Target regimen profiles for tuberculosis treatment

2023 update

World Health Organization

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Abbreviations and acronyms

BPaL	bedaquiline, pretomanid and linezolid
BPaLM	bedaquiline, pretomanid, linezolid and moxifloxacin
CSO	civil society organization
DS-TB	drug-susceptible tuberculosis
DST	drug susceptibility testing
EMA	European Medicines Agency
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FQ	fluoroquinolones
GEG	Guidance on evidence generation
HIV	human immunodeficiency virus
HRZE	isoniazid, rifampicin, pyrazinamide and ethambutol
M. tuberculosis	*Mycobacterium tuberculosis*
MDR/RR-TB	multidrug-resistant or rifampicin-resistant tuberculosis
MDR-TB	multidrug-resistant tuberculosis
MIC	minimum inhibitory concentration
NGO	nongovernmental organization
NTP	national tuberculosis programme
PK/PD	pharmacokinetic/pharmacodynamic
pre-XDR-TB	pre-extensively drug-resistant tuberculosis[1]
PTLD	post-tuberculosis lung disease
QoL	quality of life
R&D	research and development
RR-TB	rifampicin-resistant tuberculosis
RS-TB	rifampicin-susceptible tuberculosis
SOC	standard of care
SRA	stringent regulatory authority
STG	Scientific TRP Development Group
TB	tuberculosis
TPP	target product profile
TRP	target regimen profile
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis[2]

[1] Pre-XDR-TB: TB caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone.

[2] XDR-TB is TB caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone and at least one additional Group A drug.

Executive summary

There is an urgent need for simpler, shorter, safer and more effective treatment regimens for all forms of tuberculosis (TB) that are easily accessible to all patients in need. In 2016, the World Health Organization (WHO) developed the document *Target regimen profiles for TB treatment* (referred as target regimen profiles or TRPs).[3] The aim was to help the industry and drug-regimen developers to identify important regimen features and align these with patient and programmatic needs at country level. The TRPs were aimed at the pharmaceutical industry, research institutions, product development partnerships, donors, nongovernmental organizations and community based organizations, and were intended to stimulate the practice of "thinking regimens" as early as possible during the drug development process, to create regimens that were shorter, less toxic and more operationally accessible. The 2016 TRPs were constructed in the context of WHO recommending that diagnosis of TB should be done using molecular tests that also provide information on rifampicin resistance. Thus, separate TRPs were developed for the treatment of rifampicin-susceptible TB (RS-TB) and rifampicin-resistant TB (RR-TB), the latter being considered a proxy for multidrug-resistant TB (MDR-TB). In addition, a TRP was developed for pan-TB treatment, given 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.

In view of several ground-breaking advances in TB drug and regimen development over the past 5 years, WHO deemed it necessary to revise and update the TRPs produced in 2016. The process to update the TRPs included a critical review of the 2016 TRP document, a baseline drug and regimen landscape analysis, a stakeholder survey, modelling to estimate the impact and cost–effectiveness of novel TB treatment regimens, and a call for public comment on a draft document. A Scientific TRP Development Group (STG) was established to reflect and advise on the best definition of characteristics and targets throughout the process.

This 2023 update continues to present TRP tables for the categories of RS-TB, RR-TB and pan-TB TRP, as defined in 2016, using regimen characteristics that are largely similar but further harmonized and consolidated. One new characteristic was introduced – forgiveness of the regimen – which is defined as "the degree to which regimen efficacy is unaffected by suboptimal adherence". For each TRP, the regimen characteristics are described in specific tables that outline the suitable targets to be met, with the term "minimal" used to refer to the lowest acceptable output for a characteristic and "optimal" used to refer to the most favourable target that is a realistically achievable ideal target for that characteristic. The expectation is that regimens that are developed meet most of the minimal requirements, and as many of the optimal requirements as possible.

The TRPs detailed in this document present a series of characteristics that are considered essential for novel treatments of TB, such as efficacy, safety, toxicity, tolerability, duration, drug–drug interaction, forgiveness and propensity to develop drug resistance. Evidently, trade-offs can be made between these characteristics according to the respective weight they may have in decision-making at developmental or operational levels. Given these inherent trade-offs, assessments of the relative merits of satisfying various key TRP requirements will require judgement from developers and an ongoing conversation within the broader TB community (these trade-offs are discussed in a dedicated section of this document). Lastly, aspects that go beyond the direct requirements of a regimen group and pertain to all three TRPs are examined in a specific "cross-cutting" section. Among these aspects, this document suggests that developers consider providing the necessary information to allow for the

[3] Target regimen profiles for TB treatment. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/250044/9789241511339-eng.pdf?sequence=1&isAllowed=y).

development of suitable phenotypic or genotypic tests in parallel to drug development, to support the capacity for surveillance of pre-existing resistance or developing resistance to new medicines at population level and for providing guidance on individual patient care.

It is expected that developers following these proposed TRPs will ensure that any resulting product is quality-assured, affordable, widely available in a timely fashion, and supplied in sufficient quantities to meet the needs of affected populations. In terms of cost, developers should aim for new regimens and their component drugs to be cost-neutral overall (and possibly cost-saving) to the health programmes and systems, including both drug and nondrug costs. Many factors affect the price of medicines; for example, production costs, margins to recover development costs and profit margins, which in turn depend on the volume and speed of product uptake. Nevertheless, it is emphasized that profit margins should be modest and reasonable, given the wider and specific public health context. Altogether, there should be collective efforts to ensure accelerated development, commercialization and scale-up of affordable regimens satisfying the criteria laid out in these TRPs.

1. Introduction

1.1 Background

The development of target product profiles (TPPs) enables early identification of desired product characteristics. These characteristics are considered and prioritized during the product development process, with the product considered in this document being treatment regimen. The TPPs are developed through a series of interactive document reviews and consensus seeking, keeping in mind the objectives of the product to be developed and its usability and utility for the end-user. On this basis, the aim of developing target regimen profiles (TRPs) for treatment of tuberculosis (TB) is to stimulate "thinking about regimens" rather than about individual drugs as early as possible during the drug development process. To this end, the World Health Organization (WHO) developed the first TRPs for TB treatment in 2016 *(1)*; these TRPs described the targets and specifications that developers should consider for new TB treatment regimens, given the needs of end-users and programmes at country level. The landscape of drugs and regimens has changed dramatically since 2016 and improved regimens have become available; however, further advancements are urgently needed and thus an update of the TRPs was required.

TRPs specify the main characteristics of new treatment regimens. For each of these characteristics, requirements are defined and provided as either:

- "minimal" – the lowest acceptable output for a characteristic; or
- "optimal" – the most favourable, realistically achievable target.

These definitions are detailed in Table 1.1. The expectation is that any regimens that are developed will meet most of the minimal requirements, and as many of the optimal requirements as possible. Where a regimen does not meet minimal or optimal requirements, WHO would still review data on such a regimen; however, falling short of the requirements may reduce uptake of a new regimen.

Table 1.1. TRP terminology

Term	Definition
Characteristic	Specific attribute or specification that is measurable.
Minimal requirement	For a specific characteristic, refers to the lowest acceptable output for that characteristic. For clarification, regimens should generally meet the "minimal" characteristics in order to be acceptable.
Optimal requirement	For a specific characteristic, provides the "most favourable" output for that characteristic that is believed to be realistically achievable. Meeting the "optimal" characteristics will provide the greatest impact for end-users, clinicians and patients. Developers would ideally design and develop their solutions to meet the "optimal" requirements.

TRP: target regimen profile.

To complement the TRPs, WHO is developing guidance on evidence generation (GEG) on new TB treatment regimens. This TRP document describes *what* the minimal and optimal requirements for each regimen characteristic are, whereas the GEG will provide more detailed guidance on *how* the achievements of these requirements could or should be measured in clinical trials or other studies, from the perspective of evidence needed to inform WHO policy-making.

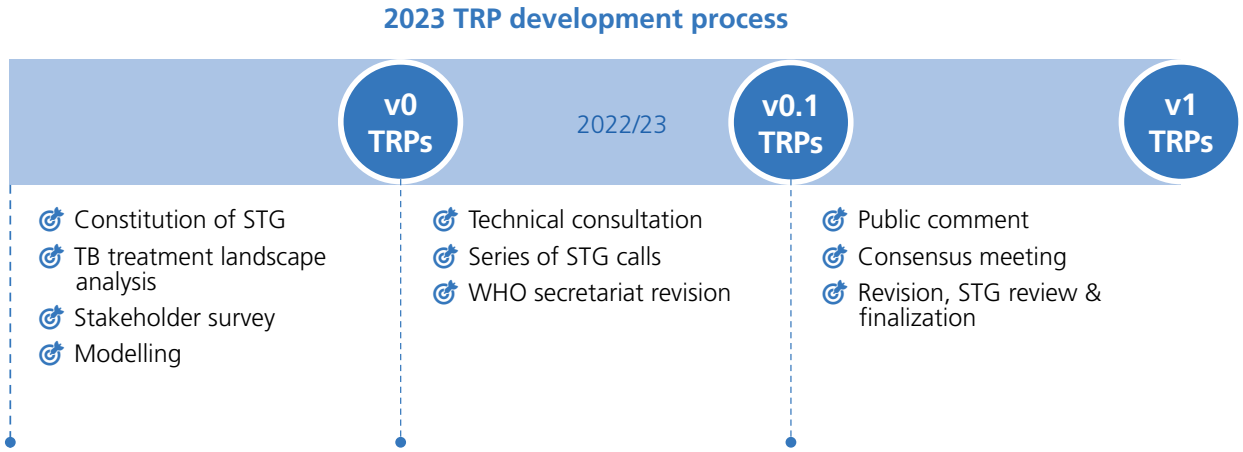
1.2 Objective and target audience

The overall objective of the TRPs 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, nongovernmental organizations (NGOs) and civil society organizations (CSOs), and donors.

2. Methodology

Fig. 2.1 provides a high-level overview of the development process of the 2023 TB TRPs. Key activities in relation to these TRPs are described in subsequent sections.

Fig. 2.1. Overview of the development process of the 2023 TB TRPs revision



STG: Scientific TRP Development Group; TB: tuberculosis; TRP: target regimen profile; WHO: World Health Organization.

2.1 Scientific TRP Development Group

In 2022, WHO constituted a Scientific TRP Development Group (STG) including leading scientists and experts, public health officials, regulators, those involved in development of WHO policy recommendations and representatives of in-country end-users. The STG served to support the entire TRP development process by reviewing drafts at several stages, contributing to discussions during meetings and having direct input into the drafting process. For the STG, the standard WHO declaration of interest procedures were followed. The list of STG members is given in Annex 1.

2.2 Landscape analysis, TRP categories and regimen characteristics

2.2.1 Landscape analysis and TRP categories

The revision process started in early 2022, with a characterization of the main aspects of the TRP update. The characterization was based on a landscape analysis that reviewed the main developments and changes occurring in the area of TB treatment since 2016, and a critical review of the existing TRP document, which drew lessons from the exercise carried out in 2016 for its production. Recent changes in treatment

recommendations were reviewed and their implications for the update of the TRPs discussed. The approach followed in 2016 to develop the TRPs was based on the efficacy of regimens prescribed for rifampicin-resistant TB (RR-TB) being substantially lower than the efficacy of regimens prescribed for rifampicin-susceptible TB (RS-TB) (about 50–60% in multidrug-resistant TB [MDR-TB] versus 80–90% in fully drug-susceptible TB (DS-TB), according to reports from the WHO Global Tuberculosis Programme. The large increase in availability and use of rapid molecular diagnostics tests allowing identification of TB bacilli and their potential resistance to rifampicin in high TB burden countries made it possible to differentiate between RS-TB and RR-TB at the time of initial diagnosis, which in turn allowed the selection of appropriate treatment. Subsequently, TRPs were developed for the treatment of RS-TB and RR-TB (the latter being considered a proxy for MDR-TB). In addition, based on the potential for a regimen of three to four entirely new anti-TB drugs for which minimal or no resistance would exist (owing to limited to no prior use in the community), a TRP was developed for a "pan-TB treatment" that could be delivered in the absence of available drug susceptibility testing (DST) to start treatment.[4] According to the 2022 Global TB Report, the availability of molecular diagnostic tests in national TB programmes (NTPs) worldwide has further expanded, and the latest WHO guidelines on diagnosis of TB reemphasized the use of such tests for the initial diagnosis of TB and for detection of rifampicin resistance in adults and children *(2)*. Therefore, for purposes of consistency, and given the expansion of triage in the field using an initial nucleic acid amplification test (NAAT), this 2023 update considers the respective TRP categories of RS-TB, RR-TB and pan-TB, as defined in 2016.

2.2.2 TRP regimen characteristics, trade-offs and cross-cutting aspects

TRP regimen characteristics from the 2016 TRPs (at that time referred to as "attributes") were critically reviewed by WHO Global Tuberculosis Programme, the core writing group and the STG, leading to overall harmonization and consolidation of characteristics. One new characteristic was introduced – forgiveness of the regimen –which was defined as "the degree to which regimen efficacy is unaffected by suboptimal adherence". This led to a total of 13 characteristics (defined in more detail in Section 3.1). As in 2016, the regimen characteristics are described in specific tables, which outline the suitable targets to be met and use the term "minimal" to refer to the lowest acceptable output for a characteristic and "optimal" to refer to the most favourable target that is realistically achievable for that characteristic. Section 3.2 lists the characteristics with *common* TRP requirements; that is, the regimen characteristics for which minimal and optimal requirements are identical across the three TRPs. Sections 3.3–3.5 then describe the TRP characteristics for requirements that are *specific* to the RS-TB, RR-TB and pan-TB TRPs.

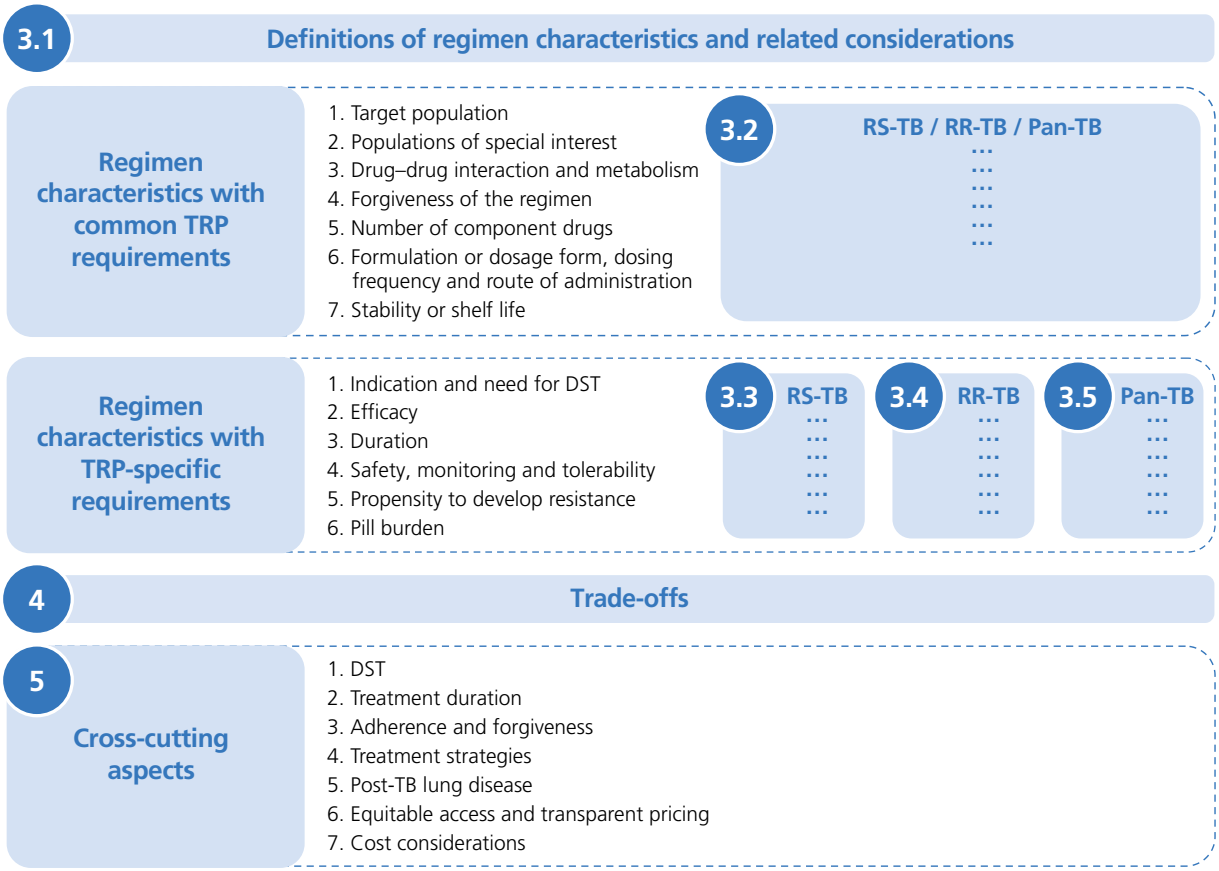
Two additional sections were developed to capture interrelations or trade-offs that may need to be considered between characteristics. These sections cover:

- situations where improving one characteristic may come at the cost of fewer or no improvements in another characteristic (Section 4); and
- aspects that go beyond the direct requirements of a regimen characteristic and pertain to all three TRPs, here defined as cross-cutting aspects (Section 5).

Fig. 2.2 provides an overview of the document structure for these sections as just described.

[4] It should be noted, however, that, following recommendations for good antibiotic stewardship to combat antimicrobial resistance, it is expected that DST would be available at population level at a minimum – and ideally at individual level.

Fig. 2.2. Overview of core sections of the TRP document structure



DST: drug susceptibility testing; RR-TB: rifampicin-resistant TB; RS-TB: rifampicin-susceptible TB; TB: tuberculosis; TRP: target regimen profile.

2.3 Stakeholder survey

To inform the overall scoping and direction of the TRP update, a stakeholder survey was conducted in May–July 2022. The specific objectives of the survey were to:

- assess the use of the 2016 document by different stakeholders as well as to appraise their perception of its strengths and weaknesses;
- open a dialogue with TB experts and the wide range of stakeholders on future needs, considering that respondents were more likely to be familiar with the conceptual framework of the TRPs;
- assess the pertinence of the previously established characteristics, considering advances made over the past decade, with the view to revise and update these as necessary; and
- prioritize the characteristics of the TRPs and evaluate potential trade-offs between critical characteristics of a regimen.

The survey questions were classified over six themes and used a series of closed or open-ended questions. The themes were:

- knowledge and use of the 2016 TRPs;
- key aspects of the development of new regimens;
- key regimen characteristics;
- feasibility, acceptability and cost aspects;

- potential trade-offs between characteristics; and
- identification of challenges of developing future regimens.

Stakeholders included experts who participated in WHO advisory groups on TB, drug developers, field practitioners and clinicians, members of CSOs and NGOs, NTP managers, scientists and researchers and other professionals. The results of the stakeholder survey were presented and made available to the STG and were used to inform subsequent discussions. Results are incorporated in the section on trade-offs (Section 4) and the report is given in Web Annex.

2.4 Mathematical modelling studies

Two modelling analyses were commissioned to support the development of the TRPs. One analysis estimated the *potential health impact* of novel regimens; the second performed *cost modelling* estimating the price thresholds below which a range of novel RS-TB and RR-TB regimens would be expected to achieve cost-neutrality and cost–effectiveness, compared with the current standards of care (SOC). The following sections briefly describe the methodology for these modelling studies; full details are provided in Annexes 2 and 3.

2.4.1 Modelling of potential health impact

A modelling analysis was conducted to quantify the impact that the different novel regimen characteristics would be expected to have on patient cure (i.e. the proportion of people being treated for RS-TB or RR-TB that would be durably cured, if a given regimen were adopted in a programmatic setting), compared with the current optimal SOC (i.e. the 6-month isoniazid, rifampicin, pyrazinamide and ethambutol [HRZE] regimen for RS-TB and the 6 months of bedaquiline, pretomanid, linezolid and moxifloxacin [BPaLM] for RR-TB) *(3, 4)*. In particular, the analyses evaluated the impact on the clinical cure of varying the following regimen attributes: efficacy, duration, ease of adherence and forgiveness (Table 2.1).

In this analysis, *efficacy* is defined as the proportion of treatment-adherent individuals (i.e. of those who complete the full regimen duration with adequate adherence) who are durably cured by the regimen. Varying levels of discontinuation and poor adherence are accounted for in the model to determine the proportion who would be cured during typical implementation of the regimen with a given efficacy. *Duration* refers to the recommended duration of the regimen (in months), and is assumed to impact regimen discontinuation (modelled via a constant weekly probability of loss to follow-up). *Ease of adherence* is designed to encompass tolerability, pill burden, formulation or dosage form, dosing frequency and route of administration. In the model, this attribute determines the proportion of prescribed doses that patients take effectively while still on treatment (i.e. not lost to follow-up). Finally, the level of nonadherence at which efficacy starts to diminish is determined by a regimen's *forgiveness*. The TRP descriptions of minimal and optimal regimen characteristics were translated into quantitative model parameters (Table 2.1). More details on the methodology used in the analysis of patient cures are given in Annex 2, and modelling results are described in Section 4.2.

Table 2.1. Regimen attributes and parameter values used in modelling probabilities of cure

Summary attribute	Corresponding TRP characteristics	Definition in modelling		RS-TB regimens			RR-TB regimens		
				SOC	Minimal	Optimal	SOC	Minimal	Optimal
Efficacy	Efficacy	% of adherent patients who complete the full regimen duration and are durably cured		94%	94%	99%	89%	89%	97%
Duration	Duration	Intended duration (months)		6	3.5	2	6	6	2
Ease of adherence[a]	Tolerability, pill burden, formulation or dosage form, dosing frequency and route of administration	% of doses taken by the patients while on treatment	≥90%	31%	31%	100%	26%	31%	100%
			85 – <90%	22%	22%	0%	10%	22%	0%
			70 – <85%	10%	10%	0%	24%	10%	0%
			<70%	38%	38%	0%	40%	38%	0%
Forgiveness	Forgiveness	Threshold of the % of doses missed above which efficacy is meaningfully diminished		10%	15%	30%	15%	15%	30%

BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; HRZE: isoniazid, rifampicin, pyrazinamide and ethambutol; RR-TB: rifampicin-resistant TB; RS-TB: rifampicin-susceptible TB; SOC: standard of care; TB: tuberculosis; TRP: target regimen profile.

[a] Ease of adherence: RS-TB SOC values are the means across three studies that measured percentage of prescribed doses taken among patients on the 6HRZE regimen using electronically monitored medication boxes *(5–8)*. For the RR-TB SOC, the minimum adherence across the three studies was used (based on the poorer tolerability of BPaLM relative to 6HRZE). Minimal adherence was assumed to equal the RS-TB SOC. Optimal adherence corresponds to what might be achieved via a long-acting injectable.

2.4.2 Cost modelling methods

Mathematical modelling was used to estimate three different price thresholds for each novel regimen considered. Each threshold answered a different question, corresponding to varying perspectives of different stakeholders and thus providing complementary information (Table 2.2). A *short-term cost-neutrality* analysis estimated the price (i.e. cost of goods for a novel regimen) at which replacing the SOC regimen would be cost-neutral on a per-treatment basis. For this analysis, only savings from costs accrued during treatment (e.g. reduction in patient care costs through shorter treatment duration) were considered. A *medium-term cost-neutrality* analysis additionally considered savings from averted future re-treatments and secondary cases (e.g. from a regimen with higher efficacy) occurring within 5 years. Finally, a *cost–effectiveness* analysis assessed the price at which a novel regimen would be cost-effective compared with the SOC, considering all cost and health impacts during and after treatment. In all analyses, we assumed that cost savings in other areas (e.g. from clinic visits and monitoring, or from future re-treatments for the medium-term cost-neutrality and cost–effectiveness analyses) could be used to offset increased spending on drugs. Each analysis was conducted for India, the Philippines and South Africa (these countries were chosen to provide epidemiological and economic diversity, among high TB burden countries with estimates of TB-related unit costs available in the published literature).

Table 2.2. Overview of price threshold analyses

Analysis	Criteria for setting drug price threshold	Cost savings considered to offset increased drug costs	Health impacts included
Short-term cost-neutrality	Novel regimen is immediately cost-neutral vs SOC	Savings from costs accrued during treatment	Not applicable
Medium-term cost-neutrality	Novel regimen is eventually cost-neutral vs SOC	Savings from costs accrued during treatment, averted future re-treatments and averted secondary cases within 5 years	Not applicable
Cost–effectiveness	Novel regimen is cost-effective vs SOC	Savings from costs accrued during treatment, averted future re-treatments and lifelong averted secondary cases	DALYs averted during and after treatment, re-treatment and treatment of secondary cases

DALY: disability-adjusted life year; SOC: standard of care.

For the analysis that focused on cost–effectiveness, health outcomes (including adverse events and TB and post-TB morbidity and mortality) were expressed in disability-adjusted life years (DALYs); costs were expressed in 2021 US dollars; both costs and DALYs were considered over a lifetime horizon (discounted at 3% annually *(9)*); and cost-effective price thresholds were assessed using country-specific willingness-to-pay thresholds (taken from a study that estimated thresholds based on empirical estimates of health opportunity costs *(10)*). All three analyses adopted a societal perspective that included medical costs (borne mostly by the health system) and nonmedical costs (e.g. transportation costs and lost wages, borne mostly by patients). We also estimated analogous thresholds from a health systems perspective, in which only medical costs were included as a secondary analysis.

We modelled novel RS-TB and RR-TB regimens. In each case, the primary cost analyses evaluated a novel regimen that was optimized on five summary attributes, corresponding to meeting the optimal targets of the corresponding TRP for several characteristics (Table 2.3). Such an optimized novel regimen would reduce the costs of treatment delivery (use of outpatient visits, laboratory tests, patient support and adverse event management), while also improving patient outcomes and thus reducing morbidity and mortality, re-treatments and secondary cases. In one-way sensitivity analyses, we also estimated the cost-neutral price of a regimen meeting all but one of the optimal targets or meeting only one optimal target (while achieving only the minimal target for other attributes). These sensitivity analyses were carried out with India as the setting and focusing primarily on the medium-term cost-neutrality analysis.

All analyses used an ingredients-based costing approach that multiplied country-specific unit costs *(11–21)* by the quantities used for each cost component. Quantities under the SOC were based on TB treatment guidelines and protocols from WHO and (where available) from the particular country *(3, 4, 22–26)*. Costs of SOC drugs were modelled as constant across countries: for RS-TB, US$ 46 for a full course of the 6-month HRZE regimen, with levofloxacin replacing isoniazid for patients with detected isoniazid monoresistance; and for RR-TB, US$ 592 for a full course of the 6-month BPaLM regimen, with moxifloxacin omitted for patients with detected fluoroquinolone resistance (prices as of March 2023 *(27)*).

Table 2.3. Regimen attributes and their effects in the cost modelling analysis

Attribute[a]	Effects of regimen optimization in the economic model
Efficacy	More patients are cured, averting morbidity, mortality and re-treatment costs and reducing transmission
Duration	A higher proportion of patients complete enough treatment to be cured Fewer outpatient visits and laboratory tests are required Treatment support costs are lower Patient out-of-pocket and indirect (time) costs are lower Fewer cumulative adverse events occur
Safety	Less monthly safety monitoring is required Monthly incidence of adverse events is lower
Ease of adherence	Adherence levels are improved leading to higher cure rates
Forgiveness	More patients with imperfect adherence are cured

[a] The term regimen "attributes" is used for this cost modelling work to differentiate from the regimen "characteristics", which are used in the TRP tables because the modelling "attributes" sometimes incorporate multiple TRP "characteristics". In particular, ease of adherence encompasses several TRP characteristics, including tolerability, pill burden, formulation or dosage form, dosing frequency and route of administration. The other four attributes (efficacy, duration, safety and forgiveness) correspond directly to the efficacy, duration, safety and forgiveness characteristics in the TRP tables.

More details on the methodology used in the cost analysis are given in Annex 3.

2.5 Consultative process supporting the development of draft TRPs

The core writing group developed an initial draft of the TRP tables (draft v0), based on the outputs of the initial stakeholder survey, the results of the landscape analysis and initial modelling analyses of the relative impact of various regimen characteristics.

WHO Global Tuberculosis Programme organized a virtual technical consultation over the course of 3 days, inviting NTP managers, clinicians, TB survivors, implementing partners, academia, funders, regulators and other partners. The draft results of the stakeholder survey, analytic plans for the modelling work and the v0 TRP tables were shared before the consultation and presented during the meeting. Comments on these documents were invited and specific questions were posed to the participants to obtain their input and further refine the plans and documents.

Continuing from this initial work, WHO Global Tuberculosis Programme organized a series of web-based meetings (four for each TRP) involving the WHO core group and three subgroups of the STG (one subgroup for each TRP). During these meetings, the minimal and optimal targets for each characteristic from draft v0 were reviewed and debated. This process was used to finalize the next draft version of the TRPs (draft v0.1).

To allow the broadest possible input into the document, in early February 2023, WHO posted the draft v0.1 TRP document for public comment via the WHO Global Tuberculosis Programme newsflash, and disseminated it to more than 7000 subscribers worldwide, allowing any interested parties to provide comments. The objectives of the public comment were to promote transparency and accountability in the decision-making process, and to enhance the quality of the TRP document by integrating input from stakeholders, and thus raise their engagement and awareness in the process. During the public comment stage, feedback was received from 58 people: members of NGOs, researchers, field practitioners, NTP managers and representatives of community and advocacy networks. Among these 58 respondents, 50 agreed with the TRP document content and did not suggest any changes, and eight offered comments and suggestions for improvement, all of which were considered and discussed in the final consensus meeting (further detail is provided in Annex 4).

2.6 Consensus meeting

In March 2023, WHO organized an in-person meeting with the STG to achieve full consensus on the proposed characteristics and targets of the TRPs, with a focus on the intended use of the regimens in clinical and operational practice. Participants were scientists, clinical trialists, implementers, and representatives from NGOs and CSOs and from technical and funding agencies. Participants reviewed all characteristics of each TRP with the aim of obtaining consensus on the proposed minimal and optimal requirements, and reaching agreement on the explanatory notes. They also considered the results of the modelling on cost and the impact of various TRP characteristics on cure. A revised version of the TRP document was prepared after the meeting and circulated among STG members for a final round of comments. The tables presented below with minimal and optimal targets were reviewed and endorsed during the consensus meeting. The agenda of the consensus meeting is available in Annex 5.

3. TRPs for TB treatment

The proposed TRPs are intended to guide industry, drug developers and researchers for the definition and characterization of the specific attributes of the treatment regimens, considering the current burden of disease and operational realities of NTPs worldwide, especially in high TB burden countries and in the light of the most recent scientific developments. It is important to keep in mind flexibility around the determination of the minimal and optimal targets for several of the priority characteristics listed in the tables below. Indeed, it may not be necessary to meet all targets at once in a particular regimen, and developers may prioritize one or several attributes over others according to respective drug properties and characteristics, and the public health needs being targeted. Therefore, the targets are being defined as the *most desirable improvements of current best treatment practices*, which can relate to any of the topics presented in the TRP tables, guided by patient preference and health system considerations. The TRP tables present both reasonable minimal standards that would be necessary to improve specific regimen attributes, and optimal standards, which would be the most favourable but realistically achievable targets for the given characteristics.

Following the logic of the 2016 TRP document, TRP tables are presented below for the treatment of RS-TB, RR-TB and "all TB" (i.e. a "pan-TB" treatment).

3.1 Definitions of characteristics and related considerations

This section outlines the definitions and some related considerations for the regimen characteristics used in the subsequent sections.

Table 3.1. Definitions of regimen characteristics

Characteristic	Definition
Target population	The population of people with active TB disease for whom the regimen described in a given TRP is intended.
Indication and need for DST	The specific indication of a given TRP and the needs for DST for regimens developed following that TRP.
Populations of special interest	Important population groups that may have specific needs that differ from the general requirements of adults with pulmonary TB disease and without comorbidities. Such groups include children, pregnant and breastfeeding women, and individuals jointly affected by TB and HIV or other important comorbidities (e.g. diabetes and hepatitis C).
Efficacy	This relates to durable cure; that is, a relapse-free cure 12 months after treatment completion under controlled clinical trial conditions. ***Note 1:*** A requirement for effectiveness (i.e. the performance of a regimen under "real-world" conditions) is not explicitly provided in the TRP tables. However, it is important to design regimens that are likely to retain high performance under programmatic conditions (i.e. be highly effective); for example, regimens that are highly tolerable, short and forgiving.

Characteristic	Definition
Efficacy	***Note 2:*** Demonstrating that a new regimen has efficacy that is as good as the current SOC treatment requires the ability to rule out inferiority using a margin that reflects the other benefits the regimen brings (i.e. a larger margin would be acceptable if there were substantial benefits in duration, safety, ease of delivery and so on – in the absence of such secondary benefits, a smaller margin consistent with preservation of the treatment effect would be appropriate). However, it is also important to keep in mind the potential risk of "biocreep" whereby, after an NI clinical trial, a slightly inferior treatment becomes the active control for the next generation of NI trials – over time this leads to degradation of the efficacy of the investigational treatment, which in turn leads to the possibility that an ineffective or harmful therapy might be incorrectly declared efficacious *(28)*. Demonstrating that a regimen is *better* than the current SOC treatment would require more than ruling out inferiority; it would require establishing superiority either through a conventional superiority design, or through innovative designs that include stratification, enrichment or other techniques *(29)*.
SOC regimen	The relevant "benchmark" regimen to which the requirements for a certain characteristic may be compared (e.g. efficacy should be at least as good as the SOC regimen) and to clarify which regimen would be expected to be provided to patients in the comparator arm of randomized trials or nonrandomized comparisons. Typically, the SOC regimen would be based on the latest WHO recommendations. The following are current WHO recommendations for the treatment of RS-TB and RR-TB at the time of preparation of this document. **RS-TB**: According to the 2022 WHO guidelines *(3)*, the recommended regimens for the treatment of RS-TB include: 1. A 6-month regimen containing isoniazid, rifampicin, pyrazinamide and ethambutol (2HRZE/4HR) for all new patients with pulmonary TB. (*Strong recommendation, high certainty of evidence*) 2. A 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (2HPMZ/2HPM) for people aged 12 years or older. (*Conditional recommendation, moderate certainty of evidence*) 3. A 4-month treatment regimen (2HRZ(E)/2HR) for children and adolescents aged between 3 months and 16 years with non-severe TB. (*Strong recommendation, moderate certainty of evidence*) For RS-TB treatment, the 2HRZE/4HR remains the most widely used regimen and deserves consideration as a benchmark comparator for development of new regimens. **RR-TB**: The 2022 WHO DR-TB guidelines update *(4)* suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than a regimen of 9-months or longer (18-months) in MDR/RR-TB patients (*conditional recommendation, very low certainty of evidence*). This regimen may be used programmatically in MDR/RR-TB patients without previous exposure to its component medicines. In cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued *(4)*. (These recommendations are only for adults and adolescents aged 14 years and older; they exclude children and pregnant or lactating women, given their exclusion from trials to date.) BPaLM is the preferred regimen for eligible patients and is expected to be widely implemented due to its lower cost, shorter duration and high efficacy. It is therefore a regimen that *should* be considered a benchmark for research on new regimens for RR-TB treatment. Although the current SOC for children aged below 14 years remains the 9-month regimen, it is plausible that ongoing research will allow this age group to benefit from the 6-month duration regimens in the near future. **Pan-TB:** Currently, no WHO recommendations exist for a pan-TB regimen. The SOC against which to test a putative pan-TB regimen (i.e. a regimen that would be given to both RS-TB and RR-TB patients) would be a combination of the RS-TB and RR-TB SOC described above.

<table>
<tr><th>Characteristic</th><th>Definition</th></tr>
<tr><td>Treatment duration</td><td>This attribute refers to the total duration of administration of treatment.

Note: Reports show that, for DS-TB, shorter regimens are associated with higher treatment completion rates (30). However, shorter regimens may lead to higher relapse rates, which would require post-treatment follow-up, testing and re-treatment, with increased cost to programmes. Recent evidence shows that it may be possible to optimize treatment duration for individuals using stratified medicine approaches (31). Therefore, considering that the shortest duration may be sufficient for patients with less severe or less extensive pulmonary disease (or an overall "low-risk profile"), new, shorter regimens may need to be extended in patients with severe disease or certain forms of extrapulmonary disease, that may also require treatment intensification (higher dose or additional drugs, or both).</td></tr>
<tr><td>Safety, monitoring and tolerability</td><td>Safety: The incidence and severity of adverse events observed with use of the regimen.

Safety monitoring: Frequency and type of clinical and laboratory monitoring required to ensure the safe use of the regimen.

Tolerability: Drug tolerability is defined by the FDA as "the degree to which overt adverse effects can be tolerated by patients" (32). The tolerability profile of a given drug or regimen is of comparative importance to its efficacy and safety, because it largely determines adherence to treatment and ultimately treatment success or failure. Tolerability is a key characteristic to consider because it has a direct impact on the quality of treatment intake and the risk of treatment discontinuation.

A useful complementary measure of safety and tolerability is the proportion of patients interrupting or discontinuing treatment owing to adverse effects.</td></tr>
<tr><td>DDI and metabolism</td><td>DDIs with other important medications that are widely used including those used to treat the most frequently reported comorbidities.</td></tr>
<tr><td>Propensity to develop resistance</td><td>Drugs included in the treatment regimen should protect each other against emergence of resistance. Resistance to the drugs included in the new regimen should be limited, and mutants with resistance against these drugs should not be cross-resistant to drugs used in the current "second-line regimens". This is extremely important in order not to compromise the use of potential new drugs.

As a reference, the frequency of "natural" mutations conferring resistance to some antibiotics currently used in TB treatment has been estimated as follows (33):

<table>
<tr><td>Rifampicin</td><td>2×10^{-10}</td></tr>
<tr><td>Isoniazid</td><td>2×10^{-8}</td></tr>
<tr><td>Ethambutol</td><td>10^{-7}</td></tr>
<tr><td>Double mutant INH+RIF</td><td>10^{-12}</td></tr>
<tr><td>3 drugs</td><td>10^{-20}</td></tr>
<tr><td>Delamanid</td><td>Between 10^{-5} and 10^{-6} (34)</td></tr>
<tr><td>Bedaquiline</td><td>Between 10^{-7} and 10^{-9} (35)</td></tr>
</table>

Novel regimens should be based on combinations of drugs that have different targets from one another (i.e. different classes of drugs with different modes of action and mechanisms of resistance). Drugs included in the multidrug therapy may have different PK/PD properties as well as bactericidal or sterilization capacity, and be acting on different compartments within a lesion (36). For this reason, some of the drugs may be considered as "protective" to other drugs, to avoid any risk of intermittent monotherapy that may generate drug resistance. Companion drugs should, where possible, be synergistic in activity at the lesion site and should have a half-life that is well matched with the companion, to reduce the risk of functional monotherapy.

The propensity to develop resistance could be measured in clinical trials by comparing resistance patterns in bacilli isolated at baseline to those isolated at later stages.</td></tr>
</table>

Characteristic	Definition
Forgiveness of the regimen	The degree to which regimen efficacy is unaffected by suboptimal adherence; that is, the strength of the relationship between decreasing cure rates as a result of decreasing adherence rates. The expectation is that for a regimen with high forgiveness, the drop from efficacy (as observed in explanatory trials) to effectiveness (as observed in pragmatic trials or under programmatic use) would be significantly smaller than that for a nonforgiving regimen. Within the different types of nonadherence that have been defined, we refer to forgiveness in relation to "suboptimal implementation"; that is, intermittent missed doses (treatment gaps) *(7)*. In practice, measuring the forgiveness of a regimen would require measuring adherence on an individual basis. Then efficacy could be compared between strata of patients exhibiting different levels of adherence. A high level of forgiveness is demonstrated if high cure rates are maintained in strata with low adherence compared with strata with high adherence. It would be valuable for developers to thoroughly investigate the concept of regimen forgiveness during the clinical development phase. Understanding whether a regimen is forgiving or unforgiving under expected adherence patterns is crucial for successful implementation and acceptance of the regimen in the real world. Although not required by regulators, this aspect plays a significant role in determining the regimen's effectiveness and overall success. There are various approaches to studying forgiveness. For instance, developers can quantify the PK/PD relationship during drug development, which can be used for simulations under different adherence scenarios. By linking expected adherence patterns with the PK/PD relationship, developers can provide quantitative insights via simulation into the level of forgiveness exhibited by the regimen. This approach may lead to the selection of an optimal dose that compensates for occasionally missed doses and reduced exposures. Additionally, forgiveness studies can be conducted in controlled settings using preclinical models. These studies provide valuable insights into understanding the forgiveness of the regimen and can guide the level of support required for adherence implementation. Recognizing forgiveness as a competitive advantage is important; however, it should not overshadow the need for comprehensive efforts at the programme level to support patients in adhering to the treatment. Early understanding of regimen forgiveness will facilitate the development of appropriate adherence strategies and support systems, ultimately benefiting patients and enhancing treatment outcomes.
Number of component drugs	The number of component drugs included to make up a regimen.
Pill burden	High pill burden affects tolerability, quality of life and treatment adherence, so FDC formulation is highly desirable if it can be achieved without a concomitant decrease in drug exposure. Additional considerations include, for example, –the size of pills and the availability of water-dispersible pills for paediatric use. Initial formulations studied in explanatory trials may not meet these requirements; however, developers should ideally have a viable pathway to reduced pill burden for successful regimens.
Formulation or dosage form, dosing frequency and route of administration	Formulation or dosage form: The way in which the active drug is combined with other chemical substances to yield the final product (e.g. as tablet, capsule, injectable agent or syrup). Dosing frequency: The frequency in which the regimen or individual drugs are taken (e.g. once daily). Route of administration: The way by which the drug is taken into the body (e.g. oral or intramuscular).
Stability or shelf life	The period of time (usually in years) that a product is stable at a given temperature and humidity.

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; DDI: drug–drug interaction; DR-TB: drug-resistant TB; DS-TB: drug-susceptible TB; DST: drug susceptibility testing; FDA: US Food and Drug Administration; FDC: fixed dose combination; HIV: human immunodeficiency virus; INH: isoniazid; MDR/RR-TB: multidrug-resistant TB or rifampicin-resistant TB; NI: noninferiority; PK/PD: pharmacokinetic/pharmacodynamic; RIF: rifampicin; RR-TB: rifampicin-resistant TB; RS-TB: rifampicin-susceptible TB; SOC: standard of care; TB: tuberculosis; TRP: target regimen profile; WHO: World Health Organization.

3.2 Regimen characteristics with common TRP requirements

This section outlines the requirements for regimen characteristics that are common to all TRPs; that is, where minimal and optimal requirements are identical between the three TRPs.

Table 3.2. Requirements for regimen characteristics common to all TRPs

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Target population	All groups, irrespective of severity and site of disease (including pulmonary and extrapulmonary disease), across the full age spectrum, including pregnant or lactating women, people living with HIV and people with other comorbidities, such as diabetes.		The regimen should be safe, well tolerated and efficacious in individuals of all ages (including neonates, infants and children, women of reproductive age, and those who are pregnant or lactating) and for patients with a wide range of comorbid conditions, including HIV infection, and other infectious or chronic diseases (e.g. diabetes). Severe forms of extrapulmonary TB (e.g. TB meningitis) may require special approaches or regimen modifications.
Populations of special interest	In addition to the above, the regimen should have a favourable fetal risk profile based on preclinical data.	In addition to the above, for women of childbearing potential and those who are pregnant, human data do not indicate any increased risk of structural abnormalities in the fetus, and the drugs are safe with breastfeeding. The component drugs should be compatible with common forms of hormone-based birth control for women of reproductive age who wish not to become pregnant.	**Children**: PK and safety studies will be needed in infants, children and adolescents for both minimum and optimistic scenarios; however, efficacy trials in this population are not necessarily required, given that efficacy can be extrapolated from adults. The FDA generally requires submission of an initial paediatric study plan no later than 60 days after the end-of-Phase-2 meeting or another date agreed upon between FDA and the sponsor *(37)*. The EMA requires the provision of plans for paediatric studies at the conclusion of Phase 2 studies at the latest. TB regimen developers should consider initiating paediatric studies as soon as a drug shows promising efficacy and safety in Phase 2A adult trials *(38)*. At this time, suitable paediatric formulations should also be developed to enable dosing in trials involving young children. **Pregnant and breastfeeding women**: In pregnant women, treatment benefits usually outweigh the harms. Treatment during pregnancy is indicated when the probability of TB is moderate to high. In pregnant women, the drugs used in the current SOC treatment regimen for DS-TB cross the placenta, but do not appear to have harmful effects on the fetus. Formulations should be safe for pregnant women and women of reproductive age *(39–41)*. Studies should be planned early in pregnant and lactating women, including non-clinical developmental and reproductive toxicology studies.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			Fertility and early embryonic development and embryo–fetal development studies should be completed during or no later than the end of Phase 2 registrational trials, whereas prenatal and postnatal development studies should be completed during early Phase 3 or no later than the end of Phase 3 registrational trials. Improved surveillance of pregnancy status and pregnancy and of outcomes for infants should be standardized and implemented across all studies. **People with HIV-associated TB**: Given that any new TB regimen would need to be co-administered with SOC HIV therapies, ART DDIs should be well defined (see below) *(42, 43)*. It is recommended that TB/HIV DDI studies be initiated as soon as doses are known (i.e. at the time of Phase 2 trials). **Patients with other comorbid conditions** (e.g. diabetes, viral hepatitis, alcoholism, substance use or opioid replacement therapy) may require adjustments in dose and frequency of administration, which may increase the need for clinical and laboratory monitoring. Preferably, the optimal TB regimen would be usable in all these patients with no significant alteration in metabolism and with no requirement for therapeutic drug monitoring (i.e. drug absorption should not be affected by food, DDIs and the integrity of the gut barrier).
DDI and metabolism	Ability to adjust doses and frequency while maintaining safety and efficacy (even with clinical and laboratory monitoring at only monthly intervals)[a] when provided in conjunction with: • first-line ART regimen(s) and cotrimoxazole • drugs that are a substrate for and induce or inhibit P450 liver enzymes • proarrhythmic drugs that prolong the QT/QTc interval • oral contraceptives • antidiabetes drugs • hepatitis C drugs.	Ability to use while maintaining safety and efficacy *with no dose or frequency adjustment and no active laboratory monitoring* with other medications, especially with: • first-line ART regimen(s) and cotrimoxazole • drugs that are a substrate for and induce or inhibit P450 liver enzymes • proarrhythmic drugs that prolong the QT/QTc interval • oral contraceptives • antidiabetes drugs • hepatitis C drugs.	The novel drugs in the regimen should have minimal or no DDI with other drugs that are often co-administered (e.g. ART drugs). ART regimens may include drugs that are substrates of P450 or other metabolizing enzymes (e.g. dolutegravir, CYP3A and UGT1A1) or that inhibit or induce P450 enzymes (e.g. efavirenz, CYP2B6; and ritonavir, CYP3A). Such regimens may need to be modified to permit their use with TB treatment. Since 2019, WHO HIV treatment guidelines have recommended the combination of TDF and TLD as the preferred first-line regimen for initiating ART among adults and adolescents living with HIV *(44)*. There is now good evidence that DTG-based ART is well tolerated and efficacious, and its availability as an FDC reduces potential concerns related to pill burden, toxicity and DDIs, making it among the first-line ART in people newly detected as living with HIV. However, rifampicin has been shown to lower DTG plasma concentration, so increasing the DTG dose to a twice-daily schedule is currently recommended *(45)*.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			For the *minimum* target, dose adjustment of component drug(s) may be needed to manage DDIs. Such adjustments would require that relevant dose size or formulations are readily available. For the *optimal* target, no dose adjustments are needed, including for HIV therapies; hence, it is possible to standardize the regimen across populations. Regimen developers should be mindful that certain drugs increase the risk of QT/QTc prolongation; where feasible, regimens combining several of these drugs should be avoided unless there are data to support safety of concomitant use. Regulatory guidance on QT/QTc prolongation by non-antiarrhythmic drugs is available *(46)*. Potential toxic effects of accompanying drugs should also be investigated.
Forgiveness of the regimen	Over the intended treatment duration, missing up to 15% of the doses (nonconsecutive) does not influence treatment outcomes (i.e. does not diminish cure rates).	Over the intended treatment duration, missing up to 30% of the doses (nonconsecutive) does not influence treatment outcomes (i.e. does not diminish cure rates).	For DS-TB, evidence from the TB ReFLECT patient-level pooled analysis suggested that participants receiving 6-month HRZE who missed at least 10% of treatment doses had a 5.9-fold greater risk of unfavourable treatment outcomes. The nonforgiving nature of HRZE is probably one of the reasons why trial-level cure rates are not achieved under programme conditions. Evidence on regimen forgiveness is scarce, so targets are based on expert consensus. The minimal requirement is based on the consideration that, under programmatic implementation, it can be challenging to ensure daily administration throughout the week, such that, for example, the Sunday dose may sometimes be missed in practice, even if daily dosing 7 days/week is prescribed. Therefore, a regimen that would be forgiving of this level of nonadherence would be highly desirable. The optimal requirements is a more ambitious target that aims to ensure high cure rates are obtained even under conditions of poor adherence.
Number of component drugs	Three to four	Three to four	A minimum of three drugs was judged to be likely to be required to ensure high efficacy and short duration, and to minimize the risk of developing drug resistance. Conversely, it is desirable to limit the number of component drugs in a regimen to minimize pill burden and safety risks, and to facilitate coformulation with other drugs as well as procurement by NTPs. For both minimum and optimal requirements, consideration should be given to the fact that the current regimens recommended for DS-TB (HRZE or HPMZ) and MDR/RR-TB (BPaLM) are effective four-drug regimens, and that the BPaLM regimen without moxifloxacin is an effective three-drug regimen (BPaL) for pre-XDR-TB.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			Developers should ensure that the new compounds comprising the regimen offer minimal cross-resistance and that the combination does not increase the toxicity of the individual drugs in the regimen.
Formulation or dosage form, dosing frequency and route of administration	Formulation to be all-oral, simple to administer once or twice a day, with manageable food restrictions. Child-friendly oral formulations available.	Formulation to be all-oral, with simple, age- or weight-based dose adjustment, suitable for FDC formulations, as well as for paediatric formulation, with once-a-day dosing or less (e.g. once weekly or once monthly) and no food effect. Child-friendly oral formulations available.	FDC formulation is strongly encouraged to facilitate implementation across TB programmes, community settings and private practitioners (provided these fully guarantee proper drug exposures). Therefore, developers should include in product development the means to facilitate co-administration or formulation of their drug with other drugs that would be used in combination. 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. If a regimen is intermittent, it should retain priority attributes while being administered intermittently (e.g. once weekly), and should not be likely to fail in the presence of suboptimal adherence. Child-friendly formulations should include appropriate dosage strength, and be functionally scored, dispersible and palatable – this requires early palatability and acceptability studies conducted in children. FDCs should only be developed for children once the dosing requirements are fully understood for the individual drugs, because dosing requirements may vary markedly by drug, especially in young children. Intravenous formulations should be available for severe forms of disease, such as CNS TB or disseminated TB, and for patients who have difficulty taking oral drugs or have intestinal absorption issues (e.g. ICU patients, TB meningitis patients, and those with a short or diverted gut). Alternative routes or formulations offering substantially greater efficacy or convenience may be considered. Thus, long-acting, extended-release, injectable formulations (administered intramuscularly or subcutaneously) could minimize erratic adherence and treatment interruptions and cancel the requirement for DOT. In addition, avoiding oral delivery and its associated first-pass metabolism through the liver may have additional benefits in preventing DDIs. Consideration may also be given to inhalational administration of appropriate agents.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Stability and shelf life	All component drugs stable for ≥3 years in climate zones 3 and 4 at 30 °C / 75% RH.	All component drugs stable for ≥5 years in climate zones 3 and 4 at 30 °C / 75% RH.	

ART: antiretroviral therapy; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CNS: central nervous system; DDI: drug–drug interaction; DOT: directly observed therapy; DS-TB: drug-susceptible TB; DTG: dolutegravir; ECG: electrocardiogram; EMA: European Medicines Agency; FDA: US Food and Drug Administration; FDC: fixed dose combination; HIV: human immunodeficiency virus; HPMZ: isoniazid, rifapentine, moxifloxacin and pyrazinamide; HRZE: isoniazid, rifampicin, pyrazinamide and ethambutol; ICU: intensive care unit; MDR/RR-TB: multidrug-resistant TB or rifampicin-resistant TB; NTP: national TB programme; PK: pharmacokinetics; RH: relative humidity; SOC: standard of care; TB: tuberculosis; TDF: tenofovir disoproxil fumarate; TLD: tenofovir lamivudine dolutegravir; TRP: target regimen profile; WHO: World Health Organization; XDR-TB: extensively drug-resistant TB.

[a] Laboratory monitoring includes at least ECG and safety blood tests.

3.3 TRP for RS-TB

This section outlines the requirements for regimen characteristics for RS-TB.

Table 3.3. Requirements for regimen characteristics for TRP for RS-TB

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Indication and need for DST	The regimen is indicated for patients with active TB disease caused by RS *M. tuberculosis* strains.	The regimen is indicated for patients with active TB disease caused by RS *M. tuberculosis* strains, including the forms with monoresistance to any other medicine in the current HRZE combination – except rifampicin.	All TRPs are placed within the context of recommended susceptibility testing for rifampicin at time of TB diagnosis, using WHO-recommended rapid molecular tests *(2)*.
Efficacy	The regimen has efficacy *as good as* the SOC of RS-TB.	The regimen has efficacy *better than* the SOC of RS-TB.	The current 6-month standard regimen has an efficacy for the treatment of DS-TB of about 95% under trial conditions *(47)*
Duration	3–4 months	≤2 months	The *minimum target* is selected as an improvement on the current shorter treatment being recommended by WHO (i.e. the 2HPMZ/2HPM regimen), and the *optimal target* is aspirational, as suggested in a recent publication on the potential use of a 2-month regimen strategy *(48)*.
Safety, monitoring and tolerability	The incidence and severity of adverse events should be *equal to or lower than* with the SOC. No more than monthly clinical and laboratory monitoring for drug toxicity needed, except in specific populations (e.g. pre-existing liver disease, renal disease or diabetes).	The incidence and severity of adverse events should be *lower than* with the SOC. No active clinical monitoring and no laboratory monitoring for drug toxicity needed, except in specific populations (e.g. pre-existing liver disease, renal disease or diabetes).	The current standard 6-month regimen for TB has known safety issues with the component drugs, most notably hepatoxicity *(49)*. The proportion of patients experiencing Grade 3 or 4 TEAEs when treated with HRZE was 19–25% in the 6-month HRZE control arms of the REMox trial *(50)*, the Study 31 (2HPMZ/2HPM) *(51)*, and the PaMZ Phase 2B trial *(52)*. Among participants receiving the 4-month isoniazid, rifapentine, moxifloxacin and pyrazinamide regimen in the 2HPMZ/2HPM trial, 19% experienced Grade 3 or higher adverse events *(51)*.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
	Tolerability should be *equal to or better than* with the SOC.	*Tolerability* should be *better than* with the SOC.	Lastly, data from the recently conducted SimpliciTB trial showed similar proportions of Grade ≥3 TEAEs in the 6-month HRZE arm and in the 4-month BPaMZ arm (40% and 32%, respectively) but the proportion of TEAEs leading to treatment discontinuation was higher in the 4BPaMZ arm than in the 6HRZE arm (11% vs 2%), mainly due to hepatotoxicity that was probably caused by the pretomanid/ pyrazinamide association.
Propensity to develop resistance	Potential for the acquisition or amplification of resistance during or after treatment to one or more drugs in the regimen is *equal to or lower than* with the SOC.	Potential for the acquisition or amplification of resistance during or after treatment to one or more drugs in the regimen is *lower than* with the SOC.	Drug resistance observed during regimen development should be studied intensively and expertise should be made available by developers for DST development and population-based surveillance of genomic mutations. In particular, regimen developers should transfer high-quality data and technology on active pharmaceutical ingredients (e.g. MIC distribution or mutation sites of resistant strains) to facilitate the development of suitable DST to the novel regimen components. Where possible, this should take place early in the clinical development pathway (see also Section 5.1). One study found that among patients receiving HRZE with strong patient support, 2.1% acquired resistance during or after treatment to one or more drugs in the regimen *(53)*, whereas another study found no acquisition of drug resistance (0/768) *(51)*.
Pill burden	Not greater than SOC (6-months HRZE) individual drugs.	1 pill per day for adult dose.	A high pill burden affects tolerability and treatment adherence, so an FDC formulation is highly desirable. Additional considerations include–, for example, the size of pills and the availability of scored, water-dispersible forms for paediatric use. Initial formulations studied in explanatory trials may not meet these requirements; however, developers should have a viable pathway to reduce pill burden for successful regimens. Standalone drugs should also be available in case of adverse effects due to one of the component drugs leading to treatment discontinuation.

BPaMZ: bedaquiline, pretomanid, moxifloxacin and pyrazinamide; DS-TB: drug-susceptible TB; DST: drug susceptibility testing; FDC: fixed dose combination; HPM: isoniazid, rifapentine and moxifloxacin; HPMZ: isoniazid, rifapentine, moxifloxacin and pyrazinamide; HRZE: isoniazid, rifampicin, pyrazinamide and ethambutol; *M. tuberculosis*: *Mycobacterium tuberculosis*; MIC: minimum inhibitory concentration; RS: rifampicin-susceptible; RS-TB: rifampicin-susceptible TB; SOC: standard of care; TB: tuberculosis; TEAE: treatment-emergent adverse event; TRP: target regimen profile; WHO: World Health Organization.

3.4 TRP for RR-TB

This section outlines the requirements for regimen characteristics for RR-TB.

Table 3.4. Requirements for regimen characteristics for TRP for RR-TB

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Indication and need for DST	The regimen is indicated for patients with active TB disease caused by RR strains, with or without INH resistance (MDR/RR-TB).	The regimen is indicated for patients with active TB caused by RR strains, including XDR-TB.	Under the minimal requirement, drug susceptibility would be assessed via individual DST at the start of therapy, or through information determined via drug resistance surveys. Under the optimal requirement, susceptibility to the drugs in the regimen should be established through appropriate phenotypic or genotypic DST. Resistance will inevitably emerge for any drug in the regimen. DST is needed before initiation of treatment, to establish the resistance pattern of the strains and determine whether a particular regimen is indicated. It is also needed for monitoring any potential amplification of resistance in an individual patient, and for monitoring of the prevalence of resistance in a population. *In all cases, usage should be consistent with principles of good antibiotic stewardship.*
Efficacy	A regimen with efficacy *as good as* the current SOC of MDR/RR-TB.	A regimen with efficacy *better than* the current SOC of MDR/RR-TB.	The 2022 WHO guideline update recommends that the 6-month BPaLM regimen – comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin – may be used programmatically in MDR/RR-TB patients without previous exposure to these medicines instead of the 9-month regimen or the longer (≥18 months) regimen *(4)*. This is based on the results of the TB PRACTECAL Phase 2/3 trial which showed that, in the modified intention-to-treat analysis, 55 out of 62 patients (89%) had a favourable outcome 72 weeks after randomization *(54)*. (Currently, these recommendations exclude children aged below 14 years and pregnant or lactating women, given the lack of safety data for pretomanid among these populations.) Therefore, the *minimal requirement* for the regimen is to be at least as efficacious as the BPaLM regimen for patients with MDR/RR-TB. The *optimal requirement* for the regimen is to have efficacy that is better than BPaLM.
Duration	≤6 months	≤2 months	The *minimal requirement* is for the regimen to have a duration less than or equal to the newly recommended *shorter* MDR-TB regimen (BPaLM). The *optimal requirement* is for the regimen to have a duration of 2 months or less. Of note, a regimen providing sustainable cure of MDR/RR-TB with a duration of ≤2 months is likely to require radically different pharmacokinetic/ pharmacodynamic properties with maximum impact on the regimen's efficacy, compared with the current shortest SOC, the BPaLM regimen.
Safety, monitoring and tolerability	The incidence and severity of adverse events should be *lower* than with the SOC.	The incidence and severity of adverse events should be *lower* than with the SOC.	In the most recent TB PRACTECAL trial, serious adverse events or those greater than or equal to Grade 3 occurring during treatment and up to 30 days after treatment were observed in 18% of patients in the 6-month BPaLM arm (principally, hepatic disorders, lipase increased or pancreatitis and haematological). The proportion of patients discontinuing BPaLM due to issues with tolerability was 5%.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
	No more than monthly clinical and laboratory monitoring for drug toxicity are needed except in specific populations (e.g. pre-existing liver disease, renal disease or diabetes). Tolerability should be *better* than with the SOC.	No active clinical monitoring and no laboratory monitoring for drug toxicity are needed except in specific populations (e.g. pre-existing liver disease, renal disease or diabetes). Tolerability should be *better* than with the SOC.	Any new MDR/RR-TB regimen should have significantly fewer adverse effects and toxicity, to guarantee the best tolerability and acceptability. Thus, safety data from a recent individual-level patient data study (9178 patients) showed that drugs with *low risks of adverse event* occurrence leading to permanent discontinuation included levofloxacin (1.3% [95% CI: 0.3–5.0]), moxifloxacin (2.9% [1.6–5.0]), bedaquiline (1.7% [0.7–4.2]) and clofazimine (1.6% [0.5–5.3]), whereas a relatively high incidence of adverse events leading to permanent discontinuation was seen with linezolid (14.1% [9.9–19.6]) *(55)*. *Note*: the timing of safety or toxicity events in relation to drug intake should be considered. For example, liver toxicity may occur more frequently in the first few weeks of treatment, while the risk of polyneuropathy from oxazolidinones appears to increase with time. Post-marketing surveillance should be systematically undertaken to check for the occurrence of rare serious side-effects of the regimen.
Propensity to develop resistance	Potential for the acquisition or amplification of resistance during or after treatment to one or more drugs in the regimen is *no worse* than with the SOC.	Potential for the acquisition or amplification of resistance during or after treatment to one or more drugs in the regimen is *lower* than with the SOC.	New RR-TB regimens should be built to ensure they have the lowest propensity to develop resistance to the component drugs. Regimen developers should provide preclinical and theoretical evidence that a regimen is expected to have a low risk of resistance. The *minimum requirement* is based on acquired resistance rates similar to those seen with drugs used in the SOC regimens for MDR-TB treatment *(56)*. For both minimal and optimal requirements, it is expected that the genotypic basis for resistance to drugs included in the regimen is well understood. In addition, for *optimal requirements*, resistance mechanisms would be of a nature that permits design of affordable and accessible rapid molecular tests for the detection of drug resistance. In vitro mutagenesis experiments are a useful tool for detecting pathways for emergence of high-level resistance. In parallel, mechanisms should be in place to monitor emergence of resistance, as soon as a new regimen is implemented.
Pill burden	Not greater than 5–7 pills per day (current SOC). Individual drugs, preferably as FDCs.	Not more than 4–5 pills a day for adults, preferably as FDCs.	Currently recommended BPaLM regimen consists of 5–7 pills per day. A high pill burden affects tolerability and treatment adherence, so an FDC formulation is highly desirable. Additional considerations include, for example, –the size of pills and the availability of scored, water-dispersible formats for paediatric use. Initial formulations studied in explanatory trials may not meet these requirements; however, developers should have a viable pathway to reduce pill burden for successful regimens. Standalone drugs should also be available in case of adverse effect due to one of the component drugs leading to treatment discontinuation.

BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CI: confidence interval; DST: drug susceptibility testing; FDC: fixed dose combination; INH: isoniazid; MDR/RR-TB: multidrug-resistant TB or rifampicin-resistant TB; RR: rifampicin; RR-TB: rifampicin-resistant TB; SOC: standard of care; TB: tuberculosis; TRP: target regimen profile; WHO: World Health Organization; XDR-TB: extensively drug-resistant TB.

3.5 Pan-TB TRP

A pan-TB TRP is proposed as the TB community's most high-profile opportunity to be ambitious. In principle, a pan-TB regimen is intended as the first-line TB regimen, containing novel compounds so that the regimen can be initiated for individuals with active TB disease, regardless of circulating resistant strains. Thus, such regimens should not include drugs used in currently recommended regimens (or drugs that have significant cross-resistance to currently used drugs) unless it can be demonstrated that the barrier for development of resistance to the drug is very high. The development of pan-TB regimens as outlined in Table 3.5 needs to be accompanied by the development of phenotypic DST interim testing criteria for each drug component of the regimen (i.e. interim critical concentrations that can distinguish wild-type from non-wild-type strains). These interim testing criteria (and other data, as outlined in Section 5.1) should be made available at the time of implementation for surveillance purposes and should be accompanied by appropriate capacity development for their roll out and use. Subsequently, it will be incumbent on TB programmes to perform rigorous surveillance for the emergence of resistance to the new regimens during use of the pan-TB regimen, in line with good antibiotic stewardship principles.

Table 3.5. Requirements for regimen characteristics for pan-TB TRP

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Indication and need for DST	The regimen is indicated as first-line treatment for patients with active TB disease including RS-TB and RR-TB.		The pan-TB approach relies on the assumption that simple, novel, highly effective, safe and well-tolerated regimens that could be administered to any patient with active TB without prior knowledge of the patient's drug resistance profile (so would be efficacious in patients with either RS-TB or RR-TB) could be used empirically so that treatment could begin without delay while DST is sought. This would be particularly useful in areas with a high prevalence of drug resistance and low availability of, or low access to, rapid DST, where patients may currently be treated inappropriately and may continue to transmit disease for extended periods or generate additional drug resistance. Further, the 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 of all forms of TB, and potentially increase the effectiveness of delivery systems and allow economies of scale. In parallel, it is essential that some form of DST (e.g. phenotypic or sequencing based) is available for the components of the regimen by the time it is marketed and rolled out for wider use. Thus, the development of DST (ideally a rapid DST) to the components of the novel regimen should be fully included in the development pathway and should start early in the process. It is also an essential public health measure, since the introduction of a novel pan-TB regimen would require population-based surveillance to monitor for the potential emergence of resistance to its component drugs, especially if universal DST cannot be guaranteed.
Efficacy	A regimen with *efficacy as good as* the SOC of RS-TB.	A regimen with efficacy *better than* the SOC of RS-TB.	Efficacy of the current HRZE regimen is reported to be 90–95% in clinical trial conditions. Considering that a pan-TB regimen would be used to treat **both** RS-TB and MDR/RR-TB, efficacy should be at least as good as with the RS-TB SOC (6-month HRZE), since the vast majority of patients treated would otherwise get a regimen for RS-TB. Hence, the minimal target at any given duration would certainly be *at least as efficacious as* HRZE, considering that it will be *also* as efficacious in patients with at least MDR/RR-TB.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Duration	3–4 months	≤2 months	The *minimal target* is set to be equal to, or less than, the length of the WHO-recommended shorter treatment of DS-TB (HPMZ – 4 months). The *optimal target* is set to be equal to, or less than, 2 months, based on recent results indicating that an ultra-short regimen would make it possible to provide cure through a maximum of 60 days treatment, with the condition that patients are carefully monitored, making it possible to act rapidly in case of early signs of recurrence *(48)*.
Safety, monitoring and tolerability	The incidence and severity of adverse events should be *lower* than with the SOC of RS-TB (6HRZE). No more than once per month clinical and laboratory monitoring for drug toxicity needed except in specific populations (e.g. pre-existing liver disease, renal disease or diabetes). Tolerability should be *better* than with the SOC of RS-TB.	The incidence and severity of adverse events should be *lower* than with the SOC of RS-TB (6HRZE). No active clinical monitoring and no laboratory monitoring for drug toxicity needed except in specific populations (e.g. pre-existing liver disease, renal disease or diabetes). Tolerability should be *better* than with the SOC of RS-TB.	The current standard 6-month regimen for TB has known safety issues with the component drugs, most notably hepatoxicity *(49)*. The proportion of patients experiencing Grade 3 or 4 TEAEs when treated with HRZE was 19–25% in the 6-month HRZE control arms of the REMox trial *(50)*, the Study 31 (2HPMZ/2HPM) *(51)* and the PaMZ Phase 2B trial *(52)*. Among participants receiving the 4-month isoniazid, rifapentine, moxifloxacin and pyrazinamide regimen in the 2HPMZ/2HPM trial, 18.8% experienced adverse events of Grade 3 or higher *(51)*. Data from the recently conducted SimpliciTB trial showed similar proportions of Grade ≥3 TEAEs in the 6-month HRZE arm and in the 4-month BPaMZ arm (40% and 32%, respectively) but the proportion of TEAEs leading to treatment discontinuation was higher in the 4BPaMZ arm than in the 6HRZE arm (11% vs 2%), mainly due to hepatotoxicity caused by the pretomanid/pyrazinamide association.
Propensity to develop resistance	Potential for the acquisition or amplification of resistance during or after treatment to one or more drugs in the regimen is *no worse* than with the SOC.	Potential for the acquisition or amplification of resistance during or after treatment to one or more drugs in the regimen is *lower* than with the SOC.	New pan-TB regimens should be built to ensure they have the lowest propensity to develop resistance to the component drugs. The novel drugs, for which minimal prior natural or human-made resistance would be known to exist, might be prescribed without knowledge of the patient's drug resistance profile. The distribution of resistance alleles before the introduction of a regimen of truly novel drugs would probably be similar among those currently classified as RS-TB or MDR/RR-TB, and with a correctly composed regimen may not increase rapidly after deployment. For the future adoption of a putative pan-TB regimen, it would be necessary to understand fully (including through modelling studies) the estimated risks of acquired resistance. Regimen developers should provide preclinical and theoretical evidence that a regimen is expected to have a low risk of generating resistance. In any case, specific DST (preferably NGS based) will be needed rapidly to test patients not improving during or after treatment, and for population-based drug resistance surveillance assessment studies to be conducted during early implementation.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Pill burden	Not greater than the current RS-TB SOC.	1 pill per day for adult dose.	FDC formulation is strongly encouraged, to facilitate implementation across TB programmes, community settings and private practitioners (provided these fully guarantee proper drug exposures). Additional considerations include, for example, the size of pills and the availability of water-dispersible pills for children. (Initial formulations studied in explanatory trials may not meet these requirements; however, developers should have a viable pathway to reduce pill burden for successful regimens.)

BPaMZ: bedaquiline, pretomanid, moxifloxacin and pyrazinamide; DS-TB: drug-susceptible TB; DST: drug susceptibility testing; FDC: fixed dose combination; HPM: isoniazid, rifapentine and moxifloxacin; HPMZ: isoniazid, rifapentine, moxifloxacin and pyrazinamide; HRZE: isoniazid, rifampicin, pyrazinamide and ethambutol; MDR/RR-TB: multidrug-resistant TB or rifampicin-resistant TB; NGS: next-generation sequencing; RR-TB: rifampicin-resistant TB; RS-TB: rifampicin-susceptible TB; SOC: standard of care; TEAE: treatment-emergent adverse event; TB: tuberculosis; TRP: target regimen profile; WHO: World Health Organization.

4. Trade-offs

4.1 Overview: competing characteristics and perspectives

The TRPs detailed in this document describe targets for various characteristics of novel regimens for TB treatment, such as the efficacy of treatment, safety and the potential for acquisition of drug resistance. However, optimizing one characteristic is often at odds with optimizing another. For example, shortening the intended duration of a given drug combination will generally reduce its efficacy compared with a longer duration, everything else being equal. Additionally, adding drugs to a regimen can increase efficacy and protect patients against the emergence of drug resistance, but can also increase pill burden and the incidence of side-effects. Regimen developers may therefore have to decide to prioritize one characteristic over another.

Consideration of multiple perspectives can guide such decisions by elucidating these trade-offs. Perspectives relevant to novel TB treatment regimens include the:

- clinical perspective – where probability of cure may be a priority;
- economic perspective – for example, costs to health systems and patients;
- perspective of people with TB – for example, drawing on experiences of TB survivors and other stakeholders; and
- long-term population-level perspective – for example, considering impacts on TB incidence and drug resistance.

This chapter discusses how each of these perspectives may inform the prioritization of different TRP characteristics, and synthesizes overarching conclusions for drug developers. In doing so, it updates and expands on an earlier modelling analysis that was conducted to inform the 2016 TRPs, which considered a subset of these perspectives and outcomes *(57)*.

4.2 Prioritizing regimen characteristics based on probability of cure

As part of the 2023 TRP development process, a modelling analysis was conducted to quantify the impact of different characteristics of a novel regimen on the regimen's ability to durably cure patients under programmatic conditions. In particular, the analysis estimated the proportion of people with RS-TB or RR-TB who would be durably cured after initiating a given treatment regimen under programmatic conditions, and compared this outcome for various combinations of regimen attributes (i.e. efficacy, duration, ease of adherence and forgiveness). Variation in each regimen characteristic was evaluated in the context of regimens that otherwise resembled the current SOC (i.e. the 6-month HRZE regimen for RS-TB and 6 months of BPaLM for RR-TB) *(3, 4)*, or that otherwise met all the minimal TRP targets or all the optimal TRP targets.

In this analysis, *efficacy* was defined as the proportion of treatment-adherent individuals (i.e. of those who completed the full regimen duration with adequate adherence) who were durably cured by

the regimen; this parameter is akin to regimen efficacy observed under conditions of a controlled clinical trial that involves extensive interaction with, and treatment support for, patients. *Duration* referred to the recommended duration of the regimen, in months, and was assumed to affect the cumulative risk of premature regimen discontinuation (modelled via a constant weekly probability of loss to follow-up). *Ease of adherence* was designed to encompass tolerability, pill burden, formulation or dosage form, dosing frequency and route of administration; in the model, this attribute determined the proportion of prescribed doses that patients took while still on treatment (i.e. before any loss to follow-up). Finally, the level of nonadherence at which efficacy starts to diminish was determined by a regimen's *forgiveness*. The proportion of *patients cured* was then modelled as a result of all the above-described parameters, and could be viewed as a measure akin to regimen effectiveness that may be observed under real-world, programmatic conditions. The TRP descriptions of minimal and optimal regimen characteristics were translated into quantitative model parameters (see Annex 2 for more details).

In this analysis, *ease of adherence* was found to be the attribute that had the greatest influence on proportion of patients cured (Fig. 4.1). Perfect adherence (e.g. as might be achieved via a long-acting injectable) increased the percentage of RS-TB patients cured to 93%, compared with 83% under a regimen meeting all the minimal characteristics only (including SOC adherence, under which it was assumed that less than one third of patients took ≥90% of prescribed doses while on treatment) *(5, 6, 8)*. For RR-TB, SOC adherence was assumed to be worse (about 25% of patients taking ≥90% of prescribed doses[5]) and thus improving adherence increased the percentage cured even more, from 74% under SOC adherence to 85% under optimal adherence. Similarly, if starting from a fully optimized regimen (with 98% expected cure for RS-TB or 96% for RR-TB), reducing ease of adherence to SOC levels decreased expected cures to 90% and 88%, respectively.

The impact of other regimen characteristics varied by regimen type (RS-TB or RR-TB) and scenario (level of improvement in other characteristics). For an RS-TB regimen with characteristics similar to or minimally improved from SOC values, *forgiveness* was the next most influential characteristic. For an otherwise fully optimized regimen, forgiveness was unimportant because perfect adherence was modelled. BPaLM was modelled as a regimen that was less efficacious than HRZE (based on clinical trial data) *(54, 58, 59)* but more forgiving (based on pharmacokinetic properties of the component drugs) *(60)*; hence, improving the *efficacy* of the RR-TB regimen had more of an impact on patient cures than improving the *forgiveness*.

Although the analysis modelled higher cumulative discontinuation for longer regimens (translating into fewer cures), early discontinuation was a minor contributor to ineffectiveness, even with regimens that only met minimal duration targets (3–4 months for RS-TB and 6 months for RR-TB). This result occurred mainly because discontinuation rates in any given month are usually relatively low, and the reduction in probability of cure for those that discontinued later in a course of treatment are usually relatively small.[6] Therefore, shortening the duration was estimated to have less effect on cures than the other modelled attributes. However, there are limitations in the evidence supporting this conclusion.[7] For example, it is possible that patients take their medication more consistently when it is prescribed for a shorter duration. Given that quantitative data to support this notion was lacking, the analysis modelled the effect of treatment shortening only on retention in care and not on adherence levels while in care. Furthermore, although the analysis modelled a constant rate of treatment discontinuation, data

[5] Because BPaLM was a relatively new regimen at the time this analysis was conducted, adherence data were scarce. Owing to the lower tolerability of BPaLM compared with HRZE (e.g. side-effect profile), adherence on BPaLM was benchmarked to the lowest observed adherence across the three studies that measured programmatic adherence to HRZE *(5, 6, 8)*.

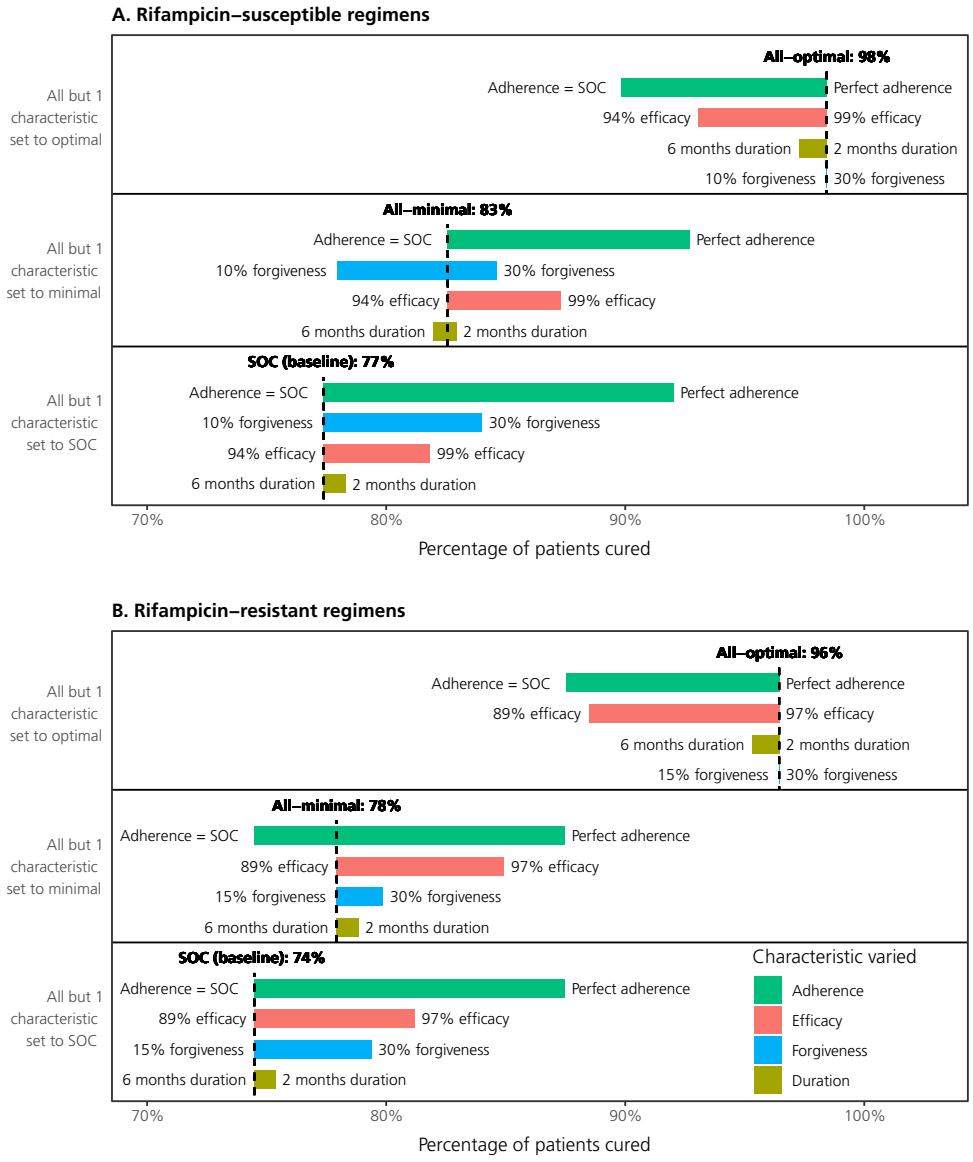
[6] Based on evidence from historical studies *(61, 62)*, it was estimated that incomplete treatment was still enough to cure 80% of those who completed only half of a treatment course, setting aside differences in regimen efficacy, ease of adherence and forgiveness.

[7] Based on evidence from historical studies *(61, 62)*, it was estimated that incomplete treatment was still enough to cure 80% of those who completed only half of a treatment course, setting aside differences in regimen efficacy, ease of adherence and forgiveness.

on the relationship between time on treatment and risk of discontinuation are inconsistent, and some studies suggest that people are more likely to discontinue towards the end of the treatment course. In this case, shortening the treatment duration could improve outcomes to a greater extent than the results of this analysis suggest.

Notably, this analysis predicts cure probabilities that, for the SOC, are lower than treatment success ratios reported by many high-burden countries (e.g. India reported a treatment success ratio of 85% in 2020, compared with the 77% probability of cure estimated here for HRZE) *(63)*. The main reason for this difference is that the analysis includes relapses that are experienced sometimes months after the end of treatment, which are typically not captured in treatment outcome data reported by NTPs; for example, a 2018 study found that 11% of people who were successfully treated in India experienced relapse *(64)*.

Fig. 4.1. Modelled impact of different novel regimen characteristics on patient cure[a]



SOC: standard of care.

[a] Fig. 4.1 shows the modelled percentage of patients cured under various novel regimens for RS-TB (panel A) and RR-TB (panel B). Coloured bars show the variation in cure when a single characteristic is varied from its SOC value to its optimal value (corresponding to optimal targets in the TRPs). The values that the remaining characteristics take on differ among the three sections of each panel. Specifically, the bottom section of both panels ("All but 1 characteristic set to SOC") show the effect of fixing all characteristics at their SOC values (vertical dashed line) and then improving one characteristic at a

time from its SOC to optimal value. The middle parts of each panel ("All but 1 characteristic set to minimal") show the results when all characteristics are fixed at their minimal TRP target values (and again, a single characteristic is varied from its SOC to optimal value); the minimal target values are not shown in this figure but are displayed in Annex 2 (Table A2.1). The top parts of each panel ("All but 1 characteristic set to optimal") show the results when all characteristics except the one being varied are fixed at their optimal TRP target values. Colours indicate which characteristic is being varied, and text labels indicate the values of each characteristic (left of the bars = SOC values for each characteristic; right of the bars = optimal values for each characteristic). Bars are ordered vertically by the impact each characteristic has on the percentage of patients cured (the vertical distance between each bar is equal and is not meaningful).

4.3 Prioritizing regimen characteristics based on costs

An economic modelling analysis estimated price thresholds at which novel RS-TB and RR-TB regimens would be cost-neutral or cost-effective compared with the SOC. This analysis made the same assumptions about the four attributes varied in the modelling of patient cures (efficacy, duration, ease of adherence and forgiveness) and described the influence of these and of a fifth attribute – regimen safety – on the costs of treating patients with TB.

In contrast to the analysis of patient cure, *duration* was found to have the greatest influence on short-term costs, through reductions in quantities of monitoring visits and tests, patient support, nonmedical out-of-pocket and indirect costs borne by patients, and the cumulative incidence of adverse events. In analyses that additionally considered savings and health benefits that would only accrue after an individual's course of treatment (through averted future re-treatments and secondary cases), *ease of adherence* was the next most influential characteristic after duration, mainly because of its influence on patient cures. Additional details can be found in the separate sections on costs (Section 5.7 provides more detail on these results and Annex 3 provides details on the methods used).

4.4 Prioritizing regimen characteristics based on TB survivor and other stakeholder perspectives

4.4.1 TB survivor perspectives

Considering only cure and cost does not fully capture the ways that regimen characteristics may affect the quality of life of people on TB treatment. From a TB survivor perspective, priorities include tolerability and side-effects, pill burden, formulation and duration, and person-centred approaches, such as support to people on treatment, that should complement all treatment regimens (Box 4.1) *(65)*. Although not included as a characteristic in the TRPs, the potential for treatment to reduce the incidence and severity of post-TB disability is also an important priority for people on treatment.

Several of the obstacles faced by people on TB treatment are nuanced in ways that are difficult to capture fully in the TRP targets. For example, the burden of taking a daily regimen of pills encompasses not just frequency and number of pills, but also pill size. Other aspects of treatment, such as care models and the broader aspect of health care access, fall outside the scope of regimens themselves but are pivotal to improving the overall treatment experience. The preference of people with lived experience of TB may differ from the perspectives of other stakeholder groups (e.g. researchers, programmes and clinicians). For example, adverse events that are perceived as mild from a clinical perspective are often still meaningful to the people experiencing them, and strategies to address them include prescribing regimens with milder toxicity profiles, but also offering drugs to reduce the severity and frequency of side-effects, and creating opportunities for ongoing communication between clinicians and patients regarding medication tolerability. Similarly, programmes might place higher priority on duration or efficacy, whereas people with lived experience might care more about safety and tolerability (e.g. they may be willing to trade a month of duration for a more tolerable regimen).

In general, more research is needed on the preferences of TB survivors and people on treatment regarding priority regimen attributes, and how to prioritize different trade-offs between regimen characteristics, and accompanying programmes and interventions. It is crucial that the experiences of people on TB treatment remain at the heart of development and prioritization efforts.

Box 4.1. Testimony from a TB survivor (2023, South Africa)

"I am Phumeza Tisile, an XDR-TB survivor. I was finally cured after 3 years and 8 months on treatment. I took the first-line TB drugs for DS-TB. They were big orange/pink tablets, really hard to swallow but at least they were only three tablets. The colour of urine, almost blood-like, gave me a shock, only to be informed that was normal with the tablets I was taking.

Few weeks later I was not getting better. I got tested again and this time they told me I have MDR-TB. The regimen at the time in 2010 had about 20–25 tablets per day with an injection every day for 6 months. The medication made me sicker than I already was, which did not make sense to me; I assumed the medication will get me better, but that was not the case. I got resistant to the injection called kanamycin and it caused irreversible hearing loss. Then I was told I had pre-XDR-TB.

Even when I was discharged to take the medication at the clinic it was not helpful. I refused the DOTs [directly observed therapies] and I have strong opinion that they were not patient-centred care at all, but rather policing. For an example, I do not know any other disease out there that requires for a patient to be watched while taking their medication.

After months of getting better and gaining weight, I was told I had XDR-TB. The doctors could not explain why I looked better, but my TB results were not. I was back again on a different injection called capreomycin, and additional tablets – about 30 – only to be told that the injection I was taking again had no effect whatsoever with the type of TB I had.

In all of these years, I was in and out of clinics and hospitals, with a pill burden that was very hard to swallow. I could not go back to university: all that mattered at the time was for me to get cured and be able to resume my life.

We need better TB regimens, drugs that are not toxic, drugs you can take on the go (like the single pill for HIV treatment), and drugs that are available for all."

4.4.2 Other stakeholder perspectives

To inform trade-offs from the perspective of other stakeholders, the TRP development process included an online survey of drug developers, NTP managers, field practitioners and clinicians, members of CSOs and NGOs, researchers and other professionals (details are given in Web Annex). The survey was completed by 95 respondents representing 50 different organizations and institutions, and over 35 countries. As part of the survey, for several pairs of regimen characteristics, respondents were asked whether they would prefer to prioritize one characteristic over another. Respondents prioritized improved regimen efficacy (especially reductions in TB mortality) and safety (especially reductions in severe adverse events) over reduced duration, and they prioritized reduced duration over reduced frequency of intake. Respondents were more evenly split on whether they thought it was more important to improve safety or efficacy. Reductions in TB mortality were judged to be the most important consideration overall to guide the development of new regimens. Other important considerations highlighted by respondents included the importance of DST as a strategy to avoid development of drug resistance; the ability to adapt duration, dosing or drugs according to disease severity; and the option for long-acting injectables (if available, safe and efficacious) as an alternative to all-oral formulations.

4.5 Prioritizing regimen characteristics from based on long-term population-level perspective

Improved treatment regimens could facilitate reductions in the burden of TB at a population level. Outcomes that may be important from a population perspective include reductions in TB incidence, prevention of TB mortality, and containment or prevention of drug resistance to ensure that regimens remain useful into the future. These outcomes are discussed below.

4.5.1 Reducing population-level incidence and mortality

As part of the 2016 TRP development process, a transmission model was used to link regimen improvements to incidence and mortality effects *(57)*. The analysis found that improvements in treatment outcomes (e.g. patient cure) have a limited ability to reduce TB incidence and mortality, because most transmission arises from people whose TB has not yet been diagnosed and, similarly, because most TB deaths also occur among untreated individuals or those who received treatment at a too-advanced stage of disease. Nevertheless, meeting the End TB goals will require taking all opportunities to reduce disease burden. Even small reductions in transmission could make an important contribution, and improved regimens can help reduce the risk of catastrophic costs to TB-affected households. A second finding of the 2016 modelling analysis was that reductions in incidence and mortality were closely linked to improvements in patient cures; thus, based on the analysis above, ease of adherence is the regimen attribute that would most strongly determine these population-level outcomes (followed by forgiveness and efficacy).

Novel regimens might, indirectly, have greater population-level impact than such models suggest, if they led to more people with TB being diagnosed and offered treatment. Identifying people with TB before they begin to seek care could both reduce transmission and prevent TB-related deaths. However, barriers to widespread screening for TB include the diagnostic, operational and resource challenges of screening itself (i.e. of identifying high-risk individuals and linking them to screening, diagnosis and care), but also the costs, complexities and risks of treatment. As better TB screening methods, programmes and tools are developed, the ability to offer treatment regimens that are well tolerated, less burdensome for patients and providers, and more affordable for TB programmes might lower the barriers to wider implementation of screening.

4.5.2 Minimizing the risk of drug resistance development

For treatment regimens to achieve meaningful population-level impact, they must be safeguarded against the emergence of drug resistance. A regimen that leads to new resistance in 1–2% of treatment episodes could result in a substantial prevalence of resistance among new TB cases within only a few years, if new resistance goes undetected or is ineffectively treated *(66)*. During regimen development, safeguarding against the emergence of resistance means considering factors such as the pharmacokinetic variability of drugs (including pharmacogenomic factors and drug–drug interactions) that may lead to suboptimal drug exposures, the penetration of drugs to sites of disease and the frequency at which spontaneous resistance occurs. It also means designing regimens to contain a sufficient number of adequately dosed drugs to minimize resistance risks (as opposed to, for example, always pursuing the minimal regimen necessary to achieve efficacy targets).

Precise knowledge of the mechanisms of resistance is key in the development of new regimens: new drugs from different categories may share similar mechanisms of resistance induced by drugs already in use, which can increase the risk of pre-introduction drug resistance. In general, drugs that target nonessential genes, and drugs whose mechanism of action involves multiple genes, may develop drug resistance at higher rates. Variability in these factors between *Mycobacterium tuberculosis* lineages should also be considered, to avoid decreased efficacy in geographical settings where certain lineages are overrepresented.

Finally, because *M. tuberculosis* acquires drug resistance through random mutations in the genome, resistance to new drugs could precede the introduction of the drug in the population. Therefore, when developing or introducing regimens, safeguarding against resistance also entails developing and using drug susceptibility tests alongside the regimen, to provide, at a minimum, population-level surveillance.

4.6 Summary: developing regimens amid conflicting priorities

When it is not possible to meet all of a TRP's optimal targets, a variety of perspectives can inform regimen development decisions. These perspectives include consideration of how competing regimen characteristics may influence patient cures; have a budgetary impact; align with stakeholder preferences; influence population incidence, mortality and drug resistance burden in the longer term; and affect the subjective treatment experience of people on TB treatment. As with regimen characteristics themselves, these perspectives may not always align, necessitating the assignment of different weights to the perspectives while ensuring that none are overlooked. Some regimen characteristics (e.g. efficacy, duration, safety and propensity to develop resistance) and factors that contribute to the quality of life of people on TB treatment (e.g. tolerability, pill burden and formulation) are likely to be seen as valuable from many of these perspectives.

As we continue to move towards regimens that are more efficacious, safer and shorter, considering the experiences of people on treatment becomes ever more important. Ease of adherence was identified as a priority in the modelling analyses of both patient cures and costs. It is also likely to be important from the perspectives of reducing population-level incidence, mortality and drug resistance. The experiences and preferences of people on treatment are central to efforts to improve adherence. Although some of these experiences fall outside the scope of regimens themselves (e.g. supportive interventions), others are linked to features of a regimen (e.g. the frequency and severity of side-effects and the daily pill burden); however, we lack data to quantify the relationship between these underlying factors and adherence levels.

Future research can help in valuing these and other regimen improvements appropriately. Valuation of characteristics such as tolerability, pill burden and formulation could benefit from research to understand and quantify how these characteristics contribute to adherence and how they affect TB survivor experiences. Another important evidence gap highlighted in the modelling analysis was regimen forgiveness – especially for new regimens such as BPaLM (see Section 5.3 for additional discussion).

Duration – a key focus of recent TB development efforts – was judged to be less of a priority than other regimen improvements (e.g. adherence and efficacy) when modelling health outcomes or surveying stakeholder preferences. Shorter durations do have the important benefit of making regimens more feasible for country programmes to adopt by reducing costs; both the stakeholder survey and emerging evidence from clinical trials *(48)* indicate the potential of shorter and more personalized regimen durations (see Section 5.4 for additional discussion). However, given competing priorities, there may be a use-case for RS-TB regimens of 6 months duration if they are substantially improved in other domains (e.g. efficacy, ease of adherence or safety).

Given the inherent trade-offs between regimen characteristics, assessments of the relative merits of satisfying key TRP requirements will require judgement from developers and an ongoing conversation within the broader TB community. In some cases, a major advance in a priority characteristic may justify additional flexibility on other characteristics. The diversity of relevant perspectives also points to the potential value of concurrently developing and introducing multiple regimens for the same indication, to meet the needs of a variety of settings, patient populations and preferences. Moving away from a one-size-fits-all approach in TB requires major changes in attitudes and probably also in funding of TB programmes, but has the potential to improve both treatment outcomes and the experiences of people undergoing treatment. Thus, although the TRPs aim to substantiate goals for improving on currently available treatment regimens, these improvements can take multiple forms, and innovation in multiple directions is encouraged.

5. Cross-cutting aspects

The TRPs detailed in this document present a series of characteristics considered essential for novel treatments of TB, such as efficacy, safety, toxicity, drug–drug interactions and potential for the acquisition of drug resistance. Alongside these characteristics, there are cross-cutting aspects that need to be considered: DST, treatment duration, adherence and forgiveness, treatment strategies, post-TB lung disease, equitable access and transparent pricing, and cost considerations. This section discusses each of these aspects.

5.1 Drug susceptibility testing

As soon as a new regimen or drug is introduced and endorsed for clinical care, phenotypic or genotypic tests should be available and implemented in parallel. These tests are needed to support capacity for surveillance of pre-existing and developing resistance at population level, and to provide guidance in individual patient care. Stringent regulatory authorities (SRAs) require supportive data from in vitro and in vivo (animal model) microbiological studies as part of review and registration processes.

The United States Food and Drug Administration (FDA) requirements *(67)* encompass the following:

- drug activity against metabolically active, dormant and intracellular stages of *M. tuberculosis*;
- susceptibility testing against metabolically active bacilli from drug-susceptible and drug-resistant laboratory strains with known patterns of drug resistance and clinical isolates from different geographical regions around the world;
- standardized methods for susceptibility testing such as those recommended by the Clinical Laboratory Standards Institute (CLSI).

Guidance from the European Medicines Agency (EMA) on the development of antibacterial agents notes that:

> *In the EU it is usual that interpretive criteria for susceptibility testing are identified and published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). These criteria may be amended, or additional criteria may be developed (e.g. if an indication is added that requires criteria to be set for additional pathogens or to reflect a new dose regimen), in the post-approval period. Section 9 of this guideline indicates how the SmPC [summary of product characteristics] refers to current EUCAST criteria (68).*

EUCAST has recently published a reference protocol to be used as a "standard method" to test *M. tuberculosis* antimicrobial susceptibility to new drugs (69). The application dossier should include a justification for the proposed interpretive criteria, which should include reference to the pharmacokinetic/pharmacodynamic (PK/PD) analyses used to select the dose regimen or regimens.

EUCAST suggests that data should be presented, even though a relationship between minimum inhibitory concentration (MIC) values obtained from baseline pathogens and clinical and microbiological outcomes is not commonly observed. Also, the Committee for Medicinal Products for Human Use (CHMP) should be updated on progress made towards agreed interpretive criteria for susceptibility testing during the procedure; it is expected that the criteria will be finalized before an opinion is reached on the application.

In addition to these regulatory requirements, the STG noted the importance of completing the following before implementing a regimen:

- MIC distributions, including quality control ranges, including phylogenetically diverse strains from all major *M. tuberculosis* complex genotypes to investigate potential differences in the intrinsic susceptibility to an agent (i.e. strains that are intrinsically less or more susceptible);
- finalized DST interpretative criteria, with the compounds made available to reference laboratories and developers of phenotypic DST assays, to allow establishment of MIC tests using standard broth microdilution protocol or the development of commercially available DST at a selected critical concentration;
- resistant mutants at different level of resistance selected by in vitro experiment or animal models, or both, with representative resistant mutants deposited at multiple strain collections to serve as control strains, to enable the development of genotypic and phenotypic DST methods and to facilitate research;
- resistance mechanisms to the drugs included in the regimens that do not overlap with resistance mechanisms of other drugs previously used for TB or other infections, to avoid potential cross-resistance between the new agents and licensed agents of other classes;
- assessment of the frequency of selection of resistance using in vitro PD models and data that could support the use of a certain combination regimen based on a reduced risk of selecting for resistance (see Sections 4.1.2 and 4.1.4 of the EMA guideline *(68)*);
- expertise on resistance mechanisms, target genes and MIC distributions, to allow scientists and diagnostic developers to screen large genomic databases for evidence of resistance before the introduction of the drug and facilitate the development of genotypic DST; and
- detailed information about the drug, including stability, storage and solubility information, to allow DST assay development before regulatory approval by drug developers; particular care should be taken to investigate potential incompatibilities with existing diagnostic media or assays (e.g. when strains with relevant resistance mechanisms grow more slowly on particular media, such as those containing malachite green).

5.2 Treatment duration

Historically, treatments for TB and drug-resistant TB were of long duration. This was partly to compensate for the low efficacy of the individual medicines used to compose the regimen and their variable rates of penetration into the lesions, and partly to overcome *M. tuberculosis* adaptation or persistence mechanisms to achieve sterilization and eventually cure TB. The discovery of more potent medicines against *M. tuberculosis* led to the development of drug combinations that made it possible to shorten treatment duration. Through its recognized effect on improving completion rates, among other factors, treatments of shorter duration for most TB patients are expected to have an important impact on the TB epidemic, especially in high-burden countries *(30)*. Obviously, the severity, extent, localization and spread of TB disease, as well as patient characteristics, can condition the length of treatment duration; hence, stratified medicine strategies have been proposed to provide a more targeted approach to selection of a suitable treatment duration (see Section 5.4) *(31)*. Recent research showed that using a very short treatment duration as part of a "treat-follow-re-treat" approach

was able to cure most patients and may offer further flexibility in how the duration requirement could be set (see Section 5.4) *(70)*. Lastly, novel markers of treatment outcomes could help to define when it is safe to end treatment, and thus to determine the best duration in trials and in individual patient care. This underlines the need to develop suitable biomarkers to assist in defining optimal treatment duration according to the form of TB *(71)*.

5.3 Adherence and forgiveness

5.3.1 Impact of adherence and forgiveness on treatment outcomes

Imperfect adherence (i.e. missing a certain proportion of doses throughout the intended duration of a regimen) has long been considered an important driver of recurrent disease among patients treated for TB. Systematic measurement of adherence is challenging; hence, most detailed assessments come from clinical trials. Under conditions typical for explanatory trials, imperfect adherence is relatively limited, with about 4–7% of patients missing 10% of doses or more *(31)*. This is in contrast to data from pragmatic trials evaluating adherence-supporting interventions, where much higher rates of imperfect adherence have been observed (in the control arms); for example, in cluster-randomized trials in China and South Africa, the proportion of participants that missed at least 20% of doses were 30% and 49%, respectively *(5, 72)*.

Gaps remain in our knowledge about the impact of imperfect adherence on treatment outcomes and emergence of resistance. There is general consensus that imperfect adherence likely affects treatment outcome and increases the risk of developing resistance, but uncertainty remains as to the magnitude of this effect. In an individual participant meta-analysis of three Phase III efficacy trials, participants in the control arm on first-line TB treatment (6-month HRZE) who missed 10% or more of treatment doses had a 5.9-fold greater risk of unfavourable treatment outcomes *(31)*. This effect was most pronounced in "hard-to-treat" patient categories; that is, patients with a high bacillary load, low body mass index (BMI) and cavities on chest X-rays. These data suggest that imperfect adherence has a major impact on treatment outcomes and that, with the current dosing, HRZE is an unforgiving regimen, because missing as few as one in 10 doses of a regimen (or missing doses on most Sundays over 6 months) strongly increases the risk for unfavourable outcomes relative to completing treatment without any missed doses *(31)*. Conversely, data from the two trials of adherence-promoting interventions cited above suggest that improvements in adherence can result in little or no downstream effect (i.e. although adherence improves, treatment outcomes do not). These somewhat conflicting findings indicate that there is still considerable uncertainty about how treatment outcomes may be improved via improving adherence or by using more "forgiving" regimens.

Nevertheless, reducing the likely negative effects of imperfect adherence could be achieved by developing regimens that are easier to adhere to, improving regimens through interventions that support people better during their treatment or developing regimens that are more forgiving of imperfect adherence. It is important to consider these factors early in development because regimens with excellent efficacy under tightly controlled clinical trial conditions that are unforgiving of missed doses may be less effective under programmatic conditions.

5.3.2 Making good adherence easier

Some characteristics of drugs are important in facilitating, or impeding, adherence. These characteristics are the drug formulation, the dosing frequency, the route of administration, the pill burden and the palatability of pills and, most importantly, the safety and toxicity, as well as the overall treatment duration. These characteristics, which should be considered at the time of drug development, are discussed in the TRP tables in Section 3. To maximize adherence to therapy, current guidelines recommend the

use of a broad range of *patient-centred* case management strategies, including treatment support, video-supported treatment (VOT), education, incentives and digital treatment adherence technologies (DATs) *(73, 74)*. In the TRP tables in Section 3, it was generally considered that, ideally, most patients on the new regimen would be able to complete therapy (even if there is only limited support to ensure adherence), and that only some populations would require specific support activities. Optimally, it would be expected that the regimen be completed, at least in adults, through *self-administration*, without requiring close supervision or other interventions to ensure adherence. Having regimens that are easier to adhere to does not diminish the importance of providing education, counselling, care and support for people affected with tuberculosis.

5.3.3 Developing more forgiving regimens

Consideration of forgiveness in drug development may help guide the choice of optimal drug doses and drug combinations. However, it is challenging to study and score forgiveness in the context of drug development. Forgiveness should be based first on PK/PD data, because a potent regimen with favourable PK/PD characteristics (e.g. high plasma concentrations and longer half-life of drugs) should permit missed doses.[8] It is also closely linked with adequate dosing, which is one of the weakest points in TB drug development, because the dose is often chosen based on relatively short early bactericidal activity (EBA) monotherapy studies, and for some medicines is known to be influenced by other, nonpharmacological factors (e.g. cost) as seen, historically, in the selection of the lower end of the range (10–20 mg/kg) of rifampicin dosage and its initial dose-capping at 600 mg daily *(75)* that was eventually removed from recommended practice. Treatment forgiveness is heavily related to effectiveness, which is best assessed in pragmatic trials and post-approval implementation studies that occur late in the drug development pathway. Therefore, developers may conduct *simulation studies* to predict the effectiveness of the regimen in the field so as to estimate its probable forgiveness, based on the known PK/PD characteristics of individual drugs.

5.4 Treatment strategies

Beyond the description of a treatment regimen (defined by component drugs, doses and regimen duration), regimens can be implemented as part of a "treatment strategy" that describes how the regimen can be employed to maximize benefits and minimize harms. Treatment strategies may, for example, go beyond a simple one-size-fits-all approach and provide a framework for how certain regimen characteristics (e.g. dose or duration) should be varied, depending on patient characteristics or other factors. This section provides some examples of such strategies or approaches.

5.4.1 Stratified medicine approach

Data from registration-quality contemporary trials with over 6000 TB patients suggest that about 75% of patients with DS-TB could be successfully treated with a regimen duration of 4 months or less, while a minority of patients (18–25%) with "hard-to-treat" disease would require intensified treatment with longer duration or different drug doses. Taken together, data from the TB ReFLECT and S31/A5349 studies indicate that high-risk patients (defined using several specific parameters) require a treatment duration of longer than 6 months of SOC to reach target cure rates, and even with a high-dose rifapentine regimen (in the S31/A5349 study) the high-risk group still needs longer treatment. For any given regimen potency, an extended treatment duration for patients at higher risk increases cure rates.

[8] For HIV, for example, integrase inhibitor dose is much higher than is needed to suppress the virus and the duration of binding to target is prolonged. This means that a patient can miss doses frequently and still have a good outcome.

Similarly, work on RR-TB has shown that treatment for severe disease may need to be longer, but that patients with less severe disease could be cured with regimens of shorter duration. Thus, it is likely that a spectrum of different treatments and durations will be needed for different manifestations of TB, to match the spectrum of TB disease, as mentioned above. In this respect, modelling studies suggest that easy-to-treat patient groups can achieve cure with shorter treatment regimens, the exact durations of which will decrease with more potent regimens, whereas patients in high-risk groups will always need a longer regimen to reach adequate cure rates *(76)*.

A framework for stratification based on pragmatic markers could provide a basis for the decision on the duration of treatment. Further research is needed to ensure that a stratified approach can be applied under programmatic conditions. Access to better tests for tuberculosis treatment monitoring and optimization as recently described in WHO TPPs would provide additional options to the application of a stratified medicine approach to TB treatment *(71)*.

5.4.2 Dose adjustment

Dose adjustment was used successfully within the allocation of the bedaquiline, pretomanid and linezolid (BPaL) regimen to people with MDR-TB or extensively drug-resistant TB (XDR-TB) to allow linezolid to be given at a high dose for those who can tolerate it – while those who do not could still receive linezolid and benefit from its action at a lower dose *(59)*. Similarly, higher doses for rifampicin and rifapentine are being explored but show some tolerability issues – a dose adjustment strategy could allow patients to benefit from lower doses while preserving treatment efficacy or increase dose without affecting the safety of the regimen. Further implementation and operational research is needed to support usability of such an approach under programme conditions.

5.4.3 The "treat-follow-re-treat" approach

The traditional approach to treatment of TB is to choose a treatment duration that ensures high cure rates for a large majority of patients. However, as indicated above, evidence suggests that many patients could be cured with a shorter duration of treatment. Therefore, an alternative approach would be to treat everyone with a shorter course of treatment (which is adequate for most patients) and to follow closely and re-treat the minority of those who relapse (and are thereby identified as needing longer treatment) with a standard treatment regimen. This would avoid treating everyone with a long course of treatment and thereby giving unnecessary treatment to the majority of patients for the sake of the minority who need it. This advantage would need to be weighed against the risks incurred by those who require re-treatment, as well as the programmatic challenges of this approach.

The approach described above has been investigated in the "Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for drug-sensitive TB" (TRUNCATE TB) trial, using four 2-month treatment arms containing novel combinations of TB drugs and comparing the results to a control arm consisting of the standard 6-month HRZE regimen. The primary composite clinical outcome of being alive, well and off TB treatment at 96 weeks did not differ between the standard treatment arm and the best-performing test arm, nor did the proportion of participants that had Grade 3 or 4 adverse events or serious adverse events, or who died *(48)*. The study provides proof of concept for another treatment strategy that, instead of stratifying patients into different risk groups before administering treatment, applies a shorter treatment duration to all and manages the higher risk group of patients differently, with an additional course of treatment. More research is needed to optimize the regimens being provided and investigate this treatment strategy in broader populations (including people living with HIV) and under programme conditions.

5.5 Post-TB lung disease

There is increasing recognition that pulmonary TB, both RS-TB and RR-TB, may result in clinically significant lung injury and functional impairment, termed post-TB lung disease (PTLD), even in patients whose treatment is otherwise deemed to be successful *(77–79)*. Multiple mechanisms triggered by chronic inflammation have been implicated. These include loss of extracellular matrix, airway remodelling and collagen deposition. These mechanisms may remain active well beyond microbiological cure. The resulting pathologic changes (cavitation, bronchiectasis and lung stiffness) hinder mucosal host defenses and favour bacterial and fungal colonization, which in turn can cause sustained inflammation and progressive structural damage and functional impairment. The resulting global burden of post-TB disease – mainly cardiopulmonary disability and mortality – appears to almost equal that due to acute TB *(80)*.

There is growing clinical evidence that host-directed disease-modifying drugs, including antioxidants (e.g. *N*-acetylcysteine), phosphodiesterase inhibitors (e.g. CC-11050) and mammalian target of rapamycin (mTOR) inhibitors (e.g. everolimus) may be able to mitigate these risks, particularly if treatment is initiated early *(81–83)*. Other adjunctive therapies (including statins, imatinib and metformin) are also being considered, based on their ability to activate host antimicrobial mechanisms in preclinical models *(84–86)* and some initial clinical studies have been completed *(87, 88)*. Correlates of immune protection and the "right" quantity and quality of anti-TB immune responses are unknown. It is likely that one type of host-directed therapy is not beneficial for all individuals affected by TB, and that endotype-specific host-directed therapies may provide benefits for different types of patients *(89, 90)*. It has also been suggested that host-directed therapy during TB treatment could contribute to further treatment shortening for pulmonary disease *(91, 92)*. Although there is emerging preclinical evidence (e.g. the integrated stress response inhibitor ISRIB) *(93)*, there is currently no clinical evidence to support this.

Little is known about whether, how or how much the composition or duration of anti-TB (microbial) therapy contributes to the risk or extent of PTLD. There is no validated standard for measuring the presence of PTLD. Efforts to date rely on general indicators of lung injury or functional impairment, including spirometry, strength or mobility tests, and questionnaires that measure the impact of respiratory symptoms on quality of life (QoL).

The recognition of the importance of PTLD has two implications for TRPs for anti-TB regimens. First, developers are encouraged to incorporate evaluation of lung injury and functional impairment into trial designs. Although these indicators are likely to change in the coming years, it is currently advisable to start with at least spirometry, strength or mobility, and respiratory QoL instruments in cases where an attempt to measure PTLD is considered. Second, developers may anticipate the development of a new characteristic of future regimens: the ability to limit lung injury and functional impairment, and therefore PTLD.

5.6 Equitable access and transparent pricing

Drug developers should ensure that any resulting products are quality-assured, affordable, widely available in a timely fashion and supplied in sufficient quantities to meet the needs of affected populations.

Developers should note that WHO will give due consideration to whether there are pathways towards equitable access to quality-assured versions of the desired formulations *(43)*. Quality of medicines can be assured through WHO prequalification or similar assessment by an SRA or WHO Listed Authority (WLA) *(94)*. Ultimately, it is expected that quality-assured formulations of the regimen, or its individual components, will be widely available in countries soon after a recommendation is made. Developers, including manufacturers of generics, should also commit to prioritization of in-country registration and sales in TB endemic countries, at the lowest sustainable price.

To achieve earlier and simplified regimen development, and to ensure that products are fit-for-purpose and can meet the needs of affected communities, particularly in low-resourced areas, developers should work within open collaborative models for TB research and development (R&D), enabling sharing of research knowledge, materials (e.g. reference products and active pharmaceutical ingredients), intellectual property (e.g. using mechanisms such as the Medicines Patent Pool) and data. With necessary controls, developers should allow their drugs to be tested and studied in combination with other drugs from other developers, including in the analyses required to allow for future development of fixed dose combinations (FDCs), where feasible. In addition, affected communities should be consulted and involved in the late stages of the drug or regimen research to ensure that gaps in care, and the needs and priorities of patients are driving the final product and use-case.

Given the significant role of public financing for TB research and innovation, new products should be appropriately priced to reflect overall investments by global actors, including governments, philanthropists, and other research and product sponsors. Any resulting product should deliver a public return on investment and be linked to public health-driven priority-setting and application of the core principles of affordability, effectiveness, efficiency and equity (as identified in resolutions WHA66.22 *(95)* and WHA69.23 *(96)*). New regimens and their component drugs should aim to be cost-neutral, if not cost-saving, to health programmes and systems, when taking into account both drug and nondrug costs. The price of medicines is determined by many factors, including production costs, margins to recover development costs and profit margins. Those margins are highly dependent on the volume and speed of product uptake; hence, the margin should be modest and reasonable, given the public health context. Furthermore, there should be collective efforts to ensure accelerated development, commercialization and scale-up of affordable generic versions of drugs and formulations included in target regimens.

Lastly, WHO suggests that developers improve the transparency of pricing by sharing the net transaction prices of pharmaceutical products with relevant stakeholders, disclosing prices along the supply and distribution chain, reporting publicly the R&D contributions from all sources, and communicating pricing and reimbursement decisions to the public.

5.7 Cost considerations

5.7.1 Overview

In many high TB burden settings, adoption of novel TB treatment regimens is unlikely if using these regimens would lead to an increased cost to the health system compared with continuing with the current SOC. Conversely, especially in higher resource settings where willingness-to-pay thresholds may be higher, cost-effective regimens that offer improvements to patient health may be adopted even if they come at increased cost. Although the determination of costs that are compatible with regimen access will depend on various factors specific to the regimen and market, identification of price ranges at which novel treatment regimens may be cost-neutral or cost-effective compared with the SOC can help drug developers to evaluate trade-offs between improved regimen characteristics and increased regimen cost.

The full costs of treatment include not only the price of the drugs themselves, but also other components of treatment, such as outpatient visits and safety monitoring tests, which often exceed the drug costs. A novel regimen whose component drugs are priced higher than those contained in the current SOC regimens may therefore still yield net cost savings if it reduces the costs of other aspects of treatment. In the longer term, novel, more effective regimens may generate additional savings by reducing re-treatments and transmission, thereby averting future treatment costs.

This section describes a modelling analysis to estimate the price thresholds below which a range of novel RS-TB and RR-TB regimens would be expected to achieve cost-neutrality and cost–effectiveness, compared with the current SOC (i.e. 6HRZE and BPaLM), across three representative settings (India, the Philippines and South Africa). The following price thresholds were estimated (each from both societal and health system perspectives):

- *short-term cost-neutrality* – considering only savings accrued during treatment (e.g. from reduced monitoring requirements);
- *medium-term cost-neutrality* – additionally considering savings from averted re-treatments and secondary cases over 5 years; and
- *cost–effectiveness* – additionally considering health improvements.

Additional details regarding the methodology are available in Section 2.4 and Annex 3.

5.7.2 Findings for RS-TB and RR-TB

Under the SOC, the societal costs of treating one patient (including resultant re-treatment and secondary case treatment costs, in the event that the patient was not cured) were estimated to be in the range US$ 430–780 per RS-TB patient and US$ 1680–2850 per RR-TB patient (Table 5.1). Patient out-of-pocket and indirect costs made up the greatest share of RS-TB costs (46–60%), whereas drugs and (in some settings) patient support, laboratory tests, and future treatments or re-treatments accounted for the greatest share of RR-TB costs.

Novel TB regimens that improve upon the respective SOC across multiple characteristics could yield substantial savings in the overall costs of treating TB, justifying higher prices for these regimens (Table 5.2). In the short term, it was estimated that an all-optimal RS-TB regimen would be cost-neutral from a societal perspective at prices in the range US$ 150–280, whereas the corresponding cost-neutral threshold for an all-optimal RR-TB regimen was in the range US$ 830–1440. In the medium term, consideration of 5-year savings from averted re-treatments and secondary cases was estimated to increase the cost-neutral thresholds by 47–61% (RS-TB) and 29–41% (RR-TB), with thresholds of US$ 240–420 for an all-optimal RS-TB regimen and US$ 1080–1890 for an all-optimal RR-TB regimen.

Considering only savings to the health care system reduced cost-neutral prices of an optimized RS-TB regimen by 53–66% and of an optimized RR-TB regimen by 1–27% (with variation by country, depending on the extent to which patient-borne costs are offset by treatment vouchers and in-kind support covered by the health system). The cost-effective price thresholds, which incorporated the value ascribed to health improvements in addition to costs, were substantially higher and varied more by country income level, being US$ 1530–8930 for RS-TB and US$ 2320–10 640 for RR-TB.

Among novel regimen characteristics, improvements in duration and (in the medium term) ease of adherence were particularly important in facilitating cost-neutrality at higher regimen prices (Fig. 5.1). In India, for example, a 6-month RS-TB regimen (otherwise fully optimized) resulted in nondrug costs that were 60% higher than with an otherwise equivalent 2-month regimen. Thus, whereas the 2-month regimen could achieve cost-neutrality in the medium term at a price as high as US$ 320, the 6-month regimen would have to be priced substantially lower (US$ 150) to be cost-neutral. Similarly, for an otherwise-optimal RR-TB regimen in India, increasing the duration from 2 months to 6 months lowered the cost-neutral price from US$ 1080 to US$ 890. Improvements in regimen duration led to twofold to fivefold increases in the prices at which RS-TB regimens would be cost-neutral and 1.3-fold to 1.5-fold increases in the cost-neutral prices for RR-TB regimens. Optimizing adherence (such as might be achieved via a long-acting injectable regimen) yielded less savings than optimizing duration, but still substantially increased the thresholds at which regimens would be cost-neutral, resulting in cost-neutral prices that were 1.2–2.5 times higher (RS-TB) and 1.2–1.4 times higher (RR-TB) than otherwise equivalent regimens with a level of adherence similar to the SOC.

After duration and ease of adherence, the next most influential attributes in the medium term were efficacy (for RR-TB regimens and otherwise fully optimized RS-TB regimens) and forgiveness (for RS-TB regimens with less optimized levels of adherence and efficacy). This variation across regimen types was determined by which attributes had the most room for improvement: efficacy was more important for RR-TB regimens given the lower efficacy estimates for BPaLM compared with HRZE, whereas forgiveness was more important for RS-TB regimens given lower assumed SOC forgiveness for HRZE than BPaLM (see Section 4 and Annex 2 for more details). Regimen safety was more influential for RR-TB regimens, given the greater room for improvement over the SOC. In the short term, with costs of re-treatment and transmission excluded from consideration, the cost-neutral price was sensitive only to duration (which remained the most influential attribute) and safety. Savings from improvements in ease of adherence, forgiveness and efficacy accrued in the form of averted future re-treatments and secondary cases, while savings from improvements in duration and safety mostly accrued in the form of more direct cost reductions (e.g. fewer clinic visits, less monitoring and lower patient costs).

Table 5.1. Total 5-year costs (in US$) per patient under SOC TB regimens[a]

	Cost of RS-TB treatment using SOC regimen (6HRZE)		Cost of RR-TB treatment using SOC regimen (BPaLM/BPaL)	
	Health system perspective	Societal perspective	Health system perspective	Societal perspective
India	$180	$670	$1050	$1660
Philippines	$170	$430	$1640	$1810
South Africa	$290	$780	$2650	$2850

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; HRZE: isoniazid, rifampicin, pyrazinamide and ethambutol; RR-TB: rifampicin-resistant TB; RS-TB: rifampicin-susceptible TB; SOC: standard of care; TB: tuberculosis.

[a] Shows the 5-year costs under the SOC regimens for RS-TB and RR-TB. Costs were estimated under a societal perspective (medical and nonmedical costs; main analysis) or a health system only perspective (medical costs; sensitivity analysis).

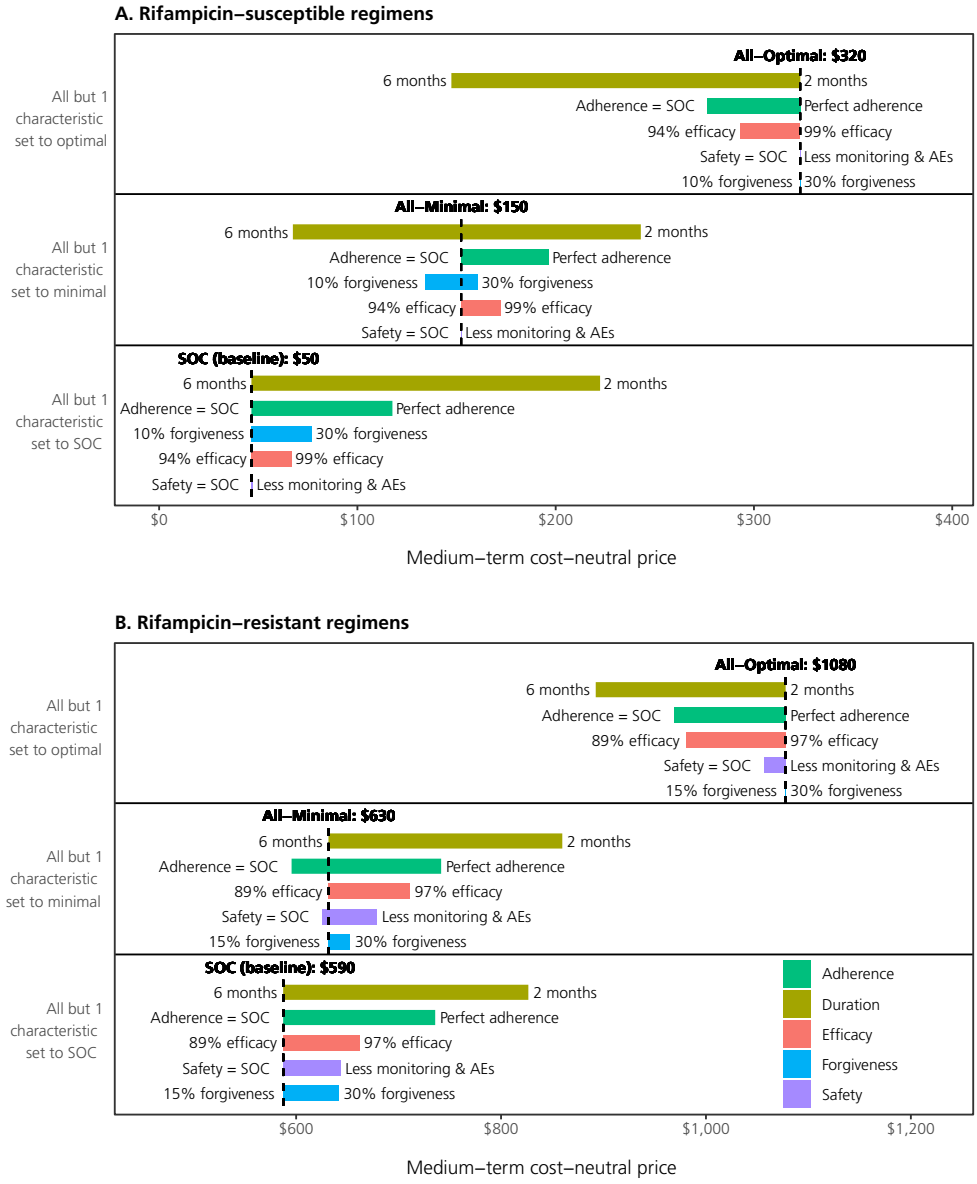
Table 5.2. Cost-neutral and cost-effective price thresholds (in US$) for all-optimal novel TB regimens[a]

	Cost of novel regimen drugs at which novel regimen meets each threshold						Cost of SOC drugs (for comparison)
	Short-term cost-neutrality		Medium-term cost-neutrality		Cost–effectiveness		
	Health system perspective	Societal perspective	Health system perspective	Societal perspective	Health system perspective	Societal perspective	
RS-TB regimens							
India	$80	$220	$110	$320	$1310	$1530	
Philippines	$70	$150	$110	$240	$2040	$2180	$46
South Africa	$120	$280	$170	$420	$8680	$8930	
RR-TB regimens							
India	$630	$830	$780	$1080	$2020	$2320	
Philippines	$870	$880	$1200	$1240	$3310	$3270	$592
South Africa	$1400	$1440	$1820	$1890	$10 570	$10 640	

RR-TB: rifampicin-resistant TB; RS-TB: rifampicin-susceptible TB; SOC: standard of care; TB: tuberculosis; TRP: target regimen profile.

[a] Shows the short-term cost-neutral, medium-term cost-neutral and cost-effective price thresholds for novel regimens for RS-TB and RR-TB, with characteristics meeting the optimal values in the TRPs. Thresholds were calculated under a societal perspective (medical and nonmedical costs; main analysis) or a health system only perspective (medical costs; sensitivity analysis).

Fig. 5.1. Medium-term cost-neutral price thresholds (in US$) in India, under varying regimen attributes[a]



AE: adverse event; SOC: standard of care.

[a] Fig. 5.1 shows the medium-term cost-neutral price thresholds for novel regimens for RS-TB (panel A) and RR-TB (panel B) regimens in India under the societal perspective. Coloured bars show the variation in the price threshold when a single characteristic is varied from its SOC value to its optimal value (corresponding to optimal targets in the TRPs). The values that the remaining characteristics take on differ between the three sections of each panel. Specifically, the bottom section of both panels ("All but 1 characteristic set to SOC") show the effect of fixing all characteristics at their SOC values (vertical dashed line) and then improving one characteristic at a time from its SOC to its optimal value. The middle parts of each panel ("All but 1 characteristic set to minimal") show results when all characteristics are fixed at their minimal TRP target values (and again, a single characteristic is varied from its SOC to its optimal value); the minimal target values are not shown in Fig. 5.1, but are displayed in Annex 3. The top parts of each panel ("All but 1 characteristic set to optimal") show results when all characteristics except the one being varied are fixed at their optimal TRP target values. Colours indicate which characteristic is being varied, and the text labels indicate the values of each characteristic (left of the bars = SOC values for each characteristic; right of the bars = optimal values for each characteristic). Bars are ordered vertically by the impact each characteristic has on the cost-neutral price threshold (the vertical distance between each bar is equal or not meaningful). Forgiveness has no impact on the costs of otherwise all-optimal regimens because adherence is assumed to be perfect.

5.7.3 Generalizability to pan-TB regimens

This analysis did not estimate price thresholds for pan-TB regimens, because savings from a pan-TB regimen would depend strongly on country-specific complexities (e.g. current DST practices) and cost components that are difficult to estimate using an ingredients approach (e.g. supply chain and training costs). However, if a pan-TB regimen were introduced today that met the same optimal targets as the novel RS-TB regimen modelled here, but which could also treat RR-TB, then the considerable reduction in the cost of treating RR-TB patients (and, for longer term price thresholds, improved outcomes among patients with both detected and undetected rifampicin resistance) means that the cost-neutral and cost-effective prices for a pan-TB would be somewhat higher than those estimated here for an RS-TB regimen with otherwise-similar characteristics. In addition, because the number of RR-TB patients for whom large savings could be achieved is small relative to the size of the RS-TB patient population, a cost-neutral pan-TB regimen would still need to be priced considerably lower than the prices estimated as possibly being cost-neutral for a novel RR-TB regimen.

5.7.4 Limitations

These results do not incorporate the potential for novel regimens to achieve additional cost savings among children and other physiologically special populations, nor do they incorporate the potential to eventually reduce the scale and costs of nontreatment-related TB services through reductions in TB incidence. In the nearer term, however, these results may be optimistic estimates of the ability of existing budgets to absorb increased drug costs, because they are based on total spending across a variety of health care categories and patient expenditures with different budgetary sources. The results include estimates from the health system perspective, which can allow decision-makers to judge what prices would be cost-neutral or cost-effective from the standpoint of only health system expenditures; however, even within the health system, different spending categories (e.g. laboratory testing, clinical staffing and drug purchasing) may be siloed. Savings may accrue to different payers than those responsible for purchasing a novel regimen, and reallocation of funding to novel drug purchasing may pose challenges of coordination and buy-in across multiple funding sources and budgets. Furthermore, savings are not expected to accrue immediately, and it is possible that not all projected savings will be fully realized, even in the medium term; for example, a twofold reduction in clinic visits does not translate into twofold cost savings without reductions in the size (or salary) of the health care workforce.

Other limitations of this analysis include the uncertain risks (and costs) of further drug resistance acquisition; uncertain costs of future DST; limited evidence on SOC forgiveness and adherence (important because better regimen forgiveness reduces the importance of adherence improvements, and vice versa), which are currently estimated for all regimens based only on limited data for existing RS-TB regimens; and the possibility that reductions in SOC costs make it more difficult to achieve comparative savings for novel regimens (significant reductions in the cost of RS-TB SOC are unlikely but are possible for RR-TB SOC). As the price of bedaquiline (or any other component drug of the standard of care regimens) declines, the prices at which novel regimens would be cost-neutral or cost-effective will also decline. The magnitude of declines in these price thresholds will be approximately commensurate with the magnitude of standard of care price declines, with some minor variation due to differences in loss to follow up and treatment of failures, relapses, and secondary cases between the standard of care and novel regimens. Finally, thresholds will vary across settings, and improved regimens can yield greater savings in settings with higher unit costs, as demonstrated by the higher thresholds in South Africa, an upper-middle-income country with generally higher unit costs (and a higher cost–effectiveness threshold) than India and the Philippines.

5.7.5 Conclusions

Although there are many stakeholders and mechanisms that influence price-setting (and payment) for TB drugs, the results presented here provide a starting point for understanding the prices at which improved treatment regimens for RS-TB and RR-TB could be affordable in high TB burden countries. Although consideration of budgetary impacts from adopting new regimens is necessary, it is important not to lose sight of the broader goal of making more efficacious, tolerable and safe regimens accessible to all TB patients (for additional discussion, see Section 5.6). As exemplified by the path to safe and effective antiretroviral therapy for HIV *(97)*, adopting such an "end-in-mind" approach can, ultimately, yield affordable prices and address numerous other barriers to novel regimen adoption and access.

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Annex 2. Additional information on modelling of potential health impact

A2.1 Overview

As part of the process to revise and update the World Health Organization (WHO) target regimen profiles (TRPs) for treatment of tuberculosis (TB), both rifampicin-susceptible TB (RS-TB) and rifampicin-resistant TB (RR-TB), two modelling analyses were conducted, one focused on prioritization of regimen characteristics based on patient cures, the other on cost. This annex describes the analysis of patient cures, which estimated the impact of optimizing regimen characteristics (e.g. efficacy and duration) and provided evidence on the trade-offs between improving different characteristics.

A2.2 Modelled outcomes

The primary modelled outcome of interest was the proportion of the relevant population (i.e. diagnosed patients with RS-TB or RR-TB who do not experience pretreatment loss to follow-up and for whom a given regimen would be indicated) that are durably cured by a given regimen under programmatic conditions. Durable cure was selected as the primary outcome for the sake of transparency and based on an earlier (2016) analysis, which found that downstream impacts on TB incidence and mortality largely correlated with modelled treatment outcomes *(1)*.

A2.3 Standard of care

For RS-TB, the standard of care (SOC) for most patients was assumed to comprise 2 months of daily isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) followed by 4 months of isoniazid and rifampicin (i.e. 6-month HRZE]). The assumption is that all patients receiving the RS-TB regimen have RS-TB (i.e. that appropriate and accurate rifampin drug susceptibility testing [DST] is performed) but that only a minority of isoniazid monoresistance is detected and treated with levofloxacin plus rifampicin, pyrazinamide and ethambutol (RZE) under the SOC and the remainder of isoniazid monoresistant TB is treated with HRZE, with the efficacy of the SOC adjusted downward accordingly.

For RR-TB, the SOC was assumed to be the 6-month regimen comprising bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM). Those with fluoroquinolone resistance experience the efficacy of the 6-month regimen comprising bedaquiline, pretomanid and linezolid (BPaL) (i.e. with no moxifloxacin), either because moxifloxacin is not prescribed or because it is ineffective. Regimen efficacy was adjusted according to the proportion of patients with fluoroquinolone resistance and the efficacy of BPaL (relative to BPaLM).

A2.4 Model and regimen characteristics

The analysis modelled trade-offs between four regimen attributes: efficacy, duration, ease of adherence and forgiveness (Table A2.1). Efficacy, duration and forgiveness corresponded to their definitions in the TRP tables in Chapter 3, and the ease of adherence attribute was designed to encompass several regimen characteristics that affect adherence to treatment (i.e. tolerability and side-effects, pill burden, formulation or dosage form, dosing frequency and routine of administration).

Among patients who are eligible for and initiate a regimen, the analysis estimated the proportion of patients cured as a function of regimen efficacy, duration, ease of adherence and forgiveness. Regimen *efficacy* represents the proportion cured among patients who are 100% adherent and take the full course of treatment, and is based on outcomes from clinical trial data. The probability of cure was then reduced from this maximal amount among those who are less than fully adherent ($adj\_adherence$) or complete less than the intended duration ($adj\_duration$) :

[1] $$p\_cure_i = (efficacy_i)(adj\_adherence_i)(adj\_duration_i)$$

Specifically, with regard to adherence, the analysis modelled the proportion of patients who are less than fully adherent as depending on the *ease of adherence*, and modelled the extent to which that nonadherence reduced the probability of cure (below the regimen's maximal efficacy) as depending on the regimen's *forgiveness*. Adherence is defined as the percentage of doses a patient takes while they remain in care (i.e. are not lost to follow-up). The analysis divided patients into two adherence categories: adequate adherence ($p_{adequate}$) and reduced adherence ($p_{reduced}$), where the probability of cure is only reduced for those in the reduced adherence group. The threshold determining adequate versus reduced adherence is based on forgiveness. Specifically, forgiveness is defined as the percentage of doses that can be missed at which patients are still expected to achieve full regimen efficacy. The relative efficacy achieved by poorly adherent patients (77%) is based on evidence from the 6-month HRZE regimen *(2)* and does not vary across regimens (Fig. A2.1). For any given threshold, the proportion of patients with adequate adherence increases with better ease of adherence.

[2] $$adj\_adherence_i = \frac{1}{N}\sum_{n=1}^{N} 1\{adherence \geq threshold_{forgiveness;i}\}_{ease\_adherence;\, i} + (releff_{reduced\_adherence})(1 - \frac{1}{N}\sum_{n=1}^{N} 1\{adherence < threshold_{forgiveness;i}\}_{ease\_adherence;\, i})$$

Finally, the regimen *duration* determines the probability that a patient completes the full regimen and experiences the associated probability of cure (i.e. the efficacy modified by an adherence-dependent factor). The duration also determines what proportion of efficacy is lost when patients are lost to follow-up after a given partial duration, because a given number of treatment weeks will be a greater proportion of the full treatment course (and will thus achieve closer to full efficacy) for a regimen whose full duration is shorter. The analysis modelled the relationship between percentage of regimen completed and percentage of efficacy realized as being constant across regimens ($releff_t$; Fig. A2.2). To determine the patients lost to follow-up at each weekly time step , a nonregimen-varying loss-to-follow-up risk of 1% per month (0.23% per week) is modelled over a regimen's intended duration; thus, cumulative loss to follow-up is higher for regimens with longer durations.

[3] $$adj\_duration_i = (1 - 0.0023)^{duration_i} + \sum_{t=1}^{duration_i - 1} 0.0023(1 - 0.0023)^{t-1} releff_t$$

Outcomes among patients initiating treatment are thus determined by a product of efficacy, loss to follow-up, duration, adherence and forgiveness, as shown in equation 4.

[4] $$p_{cure;i} = efficacy_i * \left[\frac{1}{N}\sum_{n=1}^{N} 1\{adherence \geq threshold_{forgiveness;i}\}_{ease\_adherence;\, i} + (releff_{reduced\_adherence})(1 - \frac{1}{N}\sum_{n=1}^{N} 1\{adherence < threshold_{forgiveness;i}\}_{ease\_adherence;\, i})\right] * \left[0.9977^{duration_i} + \sum_{t=1}^{duration_i - 1} 0.0023(0.9977)^{t-1} releff_t\right]$$

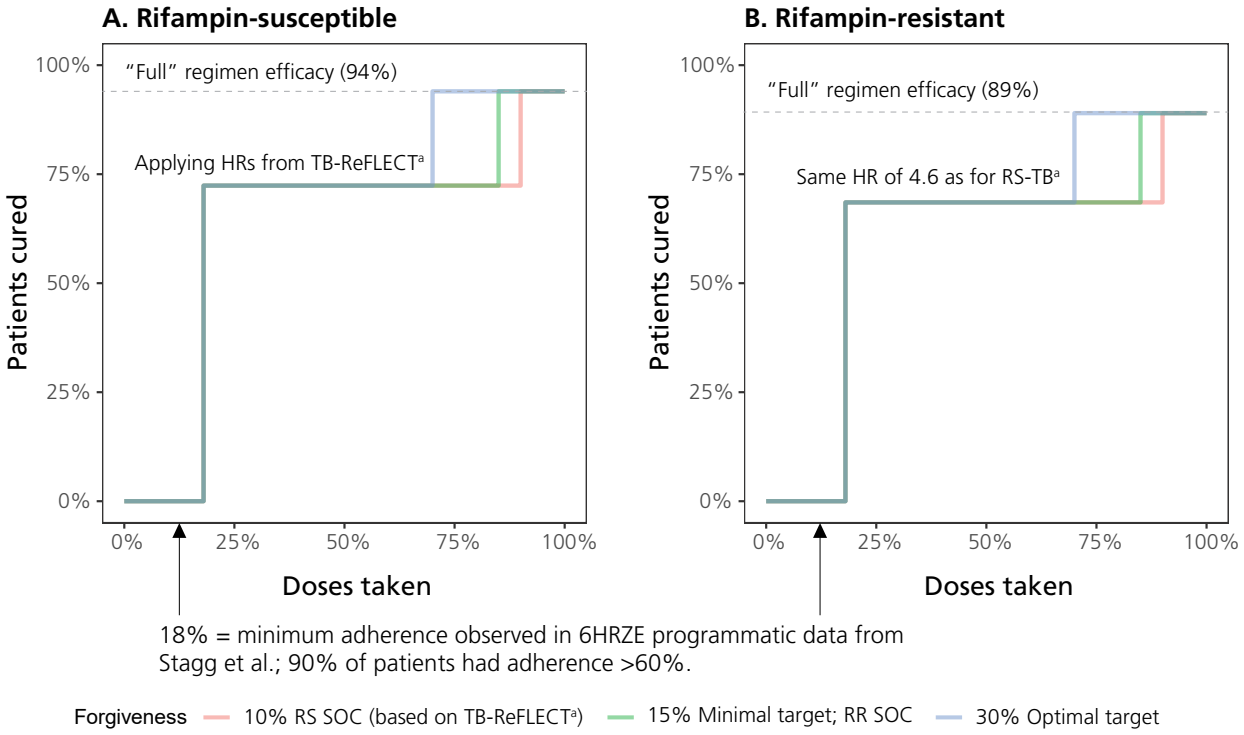
Trade-offs between improving different regimen attributes were evaluated by considering hypothetical novel regimens that achieve various combinations of SOC, minimal, or optimal efficacy, duration, ease of adherence and forgiveness (Table A2.1). The minimal and optimal values were based on the TRP targets. The analysis varied one regimen attribute at a time over its full range (SOC to optimal) while holding all others constant (i.e. at the all-SOC, all-minimal or all-optimal levels) to model each attribute's impact on proportion of patients cured.

Table A2.1. Modelled regimen attributes

RS-TB regimens		SOC	Minimal	Optimal	Sources and notes
Efficacy		94%	94%	99%	**SOC**: based on *(3–7)* **Minimal**: same as SOC **Optimal**: better than SOC (all equal to values from 2016 analysis)
Duration		6 months	3.5 months	2 months	**SOC**: assumed **Minimal**: median of TRP range (3–4 months) **Optimal**: TRP value
Ease of adherence (% of patients by adherence category)	≥90%	30.9%	30.9%	100%	**SOC**: based on *(8–10)* **Minimal**: same as SOC **Optimal**: consistent with a long-acting formulation (e.g. injection) at each treatment visit
	85 – <90%	21.7%	21.7%	0%	
	70 – <85%	9.6%	9.6%	0%	
	<70%	37.8%	37.8%	0%	
Forgiveness (% doses that can be missed while still achieving full efficacy)		10%	15%	30%	**SOC**: based on *(2)* **Minimal**: TRP value **Optimal**: TRP value
RR-TB regimens		**SOC**	**Minimal**	**Optimal**	**Sources and notes**
Efficacy		89%	89%	97%	**SOC**: based on *(11–13)* **Minimal**: same as SOC **Optimal**: better than SOC; benchmarked at median of RS-TB minimal and optimal
Duration		6 months	6 months	2 months	**SOC**: assumed **Minimal**: TRP value **Optimal**: TRP value
Ease of adherence (% of patients by adherence category)	≥90%	25.7%	30.9%	100%	**SOC**: minimum level of adherence observed across 3 studies used to parameterize RS-TB SOC *(10)*, given lack of evidence on adherence under BPaL(M) and lower tolerability (side-effect profile) **Minimal**: improvement over SOC; benchmarked as the same as RS-TB minimal **Optimal**: consistent with a long-acting formulation (e.g. injection)
	85 – <90%	9.8%	21.7%	0%	
	70 – <85%	24.3%	9.6%	0%	
	<70%	40.2%	37.8%	0%	
Forgiveness (% doses that can be missed while still achieving full efficacy)		15%	15%	30%	**SOC**: based on *(2)*, adjusted for pharmacokinetic evidence indicating that BPaL(M) has better forgiveness than HRZE (e.g. bedaquiline and pretomanid have longer half-lives than all the component drugs in HRZE *(14)*) **Minimal**: TRP value **Optimal**: TRP value

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; HRZE: isoniazid, rifampicin, pyrazinamide and ethambutol; RR-TB: rifampicin-resistant TB; RS-TB: rifampicin-susceptible TB; SOC: standard of care; TB: tuberculosis; TRP: target regimen profile.

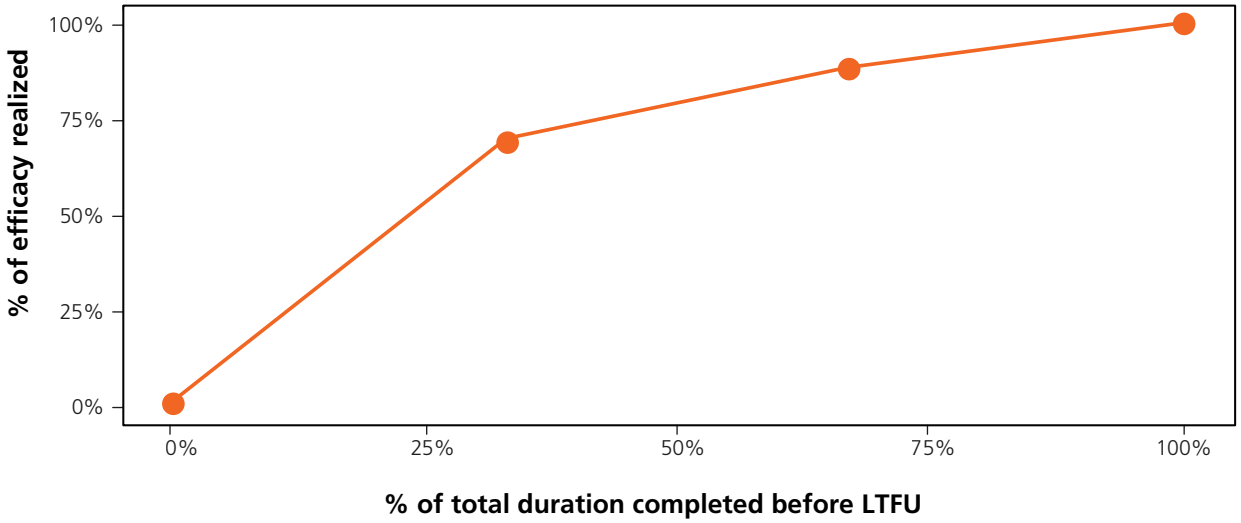
Fig. A2.1. Modelled relationship between adherence and percentage of patients cured (forgiveness – varies by regimen)



HR: hazard ratio; RR: rifampicin resistant; RS: rifampicin susceptible; RS-TB: rifampicin-susceptible TB; SOC: standard of care; TB: tuberculosis.

[a] Based on data from *(2)*. The 100% and 90–100% adherence groups were combined to calculate a 4.6 times higher risk of an unfavourable outcome if <90% versus ≥90% adherent. This figure does not include reductions in the probability of cure due to discontinuation, which is modelled separately (see Fig. A2.2).

Fig. A2.2. Modelled relationship between loss to follow-up, duration and relative efficacy (does not vary by regimen)



HRZE: isoniazid, rifampicin, pyrazinamide and ethambutol; LTFU: loss to follow-up.

Note: This figure does not include reductions in the probability of cure due to poor adherence while still on treatment, which is modelled separately (see Fig. A3.1). It is based on evidence from historical trials of shorter HRZE regimens *(15, 16)*.

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Annex 3. Additional information on cost modelling

A3.1 Overview

As part of the process to revise and update the World Health Organization (WHO) target regimen profiles (TRPs) for treatment of tuberculosis (TB), both rifampin-susceptible TB (RS-TB) and rifampin-resistant TB (RR-TB), two modelling analyses were conducted, one focused on prioritization of regimen characteristics, the other focused on cost. This annex describes the cost analysis, which estimated price thresholds for novel RS-TB and RR-TB treatment regimens at which a regimen would be considered cost-neutral or cost-effective compared with the current RS-TB and RR-TB standards of care (SOC).

A3.2 Price thresholds

The cost analysis included estimation of three price thresholds:

- **Short-term cost-neutrality:** This analysis estimated the price that would make the novel regimen cost-neutral compared with the SOC, considering only costs accrued during a patient's treatment course. Cost-neutrality of a regimen that is more costly based on the cost of drugs alone could be achieved, for example, by reductions in patient care costs (e.g. through shorter treatment duration or reduced monitoring and side-effects).
- **Medium-term cost-neutrality:** This analysis considered not just cost savings at the individual patient level, but also incorporated estimates of savings from future cases averted (e.g. by a novel regimen that increases the proportion of patients cured and thus reduces secondary transmission). It estimated the price that would be cost-neutral compared with the SOC on a 5-year time horizon.
- **Medium-term cost–effectiveness:** This analysis considered the same perspective as the medium-term cost-neutrality analysis (savings during the treatment course and savings from averted future cases and re-treatments) but estimated the price at which a novel regimen would be considered cost-effective compared with the SOC under a lifetime horizon. This analysis combined cost estimates with estimates of disability-adjusted life years (DALYs) associated with active TB, side-effects from TB treatment, TB deaths and post-TB sequelae to estimate a cost-effective drug price using country-specific cost–effectiveness thresholds. Costs and DALYs were discounted 3% annually.

A regimen priced to be cost-neutral will also be cost-effective, because the analysis modelled new regimens that improve on the SOC in terms of their safety, efficacy and other characteristics. Conversely, cost-effective regimens may not necessarily be cost-neutral in the short or medium term.

A3.3 Representative settings

Each of the three price thresholds were estimated for novel regimens in each of three representative settings: India, the Philippines and South Africa. These settings were chosen because they have high TB incidence rates; represent diversity in terms of income levels, HIV prevalence, HIV-TB co-prevalence and geographical regions; and estimates of TB-related unit costs for these countries are available in the published literature.

A3.4 SOC regimens

For RS-TB, the SOC was assumed to comprise 2 months of daily isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin (i.e. 6-month isoniazid, rifampicin, pyrazinamide and ethambutol [HRZE]) for most patients. Patients with TB that is isoniazid monoresistant receive the 6-month regimen comprising levofloxacin, rifampicin, pyrazinamide and ethambutol if their isoniazid resistance is detected. For RR-TB, the SOC is assumed to be the 6-month regimen comprising bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM); patients with fluoroquinolone-resistant TB receive the 6-month regimen comprising bedaquiline, pretomanid and linezolid (BPaL) ((i.e. no moxifloxacin) if their fluoroquinolone resistance is detected.

In addition to adjusting the efficacy of the SOC regimens to account for isoniazid resistance and fluoroquinolone resistance (see Annex 2 for details) the analysis also adjusted the costs. Cost adjustment accounted for the costs of HRZE and levofloxacin RZE for RS-TB (or BPaLM and BPaL for RR-TB); the proportion of patients receiving each regimen, based on the prevalence of and frequency of testing for isoniazid resistance (fluoroquinolone resistance for RR-TB); and the costs of testing for isoniazid resistance (fluoroquinolone resistance for RR-TB).

A3.5 Novel regimens

For the main analysis, for each of the three countries, the analysis estimated the three price thresholds for a novel regimen that has all-optimal characteristics, according to the TRPs (see Annex 2 for details). It also analysed how the cost thresholds vary when all characteristics are fixed at their SOC, minimal or optimal values, and only one characteristic (efficacy, duration, adherence, forgiveness or safety) is varied, to illustrate which characteristics have the greatest impact on cost and cost–effectiveness.

A3.6 Cost estimation details

For each SOC and novel regimen, an ingredients-based costing analysis was conducted; this involves multiplying the quantities of different inputs (i.e. services or commodities) needed to deliver the regimen by the country-specific unit costs of each input. Broad categories of costed inputs include drugs, outpatient treatment and monitoring visits, laboratory tests and diagnostics (including tests related to drug susceptibility; adverse events, side-effects or toxicity; and response to treatment), patient support, management of adverse events, and travel and time costs borne by patients. The analysis assumed that, apart from the price of regimen drugs themselves, each country-specific unit cost would be fixed across regimens (Tables A3.1 and A3.2). However, the quantities of each input required varied by regimen (Table A3.3). The quantities of each input required under the SOC were based on WHO and country-specific TB treatment guidelines and protocols, whereas the quantities under novel regimens depended on regimen duration and safety.

Several quantities scaled with regimen *duration*, including the number of outpatient visits, the amount of treatment support, the number of laboratory tests (i.e. monitoring tests for treatment response and for adverse events or side-effects) and the frequency of adverse events. Scaling was often one-to-one but depended on each country's guidelines regarding when visits and laboratory monitoring should occur (e.g. if monitoring occurs only in the first month of treatment, it was assumed that practice would continue, even with shorter regimens). Patient out-of-pocket and indirect costs also varied with duration.

The number and type of laboratory tests for adverse events and side-effects also scaled with regimen *safety*, as did the monthly incidence of adverse events.

To estimate the savings resulting from fewer treatment failures and relapses, re-treatments were costed for patients who were not durably cured; these occurred an average of 1.65 years after the initial treatment *(1)*. It was assumed that 17–24% of uncured patients die during treatment (considering TB-related causes that could be avoided through better treatment regimens only); the remaining uncured patients face country-specific case fatality ratios before being linked to care again *(2)*. Both re-treatments and new secondary cases were assumed to spend an average of 8 weeks with TB symptoms before treatment was initiated *(3)*.

To estimate the savings resulting from more secondary cases averted, the analysis estimated the number of future treatments averted by an improved regimen (accounting for transmission averted and for countries' case detection ratios); for each treatment averted, a full course of treatment was costed. It was assumed that each patient who fails treatment or relapses generates an average of one secondary case, occurring a median of 1.4 years after being treated *(4–6)* (Fig. A3.1), and that

secondary cases are subject to country-specific case fatality ratios (Table A3.4). The cost–effectiveness analysis considered disability from TB disease, post-TB morbidity and mortality, and adverse events, in addition to TB-specific deaths.

All unit costs were converted to 2021 US dollars by converting prices reported in US dollars for earlier years to local currency units (LCU), inflating to 2021 LCU using medical currency consumer price indices *(7–9)* and converting to 2021 US dollars using 2021 exchange rates *(10)*. The analysis considered both a societal perspective (health system and patient-borne costs) and a health system perspective (costs to the health system only).

Table A3.1. Country-specific health system unit costs (in US$)

Cost component	India		South Africa		Philippines	
	Estimate	Source	Estimate	Source	Estimate	Source
Outpatient treatment and monitoring visits						
Outpatient visit	$2.12	*(11)*	$14.83	*(12)*	$3.47	*(13)*
Laboratory tests and screening						
Pre-initiation DST (RS-TB)	$29.99	*(11)*	$19.09	*(12)*	$26.91	*(13)*
Sputum smear microscopy	$2.37	*(11)*	$9.02	*(14)*	$5.79	*(13)*
Sputum culture	$10.26		$20.37		$27.78	
Xpert MTB/RIF and Xpert Ultra	$25.18		$25.42		$27.74	
Xpert XDR	$35.18		$35.42		$37.74	
Chest X-ray	$3.53		$15.79		$4.84	
Liver function testing	$3.61		$9.67	*(15)*	$4.46	
Full blood count	$1.16		$4.45		$3.80	
ECG	$1.51		$14.61	*(16)*	$5.62	
Neuropathy screening	$1.06	Clinician time; assumed to be half the cost of an outpatient visit	$7.42	Clinician time; assumed to be half the cost of an outpatient visit	$1.74	Clinician time; assumed to be half the cost of an outpatient visit
Adverse events						
Liver dysfunction	$154	*(16)*	$728	*(16, 17)*	$241	*(16)*
Pancreatitis	$134		$472		$209	
Anaemia	$65		$97		$102	
Neutropenia	$8		$102		$12.50	
QTcF prolongation	$138		$517		$215	
Renal disfunction	$146		$619		$227	
Vision	$10	South Africa cost scaled by relative GNI pc	$30		$17	South Africa cost scaled by relative GNI pc
Arthralgia	$5		$14		$8	
Peripheral neuropathy	$0	Only affects DALYs and monitoring costs	$0	Only affects DALYs and monitoring costs	$0	Only affects DALYs and monitoring

Cost component	India		South Africa		Philippines	
	Estimate	Source	Estimate	Source	Estimate	Source
Treatment support						
Treatment vouchers (for expenses) per month (RS-TB)	$6.75	*(18)*	$0	*(19)*	$0	Estimate from *(2, 20)*
Treatment vouchers (for expenses) per month (RR-TB)	$6.75		$134		$30	
Drugs						
Wastage	8%	*(11)*	5%	Standard assumption	5%	*(13)*
SOC RS-TB drugs (full course, HRZE)	$46	*(21)* BDQ prices account for 20% free goods, as described in the GDF price catalogue	$46	*(21)* BDQ prices account for 20% free goods, as described in the GDF price catalogue	$46	*(21)* BDQ prices account for 20% free goods, as described in the GDF price catalogue
SOC RS-TB drugs (full course, levofloxacin RZE)	$85		$85		$85	
SOC RR-TB drugs (full course, BPaLM)	$592		$592		$592	
SOC RR-TB drugs (full course, BPaL)	$563		$563		$563	
Novel regimen drugs (full course)	NA – price thresholds estimated as part of the analysis					

BDQ: bedaquiline; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; DALY: disability-adjusted life year; DST: drug susceptibility testing; ECG: electrocardiogram; GDF: Global Drug Facility; GNI pc: gross national income per capita; HRZE: isoniazid, rifampicin, pyrazinamide and ethambutol; NA: not applicable; RR-TB: rifampicin-resistant TB; RS-TB: rifampicin-susceptible TB; RZE: rifampicin, pyrazinamide and ethambutol; SOC: standard of care; TB: tuberculosis.

All costs are shown in 2021 US dollars. This table shows the cost per each cost component (i.e. each service or commodity) in the first column. These costs are assumed to be fixed across regimens. The quantities of these cost components required for each regimen are shown in Table A3.3.

Table A3.2. Country-specific costs to patients (in US$)

Cost	India		South Africa		Philippines	
	Estimate	Source	Estimate	Source	Estimate	Source
Out-of-pocket costs						
Pre-diagnosis (RS-TB)[a]	$76.51	*(22)*	$44.58	*(23)*	$21.88	*(2, 24)*
Pre-diagnosis (RR-TB)[a]	$76.51		$44.58		$29.24	
Treatment (RS-TB)[a] per month	$28.26[b]	*(22, 25–27)*	$23.77	*(23, 28, 29)*	$17	
Treatment (RR-TB)[a] per month	$25.32	*(30)*	$53.41[b]	*(31)*	$21[b]	
Indirect costs (i.e. productivity or lost wages)						
Pre-diagnosis (RS-TB)	$68.51	*(22, 25)*	$47.96	*(23)*	$45.13	
Pre-diagnosis (RR-TB)	$68.51		$47.96		$82.29	
Treatment intensive phase (RS-TB)	$63.61	*(22, 25–27)*	$81.94	*(23)*	$3 per outpatient visit + $252 per episode of hospitalization	
Treatment continuation phase (RS-TB)	$16.95 per month		$19.15 per month			
Treatment all phases (RR-TB)	$31.81 per month + $54 per episode of hospitalization		$61.49 per month + $219[b] per episode of hospitalization	*(31)*	$4 per outpatient visit + $216[b] per episode of hospitalization	

RR-TB: rifampicin-resistant TB; RS-TB: rifampicin-susceptible TB; TB: tuberculosis.

All costs are shown in 2021 US dollars.

[a] Pre-diagnosis out-of-pocket costs include medical and nonmedical costs. Treatment out-of-pocket costs include nonmedical cost components only, to avoid double counting with health system costs.

[b] Treatment support voucher costs were subtracted from RR-TB out-of-pocket + indirect costs for the Philippines and South Africa, and RS-TB costs for India to avoid double counting. Treatment support vouchers were *not* subtracted from RR-TB costs for India to avoid underestimation, because the support vouchers are for food and food was not costed in Mullerpattan 2020 *(30)*.

Table A3.3. Standard of care and novel regimen cost component quantities

Cost components	Country	SOC RS-TB	All-minimal RS-TB	All-optimal RS-TB	SOC RR-TB	All-optimal RR-TB	All-optimal RR-TB	Notes and sources
Outpatient treatment and monitoring visits								
Outpatient visits[a]	India	8	5	4	9	9	5	-SOC: *(32–35)* -Novel: scales with duration after month 2
	South Africa	8	5	4	9	9	5	
	Philippines	9	6	5	9	9	5	
Laboratory tests								
Pre-initiation DST (% patients)	India	29%	29%	29%	43%	43%	43%	-SOC: INH- and FQ-resistance testing from *(2)* -Novel: same as SOC
	South Africa	14%	14%	14%	12%	12%	12%	
	Philippines	0%	0%	0%	6%	6%	6%	
Sputum smear microscopy[a]	India	3	3	2	5	5	2	-SOC: *(32–36)* -Novel: scales with duration after month 2
	South Africa	4	4	2	7	7	3	
	Philippines	4	3	2	7	7	3	
Sputum culture[a]	India	0	0	0	3	3	2	
	South Africa	0	0	0	7	7	3	
	Philippines	0	0	0	7	7	3	
Chest X-ray[a]	India	0	0	0	3	3	2	
	South Africa	0	0	0	2	2	2	
	Philippines	0	0	0	2	2	2	
Liver function test (ALT, AST and bilirubin)[a]	India	0	0	0	7	7	0	-SOC: *(32–35, 37, 38)* -Novel: for RR-TB, optimal monitoring similar to RS-TB SOC and minimal monitoring similar to RR-TB SOC
	South Africa	0	0	0	7	7	0	
	Philippines	0	0	0	7	7	0	
Full blood count[a]	India	0	0	0	7	7	0	
	South Africa	0	0	0	7	7	0	
	Philippines	0	0	0	7	7	0	
ECG	India	0	0	0	7	7	0	
	South Africa	0	0	0	7	7	0	
	Philippines	0	0	0	7	7	0	
Neuropathy screening	India	0	0	0	7	7	0	
	South Africa	0	0	0	7	7	0	
	Philippines	0	0	0	7	7	0	
Treatment support								
Treatment support vouchers	India	6	4	2	6	6	2	Scales 100% with duration; DS-TB patients in the Philippines and South Africa are not eligible for support vouchers
	South Africa	0	0	0	6	6	2	
	Philippines	0	0	0	6	6	2	
Hospitalizations (affects patient indirect costs only)								
Hospitalization	India	1%	0.6%	0.3%	25%	25%	8%	-SOC: *(2, 24, 26)* -Novel: scales with duration
	South Africa	5%	2.9%	1.7%	30%	30%	9%	
	Philippines	3%	1.8%	1%	7%	7%	2%	

Cost components	Country	SOC RS-TB	All-minimal RS-TB	All-optimal RS-TB	SOC RR-TB	All-optimal RR-TB	All-optimal RR-TB	Notes and sources
Adverse events (% of patients)								
Liver disfunction	Assumed to be the same across all countries	0.4%	0.2%	0.07%	3.5%	1.8%	0.5%	-SOC DS-TB: -SOC DR-TB: *(16, 39–41)* -Novel: scales with duration and safety
Pancreatitis		0%	0%	0%	2%	1%	0.3%	
Anaemia		0%	0%	0%	3%	1.5%	0.5%	
Neutropenia		0%	0%	0%	4%	2%	0.6%	
QTcF prolongation		0%	0%	0%	0.5%	0.3%	0.1%	
Renal disfunction		0%	0%	0%	1%	0.5%	0.2%	
Vision		0.3%	0.2%	0.05%	0%	0%	0%	
Arthralgia		4.3%	2.6%	0.7%	0%	0%	0%	
Short-term peripheral neuropathy		0%	0%	0%	27%	14%	4.2%	
Long-term peripheral neuropathy		0%	0%	0%	5%	2.5%	0.8%	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; DR-TB: drug-resistant TB; DS-TB: drug-susceptible TB; DST: drug susceptibility testing; ECG: electrocardiography; FQ: fluoroquinolones; INH: isoniazid; RR-TB: rifampicin-resistant TB; RS-TB: rifampicin-susceptible TB; SOC: standard of care; TB: tuberculosis.

This table shows the quantity of each cost component (i.e. each service/commodity) required to deliver a full course of each regimen. The corresponding unit costs for each cost component are shown in Tables A4.1 and A4.2.

[a] Includes initiation (e.g. baseline testing; initiation visit).

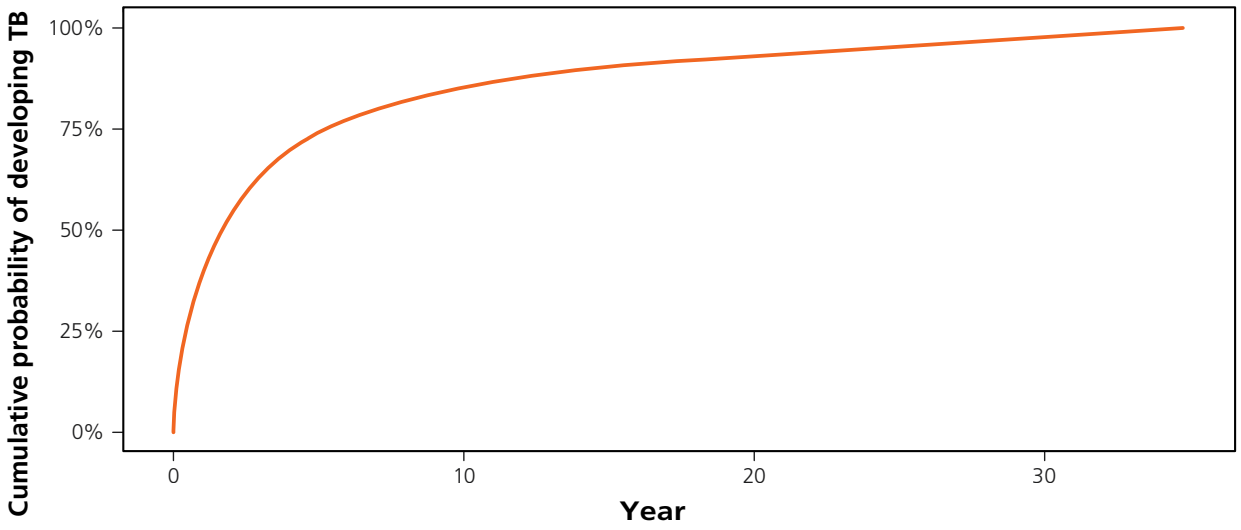
Table A3.4. Additional parameters and estimates used in the cost–effectiveness analysis

	India	South Africa	Philippines	Sources
Disability weights (per year unless otherwise noted)				
Active TB disease		0.333		*(42)*
Post-TB disability		3.06		Already cumulative and discounted *(6)*
Renal disfunction		0.104		Weight was applied for 1 month only *(42)*
Pancreatitis		0.114		
Anaemia		0.052		
Moderate vision impairment		0.031		
Arthralgia		0.117		
Peripheral neuropathy		0.133		Weight was applied for 3 months for short term, lifetime for long term *(40, 42)*
Neutropenia		0		Assumed to be asymptomatic *(16)*
QTcF prolongation		0		
Liver disfunction		0		
Parameters used in mortality estimates				
Life expectancy (at time of treatment initiation)	41.4 years	35.2 years	37.6 years	Life expectancy by age, weighted by estimated age-TB incidence distribution *(2, 43)*
Discounted life expectancy	24.1 years	22.1 years	23.2 years	
TB case fatality ratio	20%	19%	6%	(WHO 2021)

	India	South Africa	Philippines	Sources
Discounted YLLs[a] per secondary TB case	4.7 YLLs	3.3 YLLs	3.5 YLLs	Calculated (product of discounted life expectancy and the case fatality ratio)
Additional avoidable TB case fatality among treatment failures	24%	20%	17%	Based on *(2)*, assuming 50% of mortality while on treatment is avoidable and 50% is not (e.g. non-TB mortality and mortality among severe cases that occurs early in the treatment period)
Treatment-related parameters				
Case detection ratio	63%	58%	43%	*(2)*
Delay between treatment failure and re-treatment	1.65 years	1.65 years	1.65 years	*(1)*
Time spent with TB symptoms before treatment initiation	8 weeks	8 weeks	8 weeks	*(3)* Determines pretreatment DALYs
Cost–effectiveness parameters				
Cost–effectiveness thresholds	$434	$3397	$1056	*(44)* Updated to 2021 US dollars

DALY: disability-adjusted life year; TB: tuberculosis; YLL: years of life lost.

Fig. A3.1. Estimated serial interval distribution



TB: tuberculosis.

This figure shows the cumulative probability of a secondary case having developed TB disease by year since the index case developed TB disease, conditional on the secondary case eventually developing TB disease. Estimates are based on data reported in two publications *(4, 6)*.

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Annex 4. Public comments on target regimen profiles for tuberculosis treatment, 2023

The public comment on the target regimen profiles (TRPs) for tuberculosis (TB) sought to achieve several objectives. These objectives included promoting transparency, ensuring accountability in decision-making processes, enhancing the quality of the TRP document by incorporating stakeholder feedback, and increasing stakeholder engagement and awareness.

The World Health Organization Global Tuberculosis Programme published an announcement in February 2023, inviting stakeholders to provide public comments from 9 February to 9 March 2023. The announcement was distributed through Global Tuberculosis Programme Newsflash, which reaches over 7000 subscribers. The TRP document was shared using LimeSurvey, an open-source online platform. The survey comprised six groups of questions, of which three covered TRPs and one addressed general comments, definitions and characteristics applicable to all TRPs. Participants were able to save their responses, and their identities were not anonymized. From the 58 responses, 50 agreed with the TRP document's content and did not propose any changes, whereas eight provided feedback and offered suggestions for improving the document.

This annex summarizes the comments and suggested amendments. All comments were discussed with the Scientific TRP Development Group (STG) during the consensus meeting and incorporated into the revised document as per the STG's decision:

- **Section 3.1:** The comments regarding forgiveness as a characteristic under definitions and related considerations suggested the need to clarify the distinction between efficacy (performance in ideal conditions) and effectiveness (performance in real-world conditions) in the respective context. The proposed amendment suggested comparing effectiveness between different patient adherence levels and comparing it with efficacy in the original trials. High forgiveness can be inferred if high effectiveness (relative to efficacy) is maintained in patient groups with low adherence compared with those with high adherence. Another general comment recommended the early inclusion of children and pregnant women in trials, to facilitate the prompt use of the TRPs in vulnerable populations.
- **Section 3.2:** The comments on forgiveness as a characteristic common to all TRPs emphasized the need to consider the manner and timing of missed doses in relation to the patient's period of highest bacterial load. There is limited general knowledge about the precise impact of missed doses on treatment outcomes; therefore, it has been proposed to establish a threshold for an absolute or relative change in the likelihood of an unsuccessful treatment outcome, rather than relying on a fixed percentage threshold. This approach aims to provide a more nuanced understanding of the forgiveness concept and its implications for treatment effectiveness.
- **Rifampicin-susceptible TB (RS-TB) TRP:** The suggestion was made that a 4-month regimen be proposed as a potentially effective and safe alternative, to improve on the shorter treatment recommended by WHO, rather than the 3-month regimen proposed in the document. Additionally, feedback was provided regarding the need for clarification on the propensity of developing resistance. To address this, it was suggested that a separate sentence be included in the explanatory note, clearly differentiating it from the preceding sentence, as indicated in the text.
- **Rifampicin-resistant TB (RR-TB) TRP:** The comments regarding safety, monitoring and tolerability raised concerns about whether the existing monitoring requirements for bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) are in line with the minimal or optimal requirements, particularly considering the overlapping risks for QT prolongation. Suggestions have been made to address this issue by mentioning the use of electrocardiograms (ECGs) and the potential need for at least two ECGs within the first month of treatment, followed by monthly monitoring thereafter.

- **Pan-TB TRP:** Comments addressed the minimal requirement of the pan-TB TRP, emphasizing the need for clarification regarding the specific comparison being made in a study evaluating the efficacy of a new TB regimen. Furthermore, a comment regarding the pill burden recommended that the minimal requirement should not surpass the current treatment for drug-susceptible TB (DS-TB), which is 2 months of daily isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) followed by 4 months of isoniazid and rifampicin (i.e. 6-month HRZE]). However, for the optimal requirement, clarification is needed about the reasons for its divergence from the optimal requirement for DS-TB, which typically involves a once-daily pill regimen.

In addition to the feedback discussed above, several general comments were provided, suggesting the following:

- including issues pertaining to different treatment durations and drug penetration in extrapulmonary TB;
- incorporating at least one compound from completely new drug classes in the new TB treatment regimen within the respective chapters;
- highlighting a preference for using dispersible tablets instead of syrups, especially in children, to avoid the need for a cold chain; and
- considering cost–effectiveness data as a characteristic for new regimens, to justify their implementation from a programmatic standpoint, while also taking into account the cost of goods.

These suggestions aimed to enhance the comprehensiveness, effectiveness and practicality of the TB treatment regimen under consideration.

Annex 5. Consensus meeting agenda

Background

WHO developed TRPs for TB treatment in 2016, describing the targets and specifications that developers should consider for appropriate performance and adequate operational characteristics of new TB treatment regimens, considering the needs of end-users and programmes at country level. In 2022 WHO initiated the process of updating these TRPs and to this end conducted a stakeholder survey, commissioned modelling work to inform trade-offs and cost targets, conducted a series of online consultations of the Scientific TRP Development Group and made a draft TRP document available for public comment. The result of this work, and the focus of this meeting, is a draft v1 of the TRP document.

Aim and objectives

The overall aim of this meeting is to present, discuss and come to consensus on the contents of the v1 TRP document. Subsequently the WHO secretariat will finalize and publicize the document.

The specific objectives of the meeting are:

1. To present the results of modelling conducted to inform the TRPs.
2. To present the feedback received from public consultation.
3. To present and discuss draft v1 of the TRPs, and to achieve consensus on the characteristics and targets.

Chair: Christian Lienhardt

DAY 1

Session 1: Welcome, introduction and objectives of the meeting		
13:30 – 14:00	Registration	
14:00 – 14:10	Welcome & Introduction to the meeting	Matteo Zignol
14:10 – 14:30	Meeting objectives – Presentation of participants Review of DOIs	Fuad Mirzayev
14:30 – 14:50	Principles & methods for the TRP revision – *what's new compared to initial TB TRPs ?*	Samuel Schumacher
14:50 – 15:35	Modelling the potential impact and cost-effectiveness of novel TB regimens	Tess Ryckman
15:35 – 16:00	Discussion	All
16:00 – 16:30	*Coffee/Tea break*	
16:30 – 17:00	Feedback from Public comment	Medea Gegia
17:00 – 17:30	Discussion	All
17:30	*End of Day 1*	

DAY 2

Session 2: Review of Common TRP Characteristics		
8:30 – 10:00	Presentation and consensus on common characteristics	Christian Lienhardt
10:00 – 10:15	*Coffee/Tea break*	
Session 3: Consensus building on rifampicin-susceptible TRP		
10:15 – 13:00	Presentation and consensus on the rifampicin-susceptible TRP	Gerry Davies
13:00 – 14:00	*Lunch*	
Session 4: Consensus building on rifampicin-resistant TRP		
14:00 – 16:00	Presentation and consensus on the rifampicin-resistant TRP	Kelly Dooley
16:00 – 16:30	*Coffee/Tea break*	
16:30 – 17:30	Presentation and consensus on the rifampicin-resistant TRP (*contd*)	Kelly Dooley
17:30	*End of Day 2*	

DAY 3

09:00 – 09:15	Recap Day Two	Christian Lienhardt
Session 5: Consensus building on pan-TB TRP		
09:15 – 10:30	Presentation and consensus on the pan-TB TRP	Charles Wells
10:30 – 11:00	*Coffee/Tea break*	
11:00 – 12:30	Presentation and consensus on the pan-TB TRP *(contd)*	Charles Wells
12:30 – 13:30	*Lunch break*	
Session 6: Recap and next steps		
13:30 – 15:00	Cross-cutting aspects	Christian Lienhardt
15:00 – 15:30	Outstanding questions and the link with 'Guidance on Evidence Generation'	Samuel Schumacher
15:30 – 16:00	Next Steps	Fuad Mirzayev
16:00 – 16:15	Closure of meeting	Matteo Zignol
16:15	*Adjourn*	

Annex 6. Summary of declarations of interest of the STG

Several of the STG members declared conflicts of interest concerning the development of the Target Regimen Profiles 2023 edition document. These conflicts were in the areas related to employment and consulting, research support, and public statements and positions. The summary is provided in the table below:

Name	ADDITIONAL INFORMATION
Gavin Churchyard	Participation in the advisory board to Janssen Grants and drug donations for the clinical trials led by the Aurum Institute
Daniela Cirillo	Grants from Unite4TB, TB Alliance, and EUCAST for MIC testing and coordinating microbiology WP
Angela Crook	Research support for the unit from UNITAID and NIHR
Charles Daley	Member of DMC for delamanid, for Otsuka
Gerry Davies	Academic partner in several research consortia
Andreas Diacon	CEO and founder of research foundation TASK
Kelly Dooley	Involvement in TB research in various capacities. Protocol chair, principal investigator
Agnes Gebhard	Project Funding TB Alliance, BPaL operational research Letter to FDA for approval of the Pretomanid application
Norbert Heinrich	DSMB member Qurient Research funding for DECODE study and sutezolid API for SUDOCU study
Anneke Hesseling	research support to Stellenbosch University
Emily Kendall	Consulting, technical adviser to the WHO and CHAI Research support from BMGF
Christoph Lange	honorarium for lecture from Janssen
Graeme Meintjes	invited lecture at Gilead
Carole Mitnick	Institution-employer – recipient of grant for research from UNITAID and NIH
Payam Nahid	TB clinical trial methodology, protocol design TB clinical trial principal investigator
Bern Nyang'wa	Employment at MSF Presented at conferences the results of TB-PRACTECAL trial
Rada Savic	multiple research funding
Mel Spiegelman	CEO of TB Alliance
Eugene Sun	TB Alliance staff Research grants from BMGF
Elin Svensson	Research support from TB Alliance and Janssen
Francis Varaine	Co-investigator of endTB and endTB Q trials
Andrew Vernon	worked in the TB division of the US CDC

These declared conflicts of interest were carefully reviewed and considered not significant from the perspective of the TRP document but rather confirming the relevance of the expertise and experience of the group member within the scope and content of this development.

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