolerated, toxic (with significant serious adverse events) and expensive. The current conventional WHO-recommended regimen for treating MDR tuberculosis 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 MDR pulmonary tuberculosis 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 (e.g. clinical management; laboratory tests; hospitalization) can be up to fourteen times higher than the cost of the regimen itself, with costs increasing as resistance patterns expand (31).

Treatment of MDR-TB is further complicated with the emergence of resistance to a number of the second-line drugs currently available to treat MDR-TB – such as fluoroquinolones, and the second-line injectable agents (aminoglycosides, capreomycin), the addition of the two latter to rifampicin and INH resistance defining XDR-TB (32).

Presently, there are 23 different agents available 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 report in five countries from 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 strategy for 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 the key components being the fostering of 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, especially 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. 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 (35, 36).

Accurate and available diagnostics, including drug-susceptibility testing (DST), is a crucial element of designing a tailored, effective MDR-TB regimen. 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 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 the new TB drugs (37). 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 point of care and appropriate for all contexts where TB is present.

Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB[1]			
A. Fluoroquinolones[2]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
B. Second-line injectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[3]	(S)
C. Other core second-line agents		Ethionamide / Prothionamide	Eto / Pto
		Cycloserine / Terizidone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	H[h]
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	p-aminosalicylic acid	PAS
		Imipenem-cilastatin[4]	Ipm
		Meropenem[4]	Mpm
		Amoxicillin-clavulanate[4]	Amx-Clv
		(Thioacetazone)[5]	(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

Table 1.— Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB (Extracted from non-formatted WHO policy document approved by the WHO Guidelines Review Committee) (38).

Rates of Adverse Events in the WHO-recommended MDR 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

Table 2.—Rates of Adverse events observed in the WHO-recommended MDR Regimen (33)

The *conventional* or *longer* treatment proposed by the WHO is the result of expert opinion based on observational studies (1), rather than the results of properly planned and conducted randomized controlled trials, and there has been no head-to-head comparison of one MDR regimen (consisting of a specific drug regimen) versus another MDR regimen of any kind (5, 9, 39)[5]. As a consequence, the available evidence to inform clinicians on the use of current anti-TB drugs optimally in a regimen is generally of low or very low quality. The two new TB drugs, bedaquiline (approved in 2013 by the FDA and 2014 by EMA) (40, 41)and delamanid (approved in 2014 by EMA) (42) have been recommended by the WHO for use in MDR-TB under strict conditions (43, 44) and 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. In addition, some existing drugs not yet licensed for the treatment of MDR tuberculosis (such as linezolid, clofazimine, and fluoroquinolones) are already being used to treat MDR-TB.

An additional argument for the urgent need of new treatment regimens for MDR-TB is that the complexity and lack of efficacy of present regimens predisposes to the development of additional resistance (45) and will limit the 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 drug. This, in turn, could accelerate amplification of resistance to the new TB drugs if regimens are used with an insufficient of number of companion TB drugs to treat highly resistant strains.

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[5] Of note, a trial is currently underway to evaluate a short MDR regimen versus the 20-month WHO Standard.

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, IM injections and monitoring. Furthermore, and perhaps the biggest value, a more effective and user friendly MDR regimen will likely be much easier to scale up, allowing to increase significantly the number of patients with MDR-TB receiving effective regimens. There is plenty of room to prove a new MDR regimen to be superior in cost effectiveness compared to the 20-month standard WHO MDR regimen as even the 20-month MDR regimen was considered cost effective despite its low cure rate and significant side effects (46).

5.2. Intended Use Case Scenario

As mentioned earlier (*See Introduction*), a practical approach is taken that expanded scale-up and access to Xpert MTB/RIF under programmatic conditions will allow to categorise patients at diagnosis as either susceptible or resistant to rifampicin. Thus, the Rif-resistant (RR) regimen 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 aspects that the only drug susceptibility test (DST) needed to include the patient on the regimen is rifampicin. With time, it is expected that cheap, rapid, point of care DST tests for other drugs would expand a similar strategy to further refine the patients' needs, given the resistance profile of the strains responsible for their disease.

In the intended use case scenario, the preferred (optimistic) RR regimen should:

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

- be used in patients with RR-TB of all ages (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; the ability to dose intermittently or to put in the regimen drugs in a fixed-dose combination are additional desirable dosing scheduling characteristics),

- have parenteral formulations of medicines in the regimen for when oral administration is not possible,

- be effective against pulmonary and extrapulmonary RR-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,

- work in a wide range of patients with co-morbidities, including HIV, and have minimal or no drug-drug interactions. Specifically, no DDIs with:

  - ART

  - Drugs metabolized by P450 liver enzymes

  - Proarrythmic QT prolonging drugs

- be simple to implement and readily included in the operational setting where drug susceptible TB is treated. This includes country-wide national TB programmes along with most primary care clinics and private settings that have capacity to manage drugs-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 regimens should be as easy, or easier, to implement as DS-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 (47) is expected to be part of early implementation of the regimen until operational research can support the use of self-administration of the regimen,

- have an overall duration that is in the order of the current drug-susceptible TB treatment, six months or preferably much less,

- result in low patient support costs (ancillary support of monitoring and management of adverse effects, DOT, social and economic patient support and health care staff), 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) and that have a clear sterilizing effect so as to get a non-relapsing cure within a few months of start of treatment. It is expected that an optimal RR-TB regimen will function like the 6-month rifampicin-based DS-TB regimen, and RR-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 drug-drug interaction/drug toxicity and increase the ability to co-formulate the individual drugs into fixed dose combinations. It is also an assumption that the new regimen candidates will be readily accepted by national TB programmes because they will be easier to implement and will readily fit into the structures in place to manage TB.

Strategies to lower the regimen costs should be considered from the onset of regimen studies and the access to medicine principles are adhered to. Once a new regimen is established to be superior in terms of safety or efficacy, then stakeholders should continue to 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 a corresponding decrease in the price.

5.4. Summary Tables of proposed regimens' attributes with potential targets for rifampicin-resistant TB treatment

5.4.1. Priority attributes for rifampicin-resistant TB treatment regimens

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point*	Optimistic *The optimistic 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 RR regimen is indicated for patients infected with rifampicin resistant (including MDR) strains. Indication may be contingent upon additional resistance to existing first or second line drugs and supported by appropriate DST.	The RR regimen is indicated for all patients infected with RR-TB strains, with usage consistent with principles of good antibiotic stewardship.	Drug susceptibility for the minimum case would be assessed via individual DST at the start of therapy or through information determined via drug resistance surveys. For both the minimum 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 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 (bacteriologic cure without relapse in at least one-year follow up, among patients who are not lost to follow up) should be greater than 90%.	Suggested definitions of favourable and unfavourable outcomes can be found in a paper by Furin *et al* (48). At present the standard of care is the shorter MDR-TB treatment regimen under specific conditions of eligibility and the longer WHO recommended regimen, which is to be provided in those not fulfilling eligibility criteria for the shorter MDR-TB regimen. The optimistic case is based on estimated efficacy observed in a study on a short MDR Regimen in Bangladesh (49) and regimens for drug-susceptible TB.

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point*	Optimistic *The optimistic 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 the treatment emergent adverse events (TEAE) cutoffs were informed by the range of adverse events seen in a number of pivotal TB trials (5, 39, 49-51) and set by expert opinion and stakeholders consensus. For the minimal case, safety in respect to QT prolongation, a regimen should not put the patient at a risk to the degree that a stringent regulatory authority would likely not approve the regimen. The optimal target assumes that post-market surveillance demonstrates significant confidence there are no rare serious side effects of the medicine.
Duration of treatment	6-12 months	Less than or equal to 6 months	The minimum 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 minimum target in terms of duration. The optimistic target was set to be equal or less than the length of treatment of the WHO-recommended DS-TB regimen of 6 months. Three recent "duration shortening TB trials" demonstrated the challenges in shortening the first-line therapy less than 6 months. All three trials were not successful at demonstrating non-inferiority, which demonstrates the optimal target of 6 months or less for RR-TB is ambitious. A regimen with a sustainable cure with 6 months or less duration will likely have radically different pharmacokinetic–pharmacodynamic properties that influence drug efficacy.

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point*	Optimistic *The optimistic 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 safely use without active laboratory tests 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 that inhibit or induce P450 enzymes (e.g. efavirenz, CYP2B6; ritonavir, CYP3A). Minimum 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 optimistic target, no dose adjustments required, regardless of HIV status or concomitant drugs, 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, regimen 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 are 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 RR 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 taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.	The minimum target is based on an acquired resistance rate of 0-2% when five effective drugs are used in the WHO-recommended regimen (45). The optimistic target is based on experts' consensus.
Target Population	At least adolescent (age 12-19) and adults	All age groups, irrespective of severity of disease, pulmonary or extrapulmonary, or HIV status.	Pharmacokinetic and safety studies in children are compulsory, but efficacy trials in this population not necessarily required in early stages of regimen development.

5.4.2. Desirable attributes rifampicin- resistant TB treatment regimens

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Optimistic *The optimistic 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	6 or fewer	4 or fewer	Minimum is based on the current short MDR-TB regimen being an effective 7-drug regimen and optimum based on drug-susceptible regimen being an effective 4-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 to facilitate implementation across TB programmes, community settings, private practitioners. IV formulations should be reserved in cases of severe forms of disease, such as CNS TB or TB sepsis. Alternative routes or formulations offering substantially greater efficacy or convenience may be considered
Pill burden	Fewer than 10 pills a day for a 55 Kg adult patient	Not more than 4 pills a day for adults. Potential for one pill daily (using fixed dose combinations with three to four medications)	Minimum 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	3 years for all drugs in the regimen No cold chain requirements	5 Years for all drugs in the regimen No cold chain requirements	

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Optimistic *The optimistic 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 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 programs/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.

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point*	Optimistic *The optimistic 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, pediatrics, and those with significant renal or hepatic disease. Inclusions of patients with co-morbidities including: - HIV - Diabetes - Alcoholism - Viral hepatitis	Adults, pediatrics, 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 - 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, as well as increase the need for clinical and laboratory monitoring. It would be desirable, however, for the optimal TB regimen, to still 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

A highly effective, safe and well tolerated 3-4 drug oral regimen that could be administered to any patient with active tuberculosis would revolutionize treatment of TB. The drugs should be simple to administer, ideally once daily, and have minimal drug-drug interactions 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 is 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 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 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 (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 DSTs) would be valuable to 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 are necessary based on resistance detected (38). Nonetheless, it is recognised that, in settings in which laboratory capacity for 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 tuberculosis 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 be underdiagnosed, inappropriately treated and continue to transmit disease.

A pan-TB Regimen would also offer benefits over current standard of care to patients with rifampicin-sensitive disease and at a minimum confer no new disadvantage compared to current standard therapy. The development of a regimen that is no worse than standard of care for rifampicin-sensitive disease with respect to safety and tolerability, that can be used with ART, and 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 optimistic scenario, would be preferred worldwide over the use of separate rifampicin-sensitive and rifampicin-resistant regimens, and would eliminate the delay to treatment that may occur following diagnosis of TB.

6.2. Intended Use Case Scenario

6.2.1. Assumptions

The intended use case assumes this simple, novel regimen is simultaneously studied and approved for use in both rifampicin-sensitive and rifampicin-resistant patients with bacilli strains sensitive to the new drugs. The novel regimen would be used empirically so that treatment may begin without delay. This would be particularly important in areas with high prevalence of MDR and low availability of DST, where patients may be treated inappropriately and 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 programs. Looking forward 5 years, this heterogeneity will likely 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 would be available.

The use case also assumes that resistance has not yet developed to the new drugs (defined as new chemical entities or drugs that have not been used extensively in the treatment of TB) 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, DST).

6.3. Summary Tables of proposed regimens attributes with potential targets for pan-TB treatment

Goal: An oral regimen composed of 3 or 4 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	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Optimistic *The optimistic 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 minimum and optimistic scenarios, but efficacy trials in this population not necessarily required
Efficacy	Not inferior to Rifampicin-sensitive TB Standard of Care in a 6 month regimen.	Not inferior to Rifampicin-sensitive TB Standard of Care in a 4 month or shorter regimen.	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 6 month regimen for tuberculosis 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).

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Optimistic *The optimistic 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 safely use without active laboratory tests 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 that inhibit or induce P450 enzymes (e.g. efavirenz, CYP2B6; ritonavir, CYP3A). Minimum 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 optimistic target, no dose adjustments required, regardless of HIV status or companion drugs, allowing for standardization of 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 exp7 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 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 exp9 mutations/bacterium/generation Essentially no acquired resistance (<0.1%) when regimen 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 minimum target is based on an acquired resistance rate of 0-2% when five effective drugs are used in the WHO-recommended regimen (45). The optimistic target is based on experts' consensus.

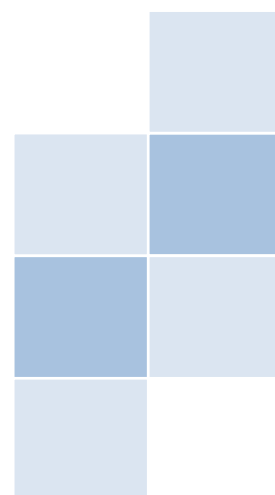### 6.3.2. Desirable attributes for pan-TB treatment regimens

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point*	Optimistic *The optimistic 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 6 months. Individual solid oral dosage form for each component of the regimen packaged in blister packs and HDPE 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 4 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 programs, 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 pediatric granule formulation or powdered/reconstituted suspension or dispersible tablet used with ≤ 60mLs of liquid should be available.
Stability / Shelf Life	Stable for ≥ 3 years in climate zones 3 and 4 at 30C / 75%RH.	Stable > 5 years in climate zones 3 and 4 at 30C / 75% RH.	
Target Countries	Global	Global	Regions with high prevalence of rifampicin-resistant TB and low availability of DST may be prioritized

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