Report of the

Consensus meeting for finalization of Target Regimen Profiles for TB treatment

7-8 July 2016

Geneva, Switzerland

World Health Organization

THE END TB STRATEGY

Note to the reader

This report condenses its account of each session of the meeting according to the themes addressed, rather than attempting to provide a chronological summary.

Instead of presenting an exhaustive summary of the meeting and listing all resultant changes to the text of the target regimen profiles, it attempts to reflect the nature of the discussions that took place and the issues of concern and interest on which they focussed. The Annexes to this report contain the final TRPs, and these reflect the precise changes in TRP attributes agreed by the group.

Points made in discussion are presented as the opinions expressed; no judgement is implied as to their veracity or otherwise.

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Acknowledgements

Overall organization of the meeting

Christian Lienhardt and Lice González-Angulo, with inputs from Christopher Gilpin, Gavin Churchyard, Dennis Falzon, Ernesto Jaramillo, Linh Nhat Nguyen, Matteo Zignol, and Anna Dean, under the overall guidance of Mario Raviglione, Director of the Global TB Programme at the World Health Organization.

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Welcome, introduction and objectives

***Chair: Professor Gavin Churchyard**, CEO, the Aurum Institute for Health Research*

Opening statements from the Chair and Dr Mario Raviglione (Director, World Health Organization Global TB Programme, WHO/GTB), recognized the work leading up to this point and emphasised the urgent need for safer, simpler, more efficacious and accessible treatment regimens for all forms of TB. Dr Raviglione acknowledged that funding from the Bill and Melinda Gates Foundation had been essential to the undertaking.

The development of Target Product Profiles for TB drug regimens (hereafter referred to as Target Regimen Profiles, or TRPs) is intended to guide drug regimen developers towards important features and align these with patient and programmatic needs at country level. As the anti-TB drug research and development (R&D) process is increasingly focused on testing TB *regimens* (rather than individual drugs), developing a drug with a regimen in mind from the start could shorten the full regimen development process from 15 or more years down to seven or eight—with the added advantage of a tested drug combination at the end. The proposed TRPs, which are based on prioritized characteristics, take into account the needs of end-users, care providers and policy-makers to create shorter, less toxic, and operationally feasible regimens. Building on early work by the TB Alliance, this meeting set out to clarify end users' needs as characteristics needed in future treatment regimens.

Current recommendations require the use of Xpert MTB/RIF diagnostics (a newer, more sensitive form of testing for TB, endorsed by WHO in 2011, that is genetically based and which can show whether bacteria are resistant to rifampicin) to determine the presence or otherwise of resistance before a regimen is chosen. But with novel drugs emerging and growing possibilities for combining new and repurposed drugs, a regimen that could be used to treat every single patient is theoretically possible. This meeting aimed to link today's diagnostics technologies with ongoing treatment innovations in an attempt to help make this a reality.

TRPs for TB treatment

***Christian Lienhardt**, WHO Global TB Programme*

Context and the TRPs

To provide context, Dr Lienhardt outlined recent advances in TB treatment and the drawbacks in the TB drug development process. Current regimens present ongoing challenges related to the treatment time necessary to achieve cure; the complexity of treatment protocols; safety issues (for example with drug-drug interactions, or DDI); the fact that drugs to treat resistant TB are less efficacious and less tolerable; and cost concerns. While there have been significant advances in TB drug development the conventional development process is slow, and is nearly doubled in length by the need for further clinical testing of regimens after constituent drugs have received regulatory approval.

The novelty of the TRP approach is to have the goal of a treatment regimen in mind very early in the process of drug development. Based on the idea that TB drug research and development (R&D) is moving towards developing and testing TB regimens rather than individual drugs, a set of targets is needed based on prioritized characteristics and representing the needs of end users.

Aimed at the pharmaceutical industry, research institutions, product development partnerships, donors, non governmental organizations (NGOs) and civil society organizations (CSOs), TRPs align those needs with targets and specifications for developers, with the view of achieving shorter, less toxic, operationally feasible and cheaper regimens.

To develop the draft profiles under discussion in this meeting, the WHO Global TB Programme, through its *Task Force on the Development of Policies for Introduction of New TB Drugs* ("Task Force") and along with a wide array of stakeholders, has conducted various activities and convened a series of consultations. This work has been ongoing since September 2015.

TB is usually diagnosed by examining sputum microscopically, but results are valid only in 60 per cent of cases, and do not indicate whether or not the germ is drug resistant. Since 2011, the Xpert MTB/RIF test is being promoted, scaled up and increasingly used in most countries where TB is a major problem. For this reason, it is expected that it will be most widely used in the near future to diagnose TB *and* give indication on whether the bacilli are rifampicin-resistant or not. For this reason– and based on Xpert availability –TRPs have been developed for rifampicin-susceptible and rifampicin-resistant treatment regimens. However, in countries where Xpert MTB/RIF is not yet scaled up or in hard-to-reach areas, a third TRP would be required for a drug regimen that can be used in any situation. This would be based solely on new drugs, in order to be able to kill all bacilli, regardless of resistance type. It is hoped that it will also be suitable for use against extensively drug-resistant (XDR) forms of TB. For these reasons, three TRPs are proposed: one for TB with no rifampicin resistance (i.e. drug-susceptible TB); one for TB resistant to rifampicin; and one that can be used regardless of the resistance profile (a 'pan TB' regimen).

Process so far

Work on the proposed TRPs started in September 2015, managed by the Task Force under the direction of WHO. The process was as follows (see Fig 1).

Phase one had three components, which ran in parallel:

(i) the development of the initial draft

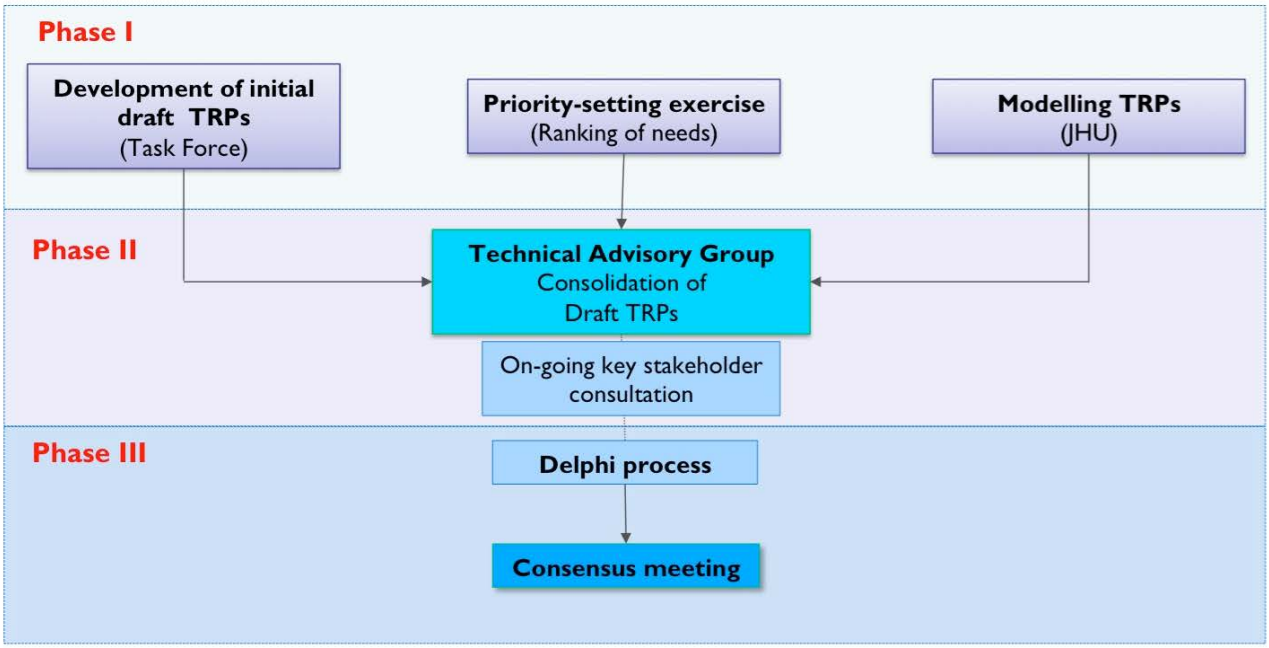

Figure 1: TRPs development process and workstreams

profiles;
(ii) a priority-setting exercise ranking the needs the TRPs would have to meet; and
(iii) a modelling exercise by a team from Johns Hopkins University.

In **phase two**, a Technical Advisory Group consolidated all these inputs into the current draft profiles and sought inputs and comments from a large array of stakeholders.

In **phase three**, a Delphi-like consultation process explored some of the underlying assumptions of these targets, trying to uncover more information that might help consensus building. The consultation allowed an overview of probable areas of agreement or disagreement for each aspect of the TRPs, with the goal of streamlining the work of the consensus meeting.

The final step of phase three was this consensus meeting. Its objectives were to review the TRPs and any uncertainties identified by the Delphi process and achieve agreement on the final version of the TRPs—with the understanding that these are living documents that can be expected to change as progress advances. Indeed, it was stressed throughout the meeting that even after consensus was reached, these profiles may still evolve, and would require a constant process of updating according to progress. Other needs requiring entirely new profiles might emerge too: for example, the possible need for future profiles for host directed therapy in response to issues such as structural damage to the lungs of patients "cured" of TB (who have been shown to have a near tenfold increase in risk of death from pneumonia). Issues that should be monitored in the context of TRP development include effect on amplification of resistance; measuring infectiousness; work to specify requirements at the beginning, rather than the end, of the treatment development pipeline; development of TRPs for different patient categories; acceptability of a regimen in the context of a rights-based approach to health; more explicit linking with Target Product Profiles (TPPs) for diagnostics development; consolidation of guidelines for drug susceptible and drug resistant TB and diagnostics; and development of TRPs for latent TB infection.

Finally, Dr Lienhardt stressed that the TRPs will serve as a *framework*. They are not a list of conditional criteria that must be fulfilled in order to achieve WHO endorsement, but rather outlines for ideal new regimens. Once launched, the WHO Task Force will monitor their use, collecting feedback and working with developers, end users and patients to make them more useful, and revising them to reflect new developments in TB treatment and diagnosis.

The profiles

The TRPs are organized into three columns for each set of criteria: (1) the mandatory **minimum** criteria are characteristics for each variable of a regimen that must be met in order to continue development; (2) the **optimistic** column describes what is desired for a new regimen, providing an ideal goal that developers can aim for; and (3) the **annotations** column adds a clear description of the rationale for the set criteria, target values where suitable, and any other notes that might be of relevance to the development process. In this way, the TRPs seek to lay out the lowest level of acceptable performance and use characteristics for anti-TB treatment regimens.

Within this structure, for each TRP the attributes were organised into three categories: the **priority** attributes (those considered 'must have' qualities); '**desirable**' attributes—nice to have, but potentially subject to trade offs; and '**additional variables of interest**,' which should be considered within the development process.

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Modelling

Dr Emily Kendall (Johns Hopkins University School of Medicine) presented the objectives and outputs of the modelling analysis carried out

within the TRP development process. The intention was to contribute a population-level, epidemiological perspective to the TRPs so as to define characteristics of major interest. The analysis examined population-level results of different sets of regimen characteristics in order to assist decision-making around potential trade-offs. The approach was to identify key characteristics of interest, link them to a population-level model of a TB epidemic, simulate novel regimen introduction and a decade of widespread use, and then vary different characteristics and evaluate how population-level outcomes such as mortality and incidence changed in response.

According to the outcome of this analysis, the **efficacy** of any novel regimen appears to be critical in reducing mortality and incidence of TB. **Duration** and **tolerability** are other particularly important attributes. **Duration shortening** also has further potential positive knock-on effects—particularly through allowing diversion of resources to other efforts, such as identifying patients and getting them on treatment more quickly, that could have great public health impact. In addition, a very **low barrier to resistance**, or lack of appropriate **drug susceptibility surveillance and testing**, could negate gains from a novel regimen; and **operational improvements** may also have additional "indirect" population-level impact.

Participants mentioned the novelty of using modelling to inform TRP development, but stressed that the models are not validated to make go/no go decisions: instead, they illustrate areas for potential trade-offs. Discussions uncovered a number of possible improvements to the modelling approach, including: the possibility of lowering the efficacy threshold, on the basis that this is rarely achieved in practice; attempting to reflect the fact that outcomes and impact will vary by *degree* of resistance; consideration of practical issues—such as how quickly new regimens will be scaled up in reality, loss to follow-up and defaults—as well as efficacy and clinical situations; inclusion of costs to determine target price; and the need for future updates as further data become available, feeding in to evolving TRPs over time.

It was argued that the tension between efficacy and effectiveness exposed by the model is of great importance. As it is reliant on the interplay between a wide range of factors, time may be required to examine the model in detail. It was concluded that the model could be refined in an ongoing manner, with a continuous cross-fertilization process between the model and the TRPs as progress is made.

Delphi-like consultation process

Ms Lice González-Angulo (WHO GTB) explained the Delphi technique used to explore underlying assumptions for the development and validation of these targets. It was designed as an online closed questions tool with interactions that continued until a pre-established level of agreement had been reached–in this case, 70 per cent. Because of this threshold, the process did not require further rounds. Ms González-Angulo gave a brief overview of various levels of agreement reached for the priority attributes outlined in each TRP.

Issues that arose in discussion of the method

included a poor response rate and the fact that those who responded may not represent a sufficiently wide variety of stakeholders; the fact that the Delphi process may be too restrictive a tool to do justice to trade-offs unless accompanied by a values and preferences survey; and limitations imposed by the formatting of the questions, resulting in a flat analysis.

In conclusion, it was agreed that while the method had both strengths and shortcomings, the immediate priority was to find consensus on a "version 1.0" of the TRPs, so they could be presented and launched formally at the European Respiratory Society (ERS) conference in September 2016. The TB community would have the possibility of refining later versions in the future, under the leadership of the WHO Task Force.

Consensus building on rifampicin-susceptible TRP

This TRP was introduced by **Dr Payam Nahid** (University of California, San Francisco), who listed relevant areas of discussion to date, arising from discussions with stakeholders. These included whether to retain rifampicin as the core of future regimens; whether non-rifampicin-based regimens for drug-susceptible TB are adequately covered by the TRP; and, with modelling linking efficacy to shortening of regimens, whether development focus should be shifted to maximizing efficacy in rifampicin-susceptible TB.

The Delphi exercise showed strong overall agreement with the various attributes and criteria of this TRP, with an average of 83 per cent of stakeholders agreeing with each of the attributes (the exception being for the drug-drug interaction (DDI) criterion, where agreement on the optimal requirement was 67 per cent).

Discussion

The fact that this TRP is for rifampicin-susceptible TB does not necessarily mean that rifampicin has to be included in the regimen, and this issue has been widely discussed with developers. If Xpert is used as a triage, the consideration has to be one of rifampicin susceptibility or resistance; but there is a future for regimens that do not contain rifampicin.

There was agreement that the mention of **fixed-dose combinations** (FDCs) in this TRP could imply that drugs are not given according to body weight, and that this should be clarified.

The wording of the TRP currently also implies that each component of the regimen has been registered separately, which arguably defeats the purpose of the TRP project, reverting to the notion of registering individual drugs that are then combined into regimens. Instead, a new process will be required for **regimen registration** that currently does not exist. Dr Marco Cavaleri of the European Medicines Agency (EMA) announced that his agency is revising guidelines for developers of TB drugs/regimens, and that one planned major change would be the option to develop regimens without having to address each drug in the new regimen separately. It is important to discuss the evidence and rationale behind each regimen, and all the clinical work and early development, in order to explain why that regimen is built in a certain way; but ultimately regulators are happy to proceed with clinical trials without the need for factorial work showing large trials for each individual component. A workshop is being organized in London in late 2016 to allow discussion with experts and developers on the EMA's new guidance.

Discussion around **cost and pricing** raised a number of questions. References to cost of goods should instead refer to the cost of entire regimens and work may be needed to model suitable pricing. While it was agreed that price is important for scale up, there was differences of opinion over whether it should be described explicitly in the TRPs. One recurrent argument was that the TRPs should avoid setting barriers that discourage manufacturers. Examples were raised of the initial high prices of HIV drugs when they first entered the market, or more recent medication for hepatitis C, with the point that a wide range of actions can be taken *after* a drug is developed and put on sale in order to decrease pricing and increase access.

Participants pointed out that **adherence risk** is about how easy it is to take the treatment, not just about high barriers to resistance; the TRPs should therefore encourage development of regimens that are easy to take and which do not require stringent directly observed therapy (DOT). With every patient defaulting at risk of developing resistance, it was argued that the TRPs should push for regimens that are suitable for **self-administered treatment (SAT)**, with a focus on drugs that have better forgiveness, so as not to lose efficacy, and that the TRPs should promote the development of drugs with half-lives sufficient to cover for missed doses. It was suggested that for adherence risk the regimen should be able to be "administered with minimal support," and that the annotation could clarify that this might relate to ability to self-administer.

However, **self-administered treatment** raised a number of questions (though there was some discussion of its relevance to developers). It was argued that an entirely self-administered regimen was not plausible; if adherence is not ensured, resistance will always occur. A recent systematic review comparing DOT with SAT showed no differences for several key outcomes of interest, including mortality and relapse, but did suggest significant improvements with culture conversion and treatment success with DOT. A wider range of case management approaches is currently being considered by WHO, including video observed therapy and follow up by text message. Case management strategies including incentives and enablers have also been shown to be effective, and new guidelines suggest use of these and other support systems. In this context, evidence to date suggests that DOT has value, even if it is difficult to study in trials; but whether or not it is crucial is up for debate. It was also pointed out that DOT is rarely realistic in many settings. Some role for DOT is likely to be retained in the future, probably to do with good antimicrobial stewardship; at a minimum it will be required for special populations, and possibly also for large populations. The conclusion was that while SAT may sometimes be acceptable, DOT is 'sometimes mandatory'. It was therefore suggested to include the following sentence: "regimens should be easy to take and should be able to be administered with minimal support".

On the **dosing frequency** it was suggested that the optimistic regimen should encourage less frequent intake, but annotations should stress that if a regimen is intermittent, it should retain priority attributes while being administered intermittently. More frequent dosing can be considered if it allows reductions in duration of treatment, increased tolerability and other benefits that offset challenges associated with more than once-daily dosing. Once daily is always better than twice, and once weekly trumps 2-3 times per week—but this has to be balanced against other attributes, including propensity for acquisition of resistance. Annotations to the TRPs must provide this context.

The final version of the TRP can be found in Annex 1.

Consensus building on rifampicin-resistant TRP

At the start of the discussion, it was emphasized that the spectrum between minimum and optimistic characteristics is one within which trade-offs will be necessary and expected; hopefully, any new

regimen would meet all minimum characteristics and some (if not all) of the optimistic ones. It was agreed that the definition of the "minimum" column would be tightened, focusing on public health criteria and attributes.

Both 'clinical trial' and 'programmatic' metrics must be used throughout the TRPs. Programmatic aspects must be taken into account in order to inform development with the needs of end users, but these metrics cannot be relied upon alone. Because measurability is required, trial metrics are needed too. Therefore it is important throughout the TRPs to make the distinction between the two types of measurements very clear when it appears.

Dr Michael Rich (Partners in Health) gave a short presentation introducing the TRP for rifampicin-resistant TB regimens. Regimens for resistant TB are currently inadequate: MDR treatment is lengthy, complex, ineffective, poorly tolerated, toxic (with significant serious adverse events) and expensive. Dr Rich concluded that there is plenty of room for a new regimen for multidrug-resistant (MDR) TB to be superior in effectiveness, safety and operational aspects compared to the 20-month conventional MDR regimen; and significant room for a new MDR regimen to be superior in those aspects compared to the current *shorter* MDR regimen, which contains an injectable agent. Strategies to lower regimen costs should be considered from the start; and once a new regimen is established as superior for safety or efficacy, stakeholders should continue to bring down its cost by working on costs of individual drugs as well as increasing the demand for the new regimen.

In the Delphi survey, on average 76% of key stakeholders agreed with the attributes outlined in the TRP for Rifampicin-resistant TB. Lower levels of agreement were observed for the minimal targets for treatment duration (54%), target population, and safety (69%); and for the optimal target proposed for clinical monitoring for drug toxicities (68%).

Safety

The biggest question was about the **use of severe adverse events (SAEs; see Box 1) as a major attribute qualifying safety in the profiles**. It was suggested that the easiest solution could be to adopt a clinical trial matrix using SAEs for trials for first line drugs, determine what an average number of SAEs might be, and set this as a minimum goal. This would require clear definitions of what constitutes an SAE, especially with regard to deaths caused by MDR-TB.

Using the current standard regimen as a benchmark against which to quantify desired improvements is a good approach, with the caveat that weighting might be required to compensate for the fact that different proportions of patients report SAEs in phase III trials than in other phases, and that MDR-TB patients tend to be more complicated cases to start with. One possible approach to dealing with significantly different populations might be to phrase the goal as a reduction in SAEs as compared to current standard of care. It should be clear, however, that

while SAEs are being measured, it is adverse events (AEs) that tend to prevent patients from completing treatment courses—and discontinuation due to an AE is a more common metric for use by developers.

There was discussion around the intimate link between safety and efficacy, and the need to separate safety (SAEs) and tolerability (AEs and discontinuations). One proposal was to keep SAEs and add prevalence of grade III and IV adverse effects, in the form of an accompanying general statement that the desired regimens should show significant improvement in this regard. But treatment emergent AEs (TEAEs) were suggested as a superior marker, which shows more clearly when patients are unable to tolerate their regimen and give up. TEAE works because it is a simple threshold: something bad enough to make a patient stop therapy.

The use of mortality as a parameter was discouraged; while it is of importance and reflects on efficacy, it has to be attributed to a cause. It is a measurement loaded with confounders, and difficult to handle in studies that are not designed around it.

In this complex area, patient preferences are very important to consider, and future consultation will be needed. For example, patients might accept permanently disability due to neuropathy, keeping going with a treatment course until their TB is cured. This observation led to the argument that if a 2.5 per cent risk of permanent disability is considered acceptable, it no longer matters why patients might discontinue therapy. For example, if they stop because of a non-disabling condition such as nausea, the salient issue might really be the fact that they did not get the proper anti-emetics.

These comments underline how difficult it can be to quantify whether a regimen is safe. In conclusion, it was agreed that SAEs within clinical trials are well defined, and that these definitions should be used to impose clarity where it might currently be lacking in the TRPs. The limits of this approach would be compensated by the use of TEAEs leading to treatment discontinuation as an additional indicator.

BOX 1: definitions of adverse events

1. Adverse event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

2. Serious adverse event (SAE)

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
    - NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalisation or results in prolongation of existing hospitalisation
- Results in persistent or significant disability/ incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event or reaction.

3. Treatment emergent adverse event (TEAE)

An event that emerges during treatment having been absent pre-treatment, or which worsens relative to the pre-treatment state.

Sources: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guidelines on:

1. *Clinical safety data management: definitions and standards for expedited reporting*

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

2. *Statistical principles for clinical trials*

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/

Duration

Discussion of treatment duration coalesced around two contrasting perspectives: one, that the minimum duration should realistically be set at nine months or more; and two, that these TRPs should be inspirational, driving developers to aim for something better than the current standard, and that this should therefore be set at six months.

After clarifying again that TRPs will not be endorsement criteria for WHO, debate covered a range of points of view: the notion of an inspirational minimum was countered by the argument that the role of the minimum criterion is not to inspire but to encourage certain parameters for trials, and that the optimistic column should be the ambitious and inspirational one. There were different arguments for optimal requirements for duration of treatment of four or six months, and minimum requirements of six, nine and twelve months. One rationale for six months was that the minimum is meant to set out parameters for the next, improved generation of trials, and a number of nine-month regimens are in trials already. A counterpoint was that trials aiming at six months are not guaranteed to succeed, and past experience has taught that treatment shortening is difficult under a certain duration threshold. It was noted, however, that even a 12-month minimum would cut XDR treatment in half.

Because the notion of a hard minimum figure was contentious for these and other reasons, a minimum *range* was suggested. It was argued that this should not be too short—the point was made that in practice, treatment continues two months beyond the first clear test to determine cure. After voting, a recommended minimum range of 6-12 months was chosen.

Population

The discussion around target population was brief, and concluded that regimens suitable for children should be a minimum requirement.

Individualized treatment

While individualized treatment is not an attribute in the TRPs, it provoked a great deal of discussion around the need to rely on drug susceptibility tests, and how this should be approached in the phrasing of the TRPs. It was argued that the availability of diagnostics and diagnostic types be considered when designing regimens, and that optimally a regimen should be based on rapid drug susceptibility testing (DST) to its various components. Participants discussed whether to include a statement that any type of diagnostic test should be needed to determine who is covered by the minimum criteria; and whether optimistic criteria should be for no diagnostics, or for rapid tests only. There was reluctance to rely on any technology that might require a long wait for results.

Individualized treatment requires that doctors assess susceptibility or resistance of patients' strains, which requires a catalogue of DSTs to potential drugs—which is not possible at present. The ideal minimum would be to have a series of choices for rifampicin-resistant patients, but the likely reality will be a combination of available drugs, some of which are likely to have a certain level of resistance. Choices must therefore be made about what type and level of resistance can be considered 'acceptable'. The most practical approach (minimum criteria) would be a regimen that can be used with MDR-TB knowing that component drugs might be liable to some resistance; for this, background resistance must be known (through baseline drug resistance surveys), so access to relevant diagnostics is a necessity. Optimistic criteria can, however, stipulate that all drugs in the regimen should be suitable for use even in resistant contexts, without any diagnostic requirement.

The point was raised that these criteria effectively ask developers to address programmatic considerations, describing guidelines for medical practice that go beyond the question of product combination. Advocacy for language around diagnostics in the TRPs was, however, based on the desire to be in a position to support the use of *any* new drug, where necessary, with appropriate diagnostic testing. It was argued that it is always preferable to have a diagnostic option, including for the optimistic regimen: even for totally novel regimens, resistance will emerge. In this respect,

linking the development of the TRPs to the current and future diagnostics TPPs becomes a necessity. Further information on the development of diagnostics TPPs can be found in the WHO/GTB document *High-priority target product profiles for new tuberculosis diagnostics,* accessible here:

http://www.who.int/tb/publications/tpp_report/en/

One recommendation was that the minimum requirement should specify the need to take into account background disease prevalence, resistance profiles and culture-based readouts of resistance. The minimum regimen should be designed for rifampicin resistance but should take into consideration other common second-line resistance, while the optimum should be suitable for all conditions and usable without considering the potential resistance to current second-line drugs (assuming that novel drugs have low prevalence for resistance in the population where the regimen is being used). It was thus proposed that the minimum column should stipulate "for patients with rifampicin resistance and supported by appropriate DST;" but it was argued that a completely novel regimen for which there is no current resistance would in fact be fulfilling the Pan-TB regimen TRP.

An important caveat is that diagnosis could be a *barrier* to access. If surveillance shows absence of background resistance, individualized diagnostics are unnecessary; and if driving down the cost of MDR-TB treatment is a goal, the discussion must move away from individualized therapy. Treatment programmes must incorporate surveillance data; and currently available data is poor. An additional, deeper conversation will be required on this issue as new regimens are developed and implemented.

The point was also made that leaving the optimistic column without any reference to diagnostics would go against the principles of AMR (antimicrobial resistance) stewardship: resistance is inevitable even with perfect adherence. In fact, it is impossible to manage treatment without proper DST: not using diagnostics contributes to the creation of resistance in the first place, and accepting this requires avoiding any language that might imply DSTs are not needed. The question then moves to regimens that are contingent on certain susceptibility situations. A number of options were offered; one was to add "indication is contingent on susceptibility to regimen's key drugs" in the minimal column and remove any language referring to additional resistance from the optimistic one; another was to cover off all the points discussed by adding "…with usage consistent with principles of good antibiotic stewardship" to the optimistic column.

It was decided that work would continue on this issue, with a view to finalizing version 1.0 of the TRP.

The final version of the TRP with modifications from the participants can be found in Annex 2.

Consensus building on pan-TB TRP

Dr Cathy Bansbach (Bill and Melinda Gates Foundation) outlined the assumptions and potential benefits of a TRP for a Pan-TB regimen which assumes that neither rifampicin nor isoniazid will be included, and that all the constituent drugs will be novel.

The Delphi exercise showed high levels of agreement on all components of this TRP except target population (62 per cent) and barrier to emergence of drug resistance (64 per cent).

Discussion

Some participants welcomed this TRP as an opportunity to be bold, but others pointed out that even with an 'all-new' regimen, drug resistance would be likely to emerge. This led to further discussion around the need for accompanying **diagnostics** for drug-susceptibility. While a new regimen would allow a grace period in which diagnostics would not be required at individual patient level, WHO would nonetheless continue to need susceptibility testing in order to monitor resistance to medicines globally. Appropriate DST should therefore be associated with treatment regimens, with the screening point changing over time. Meanwhile, a Pan TB approach will be particularly useful in countries where patients are likely to be under- or mis-diagnosed, usually because of lacking or inadequate resources. There was consensus that the TRP should make explicit reference to the fact that while DST will not be required at the outset with this pan-TB regimen, eventually population-level surveillance will have to be replaced by individual testing—in line with global efforts to address **anti-microbial resistance (AMR)**. It was agreed that this TRP (and the others) must fully fit the emerging global policies on AMR .

A **surveillance** plan will be required along with this, as the window during which individual testing is unnecessary is likely to be relatively short; and clarity will be needed on the level of resistance at which population surveillance would switch to individuals. In reality, however, most countries do not perform regular ongoing surveillance, and resistance emerging in these settings will not be recognized until a large proportion of patients are affected. This prompted further discussion of the need to link TRPs closely with the efforts of the 'new TB diagnostics working group' currently looking at point-of-care testing. Such linkage could help ensure that when a safe, non-rifampicin based pan TB regimen exists, diagnostics technology will have kept up, allowing implementation of the new Pan-TB regimen with—hopefully—accompanying, simplified, lag-free diagnostic capability.

It was suggested that this TRP offers a chance to be more ambitious and require that both minimal and optimistic regimens offer better **tolerability** than the current standard of care. Difficulties with this approach included the possibility of excluding compounds with tolerability issues; the difficulty of precision around how much better new compounds should be; and determining the most important aspects of tolerability.

Incorporating requirements for **barrier to resistance** into the TRPs appears, however, more challenging: resistance frequency is concentration dependent, and the lung contains many microenvironments where drug concentrations are low. Predicting mutation rate is difficult. It has, however, been shown to be highly concentration dependent, and the concept of mutation prevention concentration (MPC) has been devised to describe a threshold at which development of resistant mutants is stopped. For some drugs, this value is low, but there is a wide range between drugs. Modelling shows that many factors affect this threshold, including drug-drug interactions, the drugs themselves, and the transmissibility of resistant strains. Prediction of this MPC is often difficult or even impossible for a combination of drugs—and is likely to be different to the product of the individual probabilities for each drug in the regimen. It was argued therefore that the TRP should contain a requirement for a high barrier to resistance, but there was debate around what type of guidance to offer. Frequency of mutations to individual drugs might be inadequate.

The language concerning barrier to resistance in the TRP for rifampicin-resistant TB is not about specific drugs, but rather about what proportion of treatment courses results in resistance (which was set at two per cent maximum); it was suggested that the same approach be taken for the pan-TB TRP, perhaps based on animal models. A specific indication of rates of mutation (scientifically based on original studies) might be useful in the annotations column. It was suggested to mention

that the estimated frequency of spontaneous resistance to the regimen should be lower than the usual mycobacterial burden in a patient, with the expectation that this would lead to a low likelihood of emergence of resistance in an individual patient —a likelihood of around one per cent. It was pointed out, however, that while current estimates are based on adherence, realistically there will be non-adherent patients, and it is dangerous to recommend certain levels without good data on this—so, without such data, the TRPs should avoid setting hard numbers.

Determining the propensity for mutations seems particularly critical for this TRP, as it is likely to be used without diagnostics; so it was argued that mutation rates for existing drugs should be mentioned in the TRP in order to serve as a guide for developers. The Task Force would add language referring to resistance.

The final version of the TRP can be found in Annex 3.

Cross-cutting issues

Some of the cross-cutting issues identified in the meeting were swiftly resolved: **safety** and **individualized treatment** were discussed on the first day, and **target populations** were expanded to include children in all TRPs. There was wide agreement to insert language into the TRPs document addressing emergence of antimicrobial resistance and the need to refer to standards for **antibiotic stewardship**. Lastly, issues of **drug susceptibility** mean the necessary links with **diagnostics** are relevant for all TRPs.

As a general principle, greater **consistency** and **compatibility** are needed across the different TRPs. For example, shelf life requirements should be the same across all three profiles, with a minimum requirement of greater than or equal to three years and an optimal requirement of greater than or equal to five years.

Some other wider issues inspired further lively discussion, including: whether to use the TRPs to convey ambition, or to accept the minimum to meet basic needs; emergence of resistance and diagnostics requirements; acceptability; regulatory approvals for regimens; the need for FDCs; and how to make the TRPs more usable for regimen developers.

Experts also discussed the need for more consistency in reference to **QT prolongation (QTP)**. Some argued that leaving the QTP concern out of the TRPs might be preferable, in that its inclusion leaves the door open to non-dangerous QTP, but others felt this this could prove a risky approach. It was agreed that better understanding is needed of the precise meaning of QTP that compromises safety—i.e. what is clinically non-significant and what is life threatening. This would require quantification, and possibly individualizations according to safety profiles. In this regard it was questioned whether the *minimum* requirement of no need for active laboratory monitoring might set the bar too high for developers. The counterargument was that because the existing regimen requires no active ECG monitoring, developing a regimen that does require such monitoring could be seen as a step backwards unless there was an excellent trade off in the form of much shorter treatment duration.

Regarding **cost**, many felt that the cost of manufacture was too important an issue not to be addressed explicitly, with donors currently withdrawing from funding TB, and with end users' needs in mind. It was pointed out that those who cannot afford a better regimen will stay with the one they can afford, so a regimen that is too expensive might prevent implementation. It would be important to emphasize some of the potential cost savings of new regimens, and perhaps plan for future cost-modelling analyses to show what savings these could provide.

Others argued against imposing cost restrictions at the TRP stage, mainly out of fear of deterring developers. The argument was made that once a regimen exists in reality, even if it is expensive to produce, ways can be found to reduce its cost using established tools post hoc, since a wide range of variables can affect end pricing.

More widely, trade-offs must be considered, and priority given to '**delinkage'** of R&D costs from

pricing, as engaging with cost limitations at an early stage might be detrimental to the goal of invigorating TB R&D. Additionally, addressing cost and pricing with any specificity requires deep knowledge of all development costs, which is currently lacking. The TRPs may also be an inappropriate forum in which to take these issues too far—WHO has established methods of addressing issues around pricing and access. The use of any hard numbers around cost would therefore have to be based on a rigorous examination of historic examples and extensive calculations. As these are not part of the TRP process, and because the profiles are meant for drugs in the future, it was argued that costing should be addressed using more generalized language at this stage—keeping in mind issues of **access** and the potential implications for lower- and middle-income countries. It was agreed that a working group would be created to address the issue of cost and deliver its outputs in time to feed into version 1.0 of the TRPs. In addition to the analysis of potential savings, **further cost-related issues must be addressed in the TRP document**, including:

- the need to investigate approaches for funding novel regimens;
- an outline of the expenses of treating resistant TB in low-, middle- and high-income countries;
- the link between final regimen price and access strategies reflecting countries' abilities and overall costs; and
- the description of the market forces likely to emerge, and their impact on price.

It was pointed out that a number of proposals for **novel funding mechanisms** already exist—including a TB-specific project looking at delinkage, the "3P Project"—and that this question is also a major component of the AMR conversation.

While the current discourse around R&D costs is neither healthy nor transparent, the TB community can be self-limiting in its discussions of pricing. While tuberculosis may be a disease of the poor, the maintenance of a "poor man's approach" is not helpful. It was argued that the HIV community never thought about price—and as a result HIV products now exist, and their prices are falling. Setting too many restrictions around TB hinders progress. The answer may be to associate the TRPs more closely to the discussion around delinkage, and make explicit reference to the principles of access.

There was agreement that an introductory statement should describe the complexities of the cost/price issue and acknowledge its importance. A new group would be set up (led by Joel Keravec) to clarify those principles.

Considering that the TRPs are intended to inform future technologies, there was some debate around whether they showed **sufficient ambition** to encourage greater efforts from developers. There was concern that they might be seen to validate some current standards of care. Parts of the current short MDR-TB regimen, it was argued, are not acceptable—toxicity, for example—and the TRPs should avoid any implication of approval of these as the minimum standard in future. Minimums should be more ambitious than what is presently available. In this regard it will be crucial to have metrics that show if we are being ambitious enough.

The fact that the short MDR-TB regimen allows the use of simple diagnostics to prescribe drugs is a step forward—but even with existing technology it can be improved. Caution should be taken to ensure that the recommendations in the TRP do not imply that any **ongoing trial** constitutes a "wrong" trajectory. While future regimens should do better than just meet minimal requirements across the board, TRPs will be informed by all ongoing trials; simply calling for greater ambition would not be enough. The consensus was that the preamble to the TRPs should state that regimens that only meet minimum characteristics are not sufficient; and that the TRP for rifampicin-resistant TB treatment should be more ambitious on key variables—particularly toxicity, pill burden and number of component drugs.

A further debate on **acceptability** would be deferred to discussions with WHO's new civil

society task force, in anticipation of the fact that acceptability requirements can vary personally and regionally. Version 1.0 of the TRPs would contain acceptability criteria along the lines of "should adhere to principles of acceptability" as an indicator and the preamble would state that acceptability criteria are being developed by the Task Force.

Closing statements

The chair concluded that the meeting had been lively, rich and productive, and thanked all participants and contributors. He concluded that the TRPs and the thinking around them had been substantially strengthened by the discussions, and that a variety of concrete changes and improvements had been made.

Dr Lienhardt clarified the timeline: version 1.0 of the TRPs would be finalized in July and August 2016, with each TRP leader taking into account the work of the meeting, and presented at the European Respiratory Society (ERS) conference in September. Further work would be carried out by subgroups—for example on cost and finalization of the rifampicin-resistant TRP. A Task Force meeting in October would address how to get from version 1.0 to Version 2.0, with the goal of having an updated version ready by mid-2017.

Annex 1: Final target regimen profile for rifampicin-susceptible TB

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

Priority attributes for rifampicin-susceptible TB treatment targets

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper and quicker global health impact*	Annotations *For all parameters, included here is the rationale for why this feature is important and/or for the target value*
Indication	The Regimen is indicated for patients (regardless of HIV-infection status) with active TB caused by rifampicin-susceptible *M. tuberculosis* strains, or in whom there is a low likelihood of resistance to commonly used first line TB drugs.	The TB Regimen is indicated for patients (regardless of HIV-infection status) with active TB caused by rifampicin-susceptible *M. tuberculosis* strains including monoresistance to any drug except rifampicin.	INH-monoresistance is common worldwide and a TB regimen that is equally effective against both rifampicin susceptible strains and strains that are monoresistant to any drug except rifampicin would be ideal. Operationally, the regimen would be used in patients in whom there is a *low likelihood of resistance*, or in whom susceptibility to rifampicin is confirmed by a rapid molecular test, such as Xpert MTB/Rif (without additional susceptibility testing).
Efficacy	A 4 month or shorter regimen with efficacy not inferior to the current standard of care 6 month regimen for drug-susceptible TB.	A 2 month or shorter regimen with efficacy not inferior to the current standard of care 6 month regimen for drug-susceptible TB.	Durable cure is defined as relapse-free cure 12 months after end of treatment completion. The targets provided take into consideration the efficacy of the current 6-month standard regimen for DS-TB under trial conditions (approximately 95%). (Note: the term "not inferior" is intentionally used in place of non-inferiority, which is a trials design and methodology term.)
Safety and Tolerability	Incidence and severity of adverse events no worse than for standard of care. No more than monthly clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes etc).	Incidence and severity of adverse events better than for standard of care. No active clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes, etc).	The current standard 6 month regimen for tuberculosis has known safety issues with each of the component drugs, most notably hepatoxicity. In the PaMZ Phase 2B trial, Grade 3 or 4 treatment-emergent adverse events in the HRZE control arm were 25%. Discontinuation due to treatment-emergent adverse events in the HRZE control was 12%. In the REMox trial, Grade 3 or 4 AEs in the HRZE arm were approximately 20% overall (18).
Drug-drug interaction (DDI) and metabolism	Ability to safely use without active laboratory testing or monitoring with: ● First-line ART regimen(s) ● Rifamycins (if a rifamycin is included in the regimen) ● Drugs that induce or inhibit P450 liver enzymes ● Proarrhythmic drugs that prolong QT/QTc interval	*No dose adjustment* with other medications and ability to safely use without active laboratory tests monitoring with: ● first-line ART regimens and co-trimoxazole. ● Rifamycins (if a rifamycin is included in the regimen) ● Drugs that induce or inhibit P450 liver enzymes ● Proarrhythmic drugs that prolong QT/QTc interval	ART regimens may include drugs that are substrates of P450 or other metabolizing enzymes or that inhibit or induce P450 enzymes. For the minimum target, dose adjustment of component drug(s) may be needed to manage DDI. Such adjustments would require that dose size/formulations are readily available. For the optimistic target, no dose adjustments are needed, including for HIV therapies , allowing for standardization of regimen across populations. Regulatory guidance on QT/QTc prolongation in non-antiarrhythmic drugs is available (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073153.pdf). Regimen developers should be mindful that certain drugs increase the risk of QT/QTc prolongation and where feasible, regimen combining several of these should be avoided.

Priority attributes for rifampicin-susceptible TB treatment targets (Cont.)

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper and quicker global health impact*	Annotations *For all parameters, included here is the rationale for why this feature is important and/or for the target value*
Barrier to emergence of drug resistance (propensity to develop resistance, generation of cross-resistance)	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than 1/10 exp7 mutations/bacterium/generation New resistance to one or more drugs in the regimen emerges in less than 1% of treatment courses when taken as prescribed and when no pre-existing resistance to the drugs in the regimen exists.	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than 1/10 exp9 mutations/bacterium/generation Essentially no acquired resistance (<0.01%) when regimen taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.	Drugs included in this TRP should protect each other against emergence of resistance. In addition, resistance to the drugs included in this TRP should be non-existent, and mutants with resistance against these drugs should not be cross-resistant to drugs used in 'second line regimens'. This last attribute is extremely important in order not to compromise the use of potential new drugs. The minimum target is based on an acquired resistance rate of 0-2% when five effective drugs are used in the WHO-recommended regimen. The optimistic target is based on experts' consensus. Frequency of resistance to antibiotics used in MTb: Rifampin: 2.25x10-12 Isoniazid: 2.56x10-8 Ethambutol: 10-7
Target Population	All age groups, irrespective of HIV status.	All age groups, irrespective of HIV status.	Pharmacokinetic and safety studies in children will be needed in both minimum and optimistic scenarios, but efficacy trials in this population are not necessarily required. TB regimen developers should consider initiating paediatric studies, when a drug shows promising efficacy and safety in phase 2A adult trials.
Formulation Dosage and Route of Administration	Formulation to be oral for all drugs in regimen, including paediatrics.	Formulation to be oral, FDC and without a need for weight adjustment. Paediatric (oral), and IV formulations must also be available.	Fixed Drug Combination (FDC) is optimal to facilitate implementation across TB programmes, community settings, and private practitioners. I.V. formulations should be reserved in cases of severe forms of disease, such as CNS TB or TB sepsis. Alternative routes or formulations offering substantially greater efficacy or convenience may be considered.

Desirable attributes for rifampicin-susceptible TB treatment targets

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point – for the given "priority attributes"*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Pill Burden	6 or less pills per day.	As FDC, 3 or less pills per day.	Additional considerations include the size of pills, the availability of water-dispersible pills, among others.
Dosing frequency	Once or twice daily.	Preferably once a day, and with no specific food requirements.	If a regimen is to be intermittent, it should retain priority attributes while being administered highly intermittently (i.e., once weekly). More frequent dosing (i.e., twice a day) can be considered if it allows for significant reductions in duration of treatment, improvements in safety and tolerability or other substantial improvements that would offset the challenges associated with more than once daily dosing.
Duration of treatment in extrapulmonary disease	Extension of treatment for extrapulmonary disease comparable to current standard of care.	No extension of treatment needed specifically for extrapulmonary disease, including CNS TB.	
Stability / Shelf Life	Heat, humidity and light stable, with greater than or equal to 36 month shelf life for all drugs. No cold chain needed.	Heat, humidity and light stable, with greater than or equal to 60 month shelf life for all drugs. No cold chain needed.	Current therapies have at least 24 months of stability.
Target Countries	Global	Global	Optimally, DOT will not be necessary and such an infrastructure will not need to be developed where it is currently absent.
Product Registration Path	WHO GRADE evidence review for the regimen. Each individual drug component of the regimen OR the new regimen should be approved by at least one stringent regulatory authority (SRA) for use in humans to treat TB.	WHO GRADE evidence review for the regimen. Each individual drug component of the regimen OR the new regimen should be approved by at least one SRA for use in humans to treat TB.	The standard regulatory path for a ***regimen*** is currently not defined and the strategy might depend on which drugs are included in a regimen. Key sets of regulatory and products documentation must be readily available for any component of the regimen to countries which would do the expedited registration. This would require that new regimens be introduced as a comprehensive package, including guidance on use and 'how-to' tools, and an entire set of regulatory and product documentation required for a standard registration.
Cost of regimen	Projected cost of regimen (finished product) in new regimen should be compatible with wide access.	Projected cost of regimen (finished product) in new regimen should be compatible with wide access.	Access to essential medicines is part of the right to the highest attainable standard of health ("the right to health") and is well-founded in international law. Economic factors affecting price, demand and availability of the regimens will depend on many factors, including - but not limited to - how well the new regimens meet or surpass the attributes as described herein (efficacy, safety, adherence, etc.). An improved regimen may provide advantages in other costs to programs/patients by being shorter in duration, and/or better tolerated, and/or requiring minimal to no monitoring, etc. This would reduce non-drug costs in aspects such as monitoring, visits, handling of adverse events/toxicity etc.

Additional variables of interest for rifampicin-susceptible TB treatment targets

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

Annex 2: Final target regimen profile for rifampicin-resistant TB

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

Priority attributes for rifampicin-resistant TB treatment targets

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Indication	The RR regimen is indicated for patients infected with rifampicin resistant (including MDR) strains. Indication may be contingent upon additional resistance to existing first or second line drugs and supported by appropriate DST.	The RR regimen is indicated for all patients infected with RR-TB strains, with usage consistent with principles of good antibiotic stewardship.	Drug susceptibility for the minimum case would be assessed via individual DST at the start of therapy or through information determined via drug resistance surveys. For both the minimum and optimal cases, DST to the drugs in the regimen will have to be established. Resistance will inevitably emerge for any regimen and DST may be needed at the start of treatment to diagnose the resistance pattern to determine whether a particular regimen is indicated. Furthermore, DST will be needed for monitoring amplification of resistance in an individual patient and resistance prevalence in a population.
Efficacy (Probability of durable cure)	Efficacy (bacteriologic cure without relapse in at least one-year follow up, among patients who are not lost to follow up) should be not inferior to the WHO recommended standard of care for MDR-TB (22).	Efficacy (bacteriologic cure without relapse in at least one-year follow up, among patients who are not lost to follow up) should be greater than 90%.	Suggested definitions of favourable and unfavourable outcomes can be found in a paper by Furin *et al*. At present the standard of care is the shorter MDR-TB treatment regimen under specific conditions of eligibility and the longer WHO recommended regimen, which is to be provided in those not fulfilling eligibility criteria for the shorter MDR-TB regimen. The optimistic case is based on estimated efficacy observed in a study on a short MDR Regimen in Bangladesh and regimens for drug-susceptible TB.
Safety	Serious Adverse Events (SAEs) no more than 5%, and treatment discontinuation due to Treatment Emergent Adverse Events (TEAEs) no more than 2.5%. The QT prolongation and proarrhythmic effects of the regimen would not put the patient at a moderate or high risk of arrhythmias or sudden death.	SAEs are no more than 2%, and treatment discontinuation due to TEAEs no more than 2%. The regimen would have no or insignificant QT prolongation or proarrhythmic effects.	Consensus from stakeholders is that a new MDR regimen must significantly improve on the high rates of toxicity (e.g. renal failure and hearing loss) associated with the current standard of care MDR regimen. The SAE and the treatment emergent adverse events (TEAE) cutoffs were informed by the range of adverse events seen in a number of pivotal TB trials and set by expert opinion and stakeholders' consensus. For the minimal case, safety in respect to QT prolongation, a regimen should not put the patient at a risk to the degree that a stringent regulatory authority would likely not approve the regimen. The optimal target assumes that post-market surveillance demonstrates significant confidence there are no rare serious side effects of the medicine.
Duration of treatment	6-12 months	Less than or equal to 6 months	The minimum should significantly improve on the duration of the conventional 20-month MDR regimen. The recent WHO recommendation that a shorter MDR-TB regimen of 9-12 months may be used instead of a conventional regimen (typically 20 months or more) informed the minimum target in terms of duration. The optimistic target was set to be equal or less than the length of treatment of the WHO-recommended DS-TB regimen of 6 months. Three recent "duration shortening TB trials" demonstrated the challenges in shortening the first-line therapy less than 6

Priority attributes for rifampicin-resistant TB treatment targets (Cont.)

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Duration of treatment	6-12 months	Less than or equal to 6 months	months. All three trials were not successful at demonstrating non-inferiority, which demonstrates the optimal target of 6 months or less for RR-TB is ambitious. A regimen with a sustainable cure with a 6-month or less duration will likely have radically different pharmacokinetic–pharmacodynamic properties that influence drug efficacy.
Drug-drug interactions and metabolism	Ability to adjust dosing or perform safe monitoring for DDIs with: ● At least one first-line ART regimen ● Drugs that induce or inhibit P450 liver enzymes ● Proarrhythmic QT prolonging drugs	No dose adjustment with other medications and ability to safely use without active laboratory tests monitoring with: ● ART regimens and co-trimoxizole. ● Drugs that induce or inhibit P450 liver enzymes ● Proarrhythmic QT prolonging drugs	ART regimens may include drugs that are substrates of P450 or other metabolizing enzymes (e.g. dolutegravir, UGT1A1 and CYP3A) or that inhibit or induce P450 enzymes (e.g. efavirenz, CYP2B6; ritonavir, CYP3A). Minimum target allows for mitigation of DDI through dose adjustment of the TB or the HIV drug(s), provided dose size/formulations are available to achieve this. For optimistic target, no dose adjustments required, regardless of HIV status or concomitant drugs, allowing for standardization of regimen across populations. Regulatory guidance on QT/QTc prolongation in non-antiarrhythmic drugs is available (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073153.pdf). Regimen developers should be mindful that certain drugs increase the risk of QT/QTc prolongation and where feasible, regimen combining several of these should be avoided.
Clinical monitoring for drug toxicity	Active drug safety monitoring may consist of regular laboratory tests (e.g. liver function test and complete blood counts).	No active drug safety monitoring that consists of laboratory tests are needed for the monitoring of therapy. No ECG monitoring of QT interval required.	No renal monitoring, electrolyte monitoring or audiometry for minimal case scenario. This assumes any new RR regimen would be free of nephrotoxic and ototoxic drugs.
Barrier to emergence of drug resistance (propensity to develop resistance, generation of cross-resistance)	New resistance to one or more drugs in the regimen emerges in fewer than 2% of treatment courses when taken as prescribed and when no pre-existing resistance to the drugs in the regimen exists.	Essentially no acquired resistance (<0.1%) when regimen taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.	The minimum target is based on an acquired resistance rate of 0-2% when five effective drugs are used in the WHO-recommended regimen. The optimistic target is based on experts' consensus.
Target Population	At least adolescent (age 12-19) and adults	All age groups, irrespective of severity of disease, pulmonary or extrapulmonary, or HIV status.	Pharmacokinetic and safety studies in children are compulsory, but efficacy trials in this population not necessarily required in early stages of regimen development.

Desirable attributes for rifampicin-resistant TB treatment targets

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value.*
Number of component drugs	6 or fewer	4 or fewer	Minimum is based on the current short MDR-TB regimen being an effective 7-drug regimen and optimum based on drug-susceptible regimen being an effective 4-drug regimen.
Formulation Dosage and Route of Administration	Formulation to be oral for all drugs in regimen, including paediatric	Formulation to be oral FDC formulations available (desirable to have no weight adjustment for adults). Paediatric (oral), and IV formulations must also be available	FDC is optimal to facilitate implementation across TB programmes, community settings, and private practitioners. IV formulations should be reserved in cases of severe forms of disease, such as CNS TB or TB sepsis. Alternative routes or formulations offering substantially greater efficacy or convenience may be considered
Pill burden	Fewer than 10 pills a day for a 55 Kg adult patient	Not more than 4 pills a day for adults. Potential for one pill daily (using fixed dose combinations with three to four medications)	Minimum based on WHO-recommended regimen.
Dosing (incl. schedule)	Twice daily and manageable food restrictions.	Once daily or intermittent. (Preference for once weekly or once monthly as the intermittency.)	
Stability / Shelf Life	3 years for all drugs in the regimen No cold chain requirements	5 Years for all drugs in the regimen No cold chain requirements	
Target Countries	Global	Global	Regimens must work in TB high burden countries and countries with limited resources.
`Primary Target Delivery Channel	For use in national TB programmes through decentralized care (hospitalization not required).	For use in national TB programmes, primary care health care facilities, and in the private sector through decentralized care (hospitalization not required).	
Cost of regimens	Projected cost of regimen (finished product) in new regimen should be compatible with wide access	Projected cost of regimen (finished product) in new regimen should be compatible with wide access	Access to essential medicines is part of the right to the highest attainable standard of health ("the right to health") and is well-founded in international law. Economic factors affecting price, demand and availability of the regimens will depend on many factors, including - but not limited to - how well the new regimens meet or surpass the attributes as described herein (efficacy, safety, adherence, etc.). An improved regimen may provide advantages in other costs to programs/patients by being shorter in duration, and/or better tolerated, and/or requiring minimal to no monitoring, etc. This would reduce non-drug costs in aspects such as monitoring, visits, handling of adverse events/toxicity etc.

Additional variables of interest for rifampicin-resistant TB treatment targets

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

Annex 3: Final target regimen profile for pan-TB treatment

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

Priority Attributes for pan-TB treatment targets

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations *For all parameters, include here the rationale for why this feature is important and/or for the target value.*
Indication	Drug regimen indicated as first-line treatment for pulmonary TB without the requirement for determining rifampicin resistance	Drug regimen indicated as first-line treatment for pulmonary TB without the requirement for determining rifampicin resistance	Clinical trials in extrapulmonary disease are not anticipated, although regimen may be adopted for this use
Target Population	Adults and children irrespective of HIV status	Adults and children irrespective of HIV status	Pharmacokinetic and safety studies in children will be needed in both minimum and optimistic scenarios, but efficacy trials in this population not necessarily required
Efficacy	Not inferior to Rifampicin-sensitive TB Standard of Care in a 6 month regimen.	Not inferior to Rifampicin-sensitive TB Standard of Care in a 4 month or shorter regimen.	Efficacy of current HRZE regimen is reported to be as high as ~95% in clinical trial conditions.
Safety and Tolerability	Incidence and severity of adverse events no worse than for standard of care. No more than monthly clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes etc.).	Incidence and severity of adverse events better than for standard of care. No active clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes, etc). No ECG monitoring of QT interval required.	The current standard 6 month regimen for tuberculosis has known safety issues with each of the component drugs, most notably hepatoxicity. In the PaMZ Phase 2B trial, Grade 3 or 4 treatment-emergent adverse events in the HRZE control arm were 25%. Discontinuation due to treatment-emergent adverse events in the HRZE control was 12%. In the REMox trial, Grade 3 or 4 AEs in the HRZE arm were approximately 20% overall.
Drug-Drug Interactions and Metabolism	Ability to adjust dosing or perform safe monitoring for DDIs with: • At least one first-line ART regimen • Drugs that induce or inhibit P450 liver enzymes • Proarrhythmic QT prolonging drugs	No dose adjustment with other medications and ability to safely use without active laboratory tests monitoring with: • ART regimens and co-trimoxizole. • Drugs that induce or inhibit P450 liver enzymes • Proarrhythmic QT prolonging drugs	ART regimens may include drugs that are substrates of P450 or other metabolizing enzymes (e.g. dolutegravir, UGT1A1 and CYP3A) or that inhibit or induce P450 enzymes (e.g. efavirenz, CYP2B6; ritonavir, CYP3A). Minimum target allows for mitigation of DDI through dose adjustment of the TB or the HIV drug(s), provided dose size/formulations are available to achieve this. For optimistic target, no dose adjustments required, regardless of HIV status or companion drugs, allowing for standardization of regimen across populations

Priority Attributes for pan-TB treatment targets (Cont.)

Variable	**Minimum** *The minimal target should be considered as a potential go/no go decision point.*	**Optimistic** *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	**Annotations** *For all parameters, include here the rationale for why this feature is important and/or for the target value.*
Barrier to emergence of drug resistance (propensity to develop resistance, generation of cross-resistance)	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than 1/10 exp7 mutations/bacterium/generation New resistance to one or more drugs in the regimen emerges in fewer than 2% of treatment courses when taken as prescribed and when no pre-existing resistance to the drugs in the regimen exists.	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than 1/10 exp9 mutations/bacterium/generation Essentially no acquired resistance (<0.1%) when regimen taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.	To provide a high barrier to resistance, the frequency of spontaneous resistance to the regimen must be lower than the bacterial burden in the patient. Moreover, resistance rates should be balanced such that one component is not more vulnerable than the others. The minimum target is based on an acquired resistance rate of 0-2% when five effective drugs are used in the WHO-recommended regimen. The optimistic target is based on experts' consensus.

Desirable attributes for pan-TB treatment targets

Variable	**Minimum** *The minimal target should be considered as a potential go/no go decision point*	**Optimistic** *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact*	**Annotations** *For all parameters, include here the rationale for why this feature is important and/or for the target value*
Formulation Dosage and Route of Administration	Oral, once daily Containing ≤4 novel antibacterial compounds; ≤ 1 solid oral dosage form/drug/day All components of regimen given no more than once daily for up to 6 months. Individual solid oral dosage form for each component of the regimen packaged in blister packs and HDPE bottles.	Oral, once daily, no special weight banding Containing ≤3 novel antibacterial compounds; two of three or all components of the regimen in a fixed dose combination no larger than a prenatal vitamin oral tablet (i.e., size 00 capsule). All components of regimen given no more than once daily for up to 4 months Packaged in blister packs and HDPE bottles.	Oral, once daily is preferable. However, if duration of treatment can be substantially reduced, a twice-daily administration may be acceptable provided that a missed dose does not increase resistance or decrease efficacy. To optimize compliance, ease of use, delivery and stocking a fixed dose combination product is desired. FDC is optimal to facilitate implementation across TB programs, community settings, private practitioners. Blister packs and HDPE bottles are needed to serve different regions and health care settings. Consider scored tablets for adolescents. To meet regulatory requirements to demonstrate safety in children, a pediatric granule formulation or powdered/reconstituted suspension or dispersible tablet used with ≤ 60mLs of liquid should be available.
Stability / Shelf Life	Stable for ≥ 3 years in climate zones 3 and 4 at 30C / 75%RH.	Stable > 5 years in climate zones 3 and 4 at 30C / 75% RH.	
Target Countries	Global	Global	Regions with high prevalence of rifampicin-resistant TB and low availability of DST may be prioritized

Annex 4: List of acronyms

AE(s)	Adverse event(s)
AMR	Antimicrobial resistance
DDI	Drug-drug interactions
DOT	Directly observed therapy
DST	Drug susceptibility testing
ERS	European Respiratory Society
MDR-TB	Multidrug-resistant TB
MPC	Mutation prevention concentration
R&D	Research and development
SAE(s)	Severe adverse event(s)
SAT	Self-administered treatment
TB	Tuberculosis
TEAE(s)	Treatment emergent adverse event(s)
TPP	Target product profile
TRP	Target regimen profile
WHO	World Health Organization
XDR	Extensively drug-resistant TB