Target regimen profiles for long-acting injectables for tuberculosis prevention & treatment

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For Public Comment

Contents

Acknowledgements

TBD

Abbreviations and acronyms

ADR	adverse drug reaction
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
TDG	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]

Executive summary

TBD

[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 (bedaquiline or linezolid).

1 Introduction

Background

The development of target product profiles (TPPs) outlines the desired product characteristics to be considered and prioritized early on during the product development process. To inform the research and development targets for funders and developers, the World Health Organization (WHO) Global Programme on Tuberculosis (TB) and Lung Health has developed updated target regimen profiles (TRPs) for tuberculosis preventive treatment (TPT) and the treatment of rifampicin-susceptible TB (RS-TB), rifampicin-resistant TB (RR-TB), for a pan-TB treatment regimen.[3,4] TRPs 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. The current document considers drug regimens for either TPT or treatment of all forms of TB using long-acting injectables (LAIs), and aligns to the TRPs for TPT and TB treatment. For the purpose of this document and the development of the target regimen profiles, the scope is intentionally limited to Long-Acting Injectables (LAIs). While other Long-Acting Technologies (LATs) exist—such as implants, microarray patches, and long-acting oral technologies—LAIs are considered the most accessible and potentially cost-effective technology to develop and implement in the near term for TB prevention and treatment programs, particularly in low- and middle-income countries. This focused approach ensures the TRPs address the most immediately feasible and impactful product characteristics for accelerating the availability of simplified, adherence-improving TB regimens.

LAIs are a form of sustained-release medication, given by injection via the intramuscular or subcutaneous route. These represent ground-breaking technologies that have already demonstrated their potential in managing various diseases, including, for example, HIV.[5] Building on the success of bi-monthly cabotegravir, the recent introduction of lenacapavir—a twice-yearly subcutaneous capsid inhibitor—has further shifted the prevention paradigm, showing near 100% efficacy in clinical trials and receiving WHO recommendation in 2025.[6] LAIs for TB treatment and TPT are currently entering clinical development, creating a pressing need for well-defined TRPs. LAI formulations have shown better adherence and health outcomes in high-income countries for conditions like schizophrenia[7], opioid substitution therapy[8], and long-acting hormonal contraception has become the preferred method for many women in LMICs, demonstrating high efficacy.[9] Potential benefits to people affected by TB include greater ease of

[3] Target product profiles for tuberculosis preventive treatment. Geneva, World Health Organization, 2020 (https://www.who.int/publications-detail-redirect/target-product-profiles-for-tuberculosis-preventive-treatment).
[4] Target regimen profiles for tuberculosis treatment, 2023 update. Geneva, World Health Organization, 2023 (https://www.who.int/publications/i/item/9789240081512).
[5] Guidelines on long-acting injectable cabotegravir for HIV prevention. Geneva: World Health Organization; 2022.
[6] Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis. Geneva: World Health Organization; 2025
[7] Haddad PM, Correll CU. Long-acting antipsychotics in the treatment of schizophrenia: opportunities and challenges. Expert Opin Pharmacother. 2023 Mar;24(4):473-493. doi: 10.1080/14656566.2023.2181073. Epub 2023 Mar 15. PMID: 36919576.
[8] McMaster J, Abeysundera H. Effectiveness of long-acting buprenorphine - A systematic review. Australas Psychiatry. 2025 Apr;33(2):235-248. doi: 10.1177/10398562241295872. Epub 2024 Oct 29. PMID: 39470393.
[9] Bradley SEK, Shiras T. Where Women Access Contraception in 36 Low- and Middle-Income Countries and Why It Matters. Glob Health Sci Pract. 2022 Jun 29;10(3):e2100525. doi: 10.9745/GHSP-D-21-00525. PMID: 36332074; PMCID: PMC9242616.

adherence, lower risk of generating resistance due to perfect adherence, reduction in time spent interacting with the health system and time away from work with associated economic impacts (time saved, more home time, transit costs), reduced pill burden, reduced overall dosage of medication received, and reduced stigma. While LAIs could improve efficiencies, reduce long-term health system costs and have other benefits, it can be expected that the LAIs for TB treatment and prevention will enter the market with a higher price compared to the existing oral formulations. International collaboration and support may be required to ensure affordability, especially during initial roll-out.

Poor adherence to TB medication reduces regimen effectiveness and increases the risk of prolonged infectiousness, drug resistance, relapse, and death.[10] Factors contributing to erratic TB treatment adherence include health service issues, social context (poverty, lack of support), treatment-related adverse events, stigma of taking TB treatment and patient health literacy. There are a number of actions recommended by WHO to support medication adherence based on evidence, such as patient education and use of digital technologies,[11] but they require programmatic effort to implement. LAIs hold the promise to revolutionize the prevention and treatment of TB, reducing the frequency of drug administration and facilitating medication adherence.

TB preventive treatment (TPT) is one of the WHO-recommended strategies that can benefit both individual and public health, with an efficacy of about 60-90% which can last several years.[12] TPT fits within a larger array of actions that programmes can adopt to prevent TB, ranging from infection prevention and control, early detection and screening, management of health risks that predispose to TB like diabetes, smoking and undernutrition. This array of tools to prevent TB is expected to be supplemented with effective TB vaccines in the near future. The successful expansion of LAIs for TPT is anticipated to complement future TB vaccines, maximizing population coverage and ensuring a comprehensive, multi-layered approach to prevention. An efficacious TPT, if coupled with novel tests to identify those at highest risk for disease progression, is an important step to accelerate global progress to end TB. However, there are several challenges to implement TPT at scale, primarily due to the hesitancy of people offered TPT to take medication and the implications for programmatic logistics. Firstly, other than in people living with HIV and children under 5 years in contact with TB patients, current TPT guidelines recommend testing for TB infection to identify those who are more likely to benefit from medication. In many settings, these tests are not available due to logistical constraints or costs, creating a barrier to the implementation of TPT. Secondly, in every situation in which TPT is considered, TB disease needs to be ruled out, as current TPT regimens cannot be relied upon to resolve early forms of TB disease. Reliable ruling out of TB disease is at times challenging and the future development of affordable, portable, and accurate screening approaches would facilitate the ruling out of TB disease before the start of TPT and make TPT more feasible to deploy. Thirdly, while current TPT regimens are effective they are relatively long and prone to generate adverse drug reactions (ADRs). While most ADRs associated with TPT are low grade they still

[10] Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med. 2007 Jul 24;4(7):e238. doi: 10.1371/journal.pmed.0040238. PMID: 17676945; PMCID: PMC1925126

[11] WHO consolidated guidelines on tuberculosis. Module 4: treatment and care. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

[12] *WHO consolidated guidelines on tuberculosis. Module 1: Prevention - tuberculosis preventive treatment, second edition*. Geneva: World Health Organization, 2024 (https://iris.who.int/handle/10665/378536).

affect tolerability in people offered TPT, who are usually healthy and symptom-free. TPT is thus often interrupted and not completed as prescribed.[13],[14] Finally, if the infecting strain is resistant to the TPT drug(s) then TPT may be less effective. We do not yet have a TPT regimen that is reliably effective, short, and convenient as a "pan-TPT" regimen. The prospect of having TPT administered as a LAI, employing compounds that are safer than today's medication but equally or more effective, is of interest given that it has the potential to overcome a number of these challenges to TPT expansion. A TPT regimen of one month of daily rifapentine and isoniazid has been proven effective,[15] making it conceivable that LAI regimens acting over a similarly short period could also prevent TB, minimizing the number of encounters to administer compared with daily oral medication. This would simplify the programmatic management of TPT dramatically. Just as the efficacy of large-scale TPT interventions depends on their feasibility in primary care and community-based settings, it would be important that LAIs can also be administered in a decentralized setting. In conclusion, the effective implementation of LAI TPT will depend heavily on operational factors such as access to diagnostics, capacity to rule out TB disease, procurement and supply, education of health care workers, patients and contacts.

LAIs also have the potential to address a number of barriers to the successful treatment of TB disease. They can reduce the risk of acquired drug resistance by reducing treatment interruption, missed doses or ineffective monotherapy, and ensuring the desired concentration of TB medicines in serum and tissues for prolonged periods, also overcoming the pharmacokinetic variability associated with oral dosing, such as food effects and malabsorption. LAIs could simplify treatment delivery by removing the need for daily pill intake and frequent clinic visits, which are often required for TB therapy. By reducing the number of health facility contacts, they can ease the burden on both patients and health systems, minimizing risk of TB transmission, lowering service delivery costs and freeing resources for other aspects of care. Simplified, less frequent dosing may also improve adherence and treatment completion rates, particularly among patients who face structural or social barriers to consistent treatment. For TB disease, LAIs could facilitate treatment through only a few administrations spaced several months apart, offering a more manageable alternative to prolonged multidrug regimens. This approach could effectively shorten the duration of TB treatment to a few months, advancing a long-standing programmatic goal that has been difficult to achieve with conventional oral therapies.

Beyond individual adherence and system efficiency, LAIs could help reduce the stigma associated with TB prevention and treatment by limiting the visibility and frequency of medication-taking. Their use may also complement future TB vaccines and community-based interventions, supporting a more integrated approach to TB prevention and control. It is envisaged that LAIs may be given once or more times in the same individual, either with a brief initial phase of oral medication ("oral lead-in") before or as an exclusively injectable regimen. TB treatment regimens are composed of more drugs than TPT regimens

[13] Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis 2016;16:1269–1278.
[14] Melnychuk L, Perlman-Arrow S, Bastos ML, Menzies D. Systematic Review and Meta-Analysis of Tuberculous Preventive Therapy Adverse Events. Clin Infect Dis. 2023;77(2):287–294. https://doi.org/10.1093/cid/ciad246
[15] Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. New Eng J Med 2019;380:1001–1011.

and it may be possible that oral drugs will also have to be administered concurrently with LAIs to maintain efficacy and forestall resistance.

Despite the revolutionary promise of LAIs, their development and implementation face several significant limitations and operational challenges that must be addressed in the TRPs. The first key safety challenge is the difficulty of reversing administration; depending on the technology used, once injected, the medicine may remain in the patient's system for the whole coverage period and may continue causing adverse effects (AEs), making management of intolerance or toxicity particularly challenging.

Additionally, the physical experience of administration may be a barrier; the pain at site of administration of a LAI is expected to be more inconvenient than taking an oral medication. It will also require trained staff to give them. Another issue stems from the complexity of TB treatment, which typically requires a multi-drug regimen. Currently, there are not enough LAI medicines available to form a complete multi-drug regimen, which will necessitate a combination of LAIs and oral medicines. This requirement for a combined approach risks diminishing some of the core LAI benefits, such as simplified adherence and reduced pill burden.

A significant concern with LAIs is the pharmacokinetic (PK) tail—the period of prolonged, sub-therapeutic drug decline after treatment is stopped or a dose is missed. If different drugs in a regimen have mismatched tails, a patient may be exposed to functional monotherapy, where only one drug remains at an active level, potentially creating a 'selective window' for drug resistance. However, it is important to note that the clinical risk of amplifying resistance is highly dependent on the timing of this exposure. During the early 'intensive phase,' when the bacterial load is high, functional monotherapy is a major threat. Conversely, if the tail occurs toward the end of a successful treatment course—when the bacterial burden has been significantly reduced and the regimen is close to eliminating the final persister bacilli—the risk of selecting for resistance is substantially lower, as there is a smaller population of bacteria available to mutate.

Finally, the co-administration of different LAI agents may introduce operational complexities, as different compounds may be developed with varying treatment coverage periods (e.g., one monthly, one quarterly), making the administration timing and overall clinic schedule more complex to manage programmatically. These issues emphasize the need for new LAI products to prioritize a strong safety profile, high potency to reduce the number of required agents, and synchronized pharmacological coverage and wash-out periods.

This document addresses TRPs for LAI regimens for TPT and for treatment of TB disease. 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. The expectation is that any regimens that are developed will meet the minimal requirements and as many of the optimal requirements as possible. However,

potential trade-offs on performance, cost, impact and operational characteristics would need to be considered for WHO policy; thus, the criteria are indicative rather than absolute. 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 lower the strength of a recommendation (e.g. magnitude of desirable effects judged to be small or trivial) and thus reduce uptake of a new regimen.

Table 1. Target regimen profile 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. Regimens should generally meet the "minimal" requirements 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" requirements will provide the greatest impact for end-users, clinicians and patients. Developers would ideally design and develop their solutions to meet the "optimal" requirements.

Sometimes, minimal and optimal requirements are set in reference to existing comparator regimens (e.g. being safer than the comparator regimen). The comparator regimen is 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 contemporary comparator regimen that aligns with programmatic feasibility across diverse settings). It is the regimen that should be provided to patients in the comparator arm of randomized trials or nonrandomized comparisons. Typically, the comparator regimen would be based on the latest WHO recommendations for the respective indication. Note that this comparator is expected to be an all-oral treatment regimen.

In the case of multidrug regimens, some TRP attributes may be more relevant to a specific component of the regimen (e.g., dosing interval flexibility) while others may apply to the whole regimen (e.g., target population).

To complement the TRPs, WHO has developed guidance on evidence generation (GEG) on new TB regimens for treatment[16] and a GEG for TPT is currently in development. The TRPs describe *what* the minimal and optimal requirements for each regimen characteristic are, whereas the GEG provides more detailed guidance on *how* the achievement 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. While the GEG documents are tailored to the more usual oral regimens, many of the suggested measurements are also applicable to long-acting injectable (LAI) regimens. As the field develops, more details pertinent to LAIs may be added to the GEG.

[16] Guidance on evidence generation on new regimens for tuberculosis treatment. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

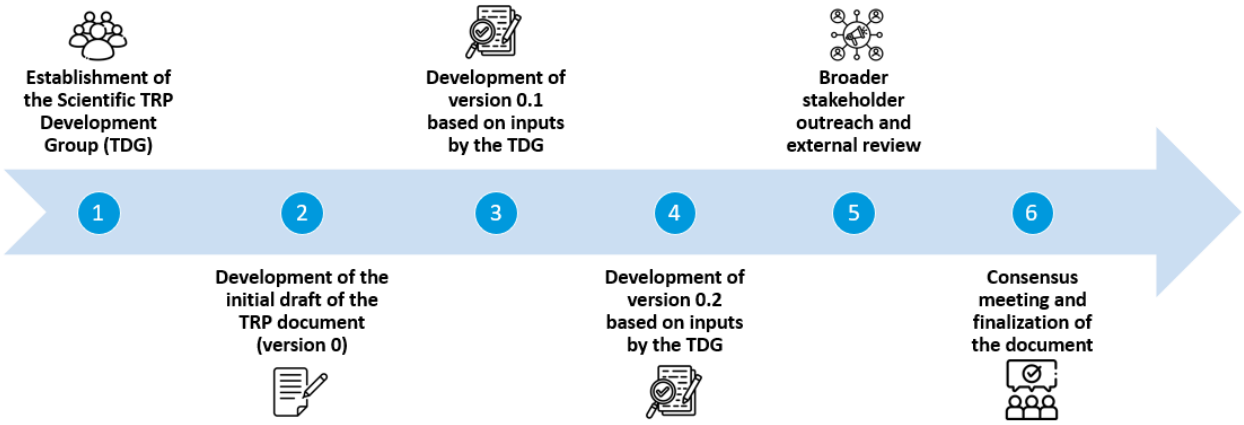
Objective and target audience

The overall objective of these WHO TRPs for LAIs for TB treatment and TPT is to align developers' performance and operational targets for new regimens with the needs of end-users, in line with the current trends in science. The target audience comprises the pharmaceutical industry, academia, research institutions, product development partnerships, TB-affected communities, nongovernmental organizations (NGOs), civil society organizations (CSOs), and donors. These TRPs will describe minimal and optimal requirements across key characteristics for LAIs.

2 Methodology

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

Fig. 2.1. Overview of the development process of the TB LAI TRPs



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

Establishment of the Scientific TB LAI TRP Development Group (TDG)

In 2025, WHO constituted a Scientific TRP Development Group (TDG) including leading scientists and experts, public health officials, regulators, those involved in the development of WHO policy recommendations and representatives of in-country end-users. The TDG served to support the entire TRP development process by reviewing drafts at several stages, contributing to discussions during meetings and providing direct input into the drafting process. All TDG members completed the WHO declaration of interest form and the declarations were presented to the whole group ahead of discussions and are summarized in Annex 1, which also includes the list of TDG members.

Landscape analysis

LAIs hold transformative potential for the programmatic management of TB, HIV, and malaria. HIV leads the way with approved therapies—such as CAB-LA, RPV-LA, and lenacapavir—demonstrating high

efficacy, including over 90% viral suppression.[17, 18, 19] In TB, LAIs are in early stages of development but show promise for both TPT and treatment of TB disease. For malaria, LAI candidates remain in preclinical or early clinical phases[20], primarily targeting prevention. While LAIs offer significant promise for improving adherence and treatment outcomes, challenges remain, particularly regarding cost, delivery logistics, and the limited availability of robust clinical data on their use in low- and middle-income countries (LMICs). Realizing the full impact of LAIs will require sustained research investment, community engagement and community-based delivery models, careful assessment of health-system capacities—including cold-chain management, training for injection-based delivery, and pharmacovigilance—especially in settings with constrained resources, enabling policy and regulatory support with policy frameworks that prioritize equitable access.

The research is advancing on long-acting formulations of existing TB drugs, with a focus on both TB prevention[21] and treatment of TB disease. Recent preclinical studies of LAI for TB have shown promising results. For instance, a long-acting formulation of bedaquiline demonstrated sustained antimicrobial activity for up to 12 weeks in a mouse model[22] and a phase 1 clinical trial was launched to evaluate bedaquiline LAI.[23] This has relevance and potential for both preventive and curative TB treatments.

The appeal of LAIs lies in their ability to reduce the number and frequency of dosing, which could make therapy more acceptable and significantly improve quality of life and adherence compared with current daily oral regimens and potentially revolutionize TB care by streamlining complex treatment protocols. Efforts to drive this innovation are underway but only one TB LAI candidate has currently entered human clinical trials, for TPT[24]; all other current efforts remain preclinical or formulation stage. Early animal studies suggest that LAIs for TPT may have a dual mechanism of action, that is both treating and preventing TB infection[25].

[17] Kityo, Cissy et al. "Switch to long-acting cabotegravir and rilpivirine in virologically suppressed adults with HIV in Africa (CARES): week 48 results from a randomised, multicentre, open-label, non-inferiority trial." The Lancet. Infectious diseases vol. 24,10 (2024): 1083-1092. doi:10.1016/S1473-3099(24)00289-5

[18] Flexner C, Owen A, Siccardi M, Swindells S. Long-acting drugs and formulations for the treatment and prevention of HIV infection. International Journal of Antimicrobial Agents 2021;57:106220.https://doi.org/10.1016/j.ijantimicag.2020.106220.

[19] Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis. Geneva: World Health Organization; 2025

[20] https://www.mmv.org/mmv-pipeline-antimalarial-drugs/mmv371-0

[21] Swindells S, Siccardi M, Barrett SE, Olsen DB, Grobler JA, Podany AT, Nuermberger E, Kim P, Barry CE, Owen A, Hazuda D, Flexner C. Long-acting formulations for the treatment of latent tuberculous infection: opportunities and challenges. Int J Tuberc Lung Dis. 2018 Feb 1;22(2):125-132. doi: 10.5588/ijtld.17.0486. PMID: 29506608; PMCID: PMC6103451.

[22] Kaushik A, Ammerman NC, Tasneen R, Lachau-Durand S, Andries K, Nuermberger E. Efficacy of Long-Acting Bedaquiline Regimens in a Mouse Model of Tuberculosis Preventive Therapy. Am J Respir Crit Care Med. 2022 Mar 1;205(5):570-579. doi: 10.1164/rccm.202012-4541OC.

[23] https://respiritbntm.eu/publications/FIH.pdf

[24] Zeitlinger M, Prager M, Guinard-Azadian C, et al. LB02-1321-19 Bedaquiline long-acting formulation: Interim results of a phase 1 pharmacokinetic and safety study for single-dose TB preventive treatment. Int J Tuber Lung Dis. 29:Suppl 1. Nov 2025 (abstract for presentation). https://documents.theunion.org/web-uploads/UNION2025_Abstracts_Medium.pdf#page=786

[25] Fontaine V, Chauffour A, Rima A et al. TBS-EP305 Long-acting bedaquiline: A novel preventive strategy against tuberculosis in a murine model. Int J Tuber Lung Dis. 29:Suppl 1. Nov 2025 (abstract for poster). https://documents.theunion.org/web-uploads/UNION2025_Abstracts_Medium.pdf#page=866

Several development efforts are ongoing, particularly focusing on equitable access in LMICs where the TB burden is highest (see Table 2 for a non-comprehensive overview; [NOTE to the TDG: inputs to expand very welcome].

Table 2. Overview of development work on LAIs

Preclinical (formulation, animal models)	
Medincell + iM4TB / ERA4TB	Developing long-acting macozinone formulations for TB treatment.
Centre of Excellence for Long-acting Therapeutics (CELT), University of Liverpool[26]	Working on LAI formulations of TB drugs, including rifapentine, isoniazid and sorfequiline, for TB treatment and prevention. Rifapentine LAI is expected to enter phase 1 in 2026. A sorfequiline LAI development is a collaboration with Johns Hopkins University and TB Alliance.
University of North Carolina, TB Alliance, Bill & Melinda Gates Foundation	Investigating long-acting injectable rifabutin and other agents using an injectable solid drug in a polymer implant (ISFI) platform.
University of Southern Denmark and Gates Foundation	Long-acting injectables for treatment using three different substances against tuberculosis. The project focuses on injection suspensions and the determination of appropriate stabilization methods and particle size to achieve a release period of 4-6 months for the three substances.
Clinical development	
Janssen Pharmaceuticals	Phase 1 trial: A Single Ascending Dose, Single-Centre Study, to Assess Pharmacokinetics, Safety and Tolerability of a Single Intramuscular Dose of Bedaquiline Long-Acting Injection Formulation in Healthy Participants
Enabling technology / Intellectual property	
Medicines Patent Pool (MPP) + Extentus Pharma Ltd. (previously Tandem Nano)	Extentus's nano-formulation platform for rifapentine and isoniazid LAIs is licensed to MPP for potential use in TB and other diseases.
Cross-disease initiatives, including TB	

[26] https://unitaid.org/project/long-acting-medicines-for-malaria-tuberculosis-and-hepatitis-c/

Unitaid / LONGEVITY Project (Medicines Patent Pool, Imperial College London, University of Liverpool, Johns Hopkins University, Clinton Health Access Initiative, Tandem Nano)	Focus on accelerating access to LAIs for malaria, hepatitis C, and TB (including rifapentine and isoniazid, as mentioned above in this table).
LEAP TB Working Group	Engaged in advocacy, target product profile development, and prioritization of TB LAI candidates.

However, significant challenges remain. Many existing TB drugs have pharmacokinetic (high target exposure and/or rapid clearance) or physicochemical properties that make them unsuitable for long-acting formulations[27] because they would either require unsuitable injection volumes or injection frequency, narrowing the list of viable candidates. Drugs with genetic variability in metabolism, like isoniazid, will be less preferred for consideration as LAI and will need to be considered in combination with other characteristics. On the implementation side, issues such as cold-chain requirements, the need for trained healthcare personnel, and high delivery costs may pose significant obstacles to large-scale deployment for the use of LAIs in resource-limited settings. Regulatory pathways for TB LAIs remain underdeveloped, and countries may require substantial guidance to evaluate pharmacovigilance and injection-site safety. Moreover, there are as yet limited data from clinical trials on the safety of TB LAIs and effectiveness data are not yet available; if initial trials exclude children, pregnant women, and people with comorbidities, such evidence gaps will affect real-world application. The development of LAI agents for paediatric TB may offer a more streamlined pathway than conventional oral therapies. Because paediatric requirements will likely be met through weight-based dose adjustments of existing formulations—rather than the design of entirely novel delivery systems—this approach could significantly accelerate development timelines for childhood TB interventions.

Stakeholders surveys

Summary of WHO-TAG-performed stakeholder surveys (full report in the annex)

In 2025, the WHO, in collaboration with the Treatment Action Group (TAG), conducted a survey to assess global perspectives on long-acting injectable (LAI) medicines for tuberculosis. This research, also supported by the London School of Hygiene & Tropical Medicine (LSHTM), gathered insights from country programmes, technical partners, and civil society representatives during regional workshops across the SEAR, WPR, and EUR regions. The findings highlighted robust stakeholder support for the development and adoption of LAI medicines for both TB treatment and prevention, noting their significant potential to enhance treatment adherence across diverse clinical settings.

[27] Ammerman NC, Nuermberger EL, Owen A, Rannard SP, Meyers CF, Swindells S. Potential Impact of Long-Acting Products on the Control of Tuberculosis: Preclinical Advancements and Translational Tools in Preventive Treatment. Clin Infect Dis. 2022 Nov 21;75(Suppl 4):S510-S516. doi: 10.1093/cid/ciac672. PMID: 36410384; PMCID: PMC10200320.

The analysis integrated data from two distinct surveys comprising 310 participants, including 102 healthcare providers and policymakers and 208 community members and patients. The sample was highly diverse, featuring civil society representatives (39%), clinicians and health workers (25%), and individuals with lived experience of TB (19%). Geographically, the data reflected a global perspective with strong representation from Africa (33%), Europe (25%), and South-East Asia (15%). While regional representation varied between the two surveys—with Survey 1 drawing more from the Western Pacific and Survey 2 from the Americas and Africa—the combined results provide a broad and nuanced understanding of stakeholder needs worldwide.

A significant majority of respondents (83%) expressed definite or probable interest in adopting LAIs for TB treatment in place of daily oral regimens, while only 8% showed reluctance. This high level of acceptance was remarkably consistent across all stakeholder groups and geographic regions, signalling that LAIs are viewed as a promising alternative modality. Notably, positive attitudes persisted even among individuals who had previously experienced injection-related side effects. Furthermore, 65% of respondents supported the use of LAIs in children, suggesting that the perceived benefits of long-acting formulations outweigh concerns regarding administration for paediatric populations.

Stakeholder preferences consistently emphasized the need for shorter treatment durations and a reduction in the total number of injections required, with a particular interest in co-formulation strategies to simplify the patient experience. Collectively, these insights provide essential evidence for guiding WHO Target Regimen Profiles and prioritizing LAI drugs development. By aligning technological innovation with the specific needs of patients and providers, the development of LAIs can be strategically directed to transform the TB care continuum. The complete report, detailing the methodology and full analysis, is provided in Annex X.

Summary of TAG performed focus group study (full report in the annex)

The treatment action group (TAG) coordinated a mixed-methods study to explore community perspectives on LAIs for both TB treatment and TPT between August to September 2025. The study was conducted in two phases, first being an online, multilingual survey of TB community networks to capture anonymous data on acceptability, preferences, and prior experiences with TB medications that generated 208 responses from 45 countries. Respondents included civil society (46%, n=95), people with TB experience (29%, n=60), clinicians/health workers (24%, n=50), and researchers (1%, n=3). 53% (n=110) participants reported prior awareness of LAIs for TB, while 38% (n=79) had prior TB treatment or TPT experience, of whom 45% (n=21) had received injectable TB medication. The second phase convened four regionally diverse group discussions (14 participants) with above survey participants to deepen understanding of community priorities, trade-offs, and contextual factors influencing uptake of LAIs.

Across all survey respondents, 82% (n=256) expressed favourable interest in adopting LAIs for TB treatment. However, prior experience with TB injectables significantly reduced acceptance: 52% of previously injected respondents reported they would likely not choose an LAI regimen, compared with 13% among those without such experience. Preferences strongly favoured shorter, simplified regimen. For TB treatment, 69% (n=215) preferred a 3-month LAI regimen over the standard 6-month oral

regimen, rising to 80% (n=249) when total injections were reduced from four to two. Trade-off scenarios demonstrated that minimizing the total number of injections was a priority. For TPT, acceptance was high, with 79% (n=246) preferring a single-dose LAI over a 1-month oral regimen. LAI use for children was viewed favourably by 65% (n=126), though negative perceptions increased among those with prior injection experience.

A significant preference exists for minimizing the number of injections per visit. While respondents favoured shorter total treatment timelines, they were willing to accept longer durations (e.g., 4 months vs. 3 months) if it meant fewer injections per session. Although respondents initially preferred subcutaneous over intramuscular delivery when queried on technology type, regimen-specific trade-offs suggest that visit rhythm and total duration are more influential than the specific route of administration. LAIs may serve as a stigma-mitigation tool by reducing the frequency of clinic visits and eliminating the need for daily oral medication within households or workplaces. While there is a baseline preference for local community-level clinics (51%), patients indicated a willingness to travel to centralized district hospitals (54%) if it resulted in less frequent visits or a shorter overall regimen. Concerns regarding persistence of side effects was prominent. Participants emphasized the need for treatment agency, including the flexibility to switch back to oral regimens if side effects become intolerable.

Summary of the Philippines pilot LAI stakeholder/user acceptability study

Between April and August 2024, the Gates Medical Research Institute supported a two-stage, mixed methods study on LAI for pan-TB treatment in one urban and one semi-urban sites in the Philippines. The study findings are intended to inform developers on the acceptability and preferences for LAI TB treatments. The methods employed included (1) key informant interviews with 15 national and regional TB experts and (2) surveys with TB patients, survivors, and care providers (N~ 350), also incorporating a discrete choice experiment to assess likely trade-offs between different LAI characteristics. Experts interviewed were receptive to new TB treatment regimens, and were optimistic about the ability of the health system to implement LAIs for TB treatment, reporting anticipated barriers to adoption mostly centred on logistics (cost, supply chain, distribution) and patient apprehension with injections. A treatment scenario with 2 injections monthly for 4 months was preferred over 4 shots, one-time treatment or a 1 month daily oral lead-in followed by 2 injections 3 months apart. The survey respondents also found the 4 shots, one-time treatment to be less acceptable (59%) than the other two options (78%). The survey identified characteristics that influenced decisions to choose an LAI treatment - one-time encounter with fewer shots, no oral lead-in, mild pain, and administration at a local clinic – as well as those that were unfavourable - 2-months oral lead-in, multiple cycles of injection, multiple injections (3+) per encounter, injection site pain requiring medication and deep muscle gluteal injection. Overall, building patient familiarity with an injectable and ensuring a less painful experience seemed to be important. Delivery of LAI at a local health centre was broadly preferred across TB patients, TB survivors, and TB care providers

3 Definitions of characteristics and related considerations

This section outlines the definitions and some related considerations for the regimen characteristics used in the subsequent sections. Characteristics apply to the regimen as a whole unless specifically indicated to apply to single drugs.

Table 3. Definitions of regimen characteristics and related considerations

Characteristic	Definition and related considerations
Target population	People with TB infection or disease for whom the regimen described in a given TRP is intended. Vulnerable populations of interest may have specific needs that differ from those of the general population. Such groups include children, pregnant and breastfeeding women, people living with HIV, and people with other conditions like undernutrition and diabetes.
Indication and need for testing	The specific indication of a given TRP (i.e., for treatment of TB infection or for TB treatment) and related needs for testing (e.g., DST, test for infection or disease).
Number of encounters for LAIs administration	The number of times a person needs to encounter the health system or the community healthcare worker during treatment to receive a dose of LAIs
Duration of coverage [single drug]	This is a pharmacokinetic (PK) metric. The duration over which injection of an individual long-acting drug is considered to lead to safe and clinically effective drug concentration in plasma or at the site of the disease. The duration of coverage for regimens containing multiple LAIs with varying duration of coverage needs to be considered. Duration of coverage determines the **dosing frequency**, i.e., the frequency at which injections need to be given (e.g., if duration of coverage is 1 month, the dosing frequency is 1x/month).
Treatment duration	This is a clinical metric. This attribute refers to the total duration of treatment administration, i.e., the time between the first and the last dose encounters. After provision of the last dose, further care, monitoring and follow-up, e.g., for

Characteristic	Definition and related considerations
	assessment of symptom resolution, cure and adverse events, also needs consideration for programmatic implementation, but is not considered part of the treatment duration characteristic.[28]
Dosing interval flexibility [single drug]	The degree of flexibility in the timing of sequential injectable dosing events—i.e., how much deviation is acceptable for the delivery of a subsequent dose after the preceding dose without compromising safety and efficacy. In other words, it is the ability of the drug's pharmacokinetic (PK) profile to absorb the impact of human and systemic variability. While "Duration of Coverage" determines the target re-dosing point (e.g., every 2 months), "Dosing Interval Flexibility" defines the permissible flexibility around that point. A regimen with 2-month coverage and ±2 weeks of flexibility effectively creates a 4-week window (from week 6 to week 10) during which the next 'Interaction' can safely occur. Dosing Interval Flexibility must address two distinct clinical risks. First, the risk of sub-therapeutic levels If a patient arrives late, the "PK tail" must be robust enough to maintain concentrations at or above the minimum inhibitory concentrations required for efficacy of the medicine. This prevents potential selection of drug-resistant mutants. The second is the risk of early-dose toxicity If a patient arrives early, the "dose overlap" must not push peak plasma concentrations into a toxic range.
Number of component drugs	The number of component drugs included to make up a regimen; the same number may be considered for use for the total duration, or alternatively a different number of component drugs may be considered for the regimens that have intensive and continuation phases of treatment.
Formulation & number of injections per encounter	**Formulation**: The way in which the active drug is combined with other chemical substances to yield the final product, including whether multiple drugs are co-formulated such that two or more drugs can be delivered in a single injection. **Number of injections per encounter**: number of injections delivered each time a person receives a dose of LAIs.

[28] In the context of LAIs, treatment duration can conceptually be divided into two distinct parts: the duration of the engagement between the patient and the healthcare system for the actual treatment administration, and the duration of the treatment's continued clinical effectiveness after the last dose is given. The latter, in the case of LAI-based treatments is dependent on another LAI-specific attribute, namely the duration of coverage. To maintain consistency between different regimens and avoid the complexity related to the potentially variable duration of coverage, the treatment duration characteristic is presented as the total duration of treatment administration (i.e., from the first event of treatment administration to the last one, oral or injectable).

Characteristic	Definition and related considerations
Combination with oral TB medications	Combination with oral TB medications may be considered for a variety of reasons and thus may be implemented using different regimen models using several possible strategies. These two scenarios assume the same medicines exist and used in oral and LAI formulations. • **Oral lead-in to test the regimen for potential adverse events.** Patients take the oral formulation of the medicines in the LAI regimen for a short period. The goal is to assess the safety and tolerability of the regimen and any potential systemic reactions in the individual before committing to a non-reversible long-acting dose that remains in the body for months and cannot be easily removed. • **Oral lead-in to cover for the slowly increasing drug concentration** - ***time to reach therapeutic levels*.** Patients take the oral formulation before or alongside the first injection. The goal is to bridge the time it takes for the LAI to reach adequate concentration levels. This largely depends on the LAI chemistry and delivery methods. The following two scenarios can take place with different medicines in oral and LAI formulations. • **Oral intensive phase with LAI continuation phase.** Intensive phase includes a combination of oral and LAI medication together, with the LAIs being continued in the continuation phase without the oral medications. This scenario (i) could allow the inclusion of LAIs in a hybrid regimen if the number of drugs available as LAIs is insufficient on its own and (ii) would permit the use of existing, highly effective oral medications if they are not available as LAIs to bring down the bacillary burden in the first months of treatment, while at the same time still preserving some of the important benefits of LAIs in particular in the later stages of treatment when patients tend to feel better and adherence can become challenging. • **Concurrent use of LAIs and oral formulations of medicines throughout the regimen** would be expected not to yield the same benefits as the above-described scenarios as high levels of adherence to take medications daily would still be required. However, this option may still have some value if the LAI use provides for a significant decrease in the pill burden, helps avoid GI-disturbance, if the oral route is not viable or suboptimal for certain drugs, e.g. due to PK properties of the drug, importance of avoiding first-pass metabolism, or issues related to bioavailability or other formulation-related constraints. While fully LAI-based regimens offer the most transformative potential in terms of adherence and programmatic use regimens that combine LAIs with oral agents can still offer partial advantages, especially in the transitional period as technologies, formulations, and delivery systems mature.
Route of administration & injection volume [single drug]	**Route of administration** refers to the way by which a pharmaceutical agent is delivered into the body to achieve systemic or local effect. For LAIs, the route of administration is typically either intramuscular [IM] or subcutaneous [SC], while lead-in or companion drugs may be given orally. Implants and depot tablets are outside the scope of these TRPs.

Characteristic	Definition and related considerations
	The selected route constrains the permissible **injection volume**: IM administration generally accommodates larger volumes (2-5 ml in adults) compared to SC (0.5-2 ml in adults), depending on the individual and injection site, due to differences in tissue capacity and absorption kinetics. However, the maximum injectable volume is further influenced by the anatomical site selected (e.g., gluteal vs. deltoid for IM) and individual patient factors such as tissue composition and tolerability.
Setting of treatment administration & training requirements	The **setting of treatment administration** refers to the physical, organizational, and procedural environment in which a treatment is delivered to a patient. The setting can have significant implications for resource utilization, patient acceptance, well-being, treatment completion, safety, and overall healthcare system burden. Typical settings for treatment administration: inpatient (hospital), outpatient/ambulatory care, primary care, home-based, self-administration. **Training requirements**: for all levels of health workers, as well as community and lay carers and members of a household helping a TB-affected person with treatment
Efficacy & effectiveness	**Efficacy** refers to the extent to which a treatment produces a beneficial outcome under ideal, controlled conditions, typically demonstrated in explanatory randomized controlled trials (RCTs). **Effectiveness** refers to the extent to which a treatment achieves the desired outcomes in real-world conditions, where factors like patient quality of life, adherence, comorbidities, health system variability, and social determinants of health come into play, which may be demonstrated in pragmatic RCTs. For regimens to treat **TB disease**, efficacy & effectiveness is evidenced by durable cure; that is, a relapse-free cure typically 12 months after treatment completion under controlled clinical trial conditions or the treatment success rate (cure and completion), taking into account challenges such as loss to follow-up, drug resistance, and health system limitations. For **TPT** regimens, efficacy & effectiveness relate to the ability to avert the occurrence of disease arising from infections that were present at the time of TPT administration, typically evaluated based on incidence of TB disease over the next 2-5 years.
Safety & safety monitoring	**Safety**: The incidence and seriousness of adverse events observed with the use of the regimen. **Safety monitoring**: Frequency and type of clinical and laboratory monitoring required to ensure the safe use of the regimen.

Drug-related tolerability	Drug tolerability is defined by the FDA as "the degree to which overt adverse effects can be tolerated by patients".[29] The tolerability profile of a given drug or regimen is of comparative importance to its efficacy and safety, because it largely determines acceptability and 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 life, treatment intake and the risk of treatment discontinuation. Measures of tolerability include the proportion of patients interrupting or discontinuing treatment owing to adverse effects and the occurrence of lower grade adverse events that may not cause imminent danger to patients but may have a detrimental effect on their quality of life.
Injection-related tolerability	Injection-related tolerability is a critical determinant of regimen acceptance, as the discomfort of an injection must be weighed against the persistent burden of daily oral medication. While healthcare providers and patients anticipate a degree of localized reaction, the targets emphasize that these symptoms—such as mild pain, redness, itching, or swelling—should remain manageable and non-cumulative. A key requirement is that subsequent injections do not exacerbate previous reactions, ensuring that tolerability remains stable throughout the treatment course. The timeframe for the resolution of symptoms serves as a primary differentiator between minimal and optimal profiles.
Drug-drug interactions (DDIs) [single drug/regimen]	Drug-drug interactions (DDIs) with other medications, including those used to treat the most frequent comorbidities.
Propensity to develop resistance to TB medicines	This parameter assesses the potential of an LAI candidate to select resistant Mycobacterium tuberculosis strains. Regimens should be structured so that included drugs protect each other against the emergence of resistance. Cross-resistance with existing TB medicines should be evaluated, but its presence should not automatically preclude LAI development when the formulation offers clear advantages for TB treatment or prevention. It is crucial to minimize the risk of undermining both current and future therapeutic options while allowing innovation in formulation and delivery. Studies have estimated the in vitro frequency of mutations that confer resistance to various TB medications. The in vivo risk of clinical resistance also depends on drug exposure, host immunity, bacterial population size, and treatment adherence; therefore, laboratory estimates do not directly reflect clinical incidence. 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[30]. For this reason, some of the drugs may be considered as "protective" to other drugs,

[29] Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry. E9 statistical principles for clinical trials. US Department of Health and Human Services, Food and Drug Administration; 1998 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9-statistical-principles-clinical-trials)

[30] Dartois VA, Rubin EJ. Anti-tuberculosis treatment strategies and drug development: challenges and priorities. Nat Rev Microbiol. 2022;20:685–701. doi: https://doi.org/10.1038/s41579–022–00731-y

	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 core drugs, to reduce the risk of functional monotherapy. The propensity to develop resistance to different antimicrobials could be measured in clinical trials of TB disease by comparing resistance patterns in bacilli isolated at baseline to those isolated at later stages. In TPT studies, it can be assessed by comparing the resistance pattern of the strains in persons who develop TB to the one in the presumed source case (if isolates are not genetically identical then it is likely that the source case was different and interpretation of differences in the resistance pattern is not meaningful).
Stability or shelf life and storage requirements [single drug]	The period of time (usually in years) that a product is stable at a given temperature and humidity, and thus influences its storage requirements.

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; TB: tuberculosis; TRP: target regimen profile; WHO: World Health Organization.

4 LAIs for TB preventive treatment

This section outlines the minimal and optimal characteristics of an LAI TPT regimen, as well as trade-offs between these characteristics.

TRPs for LAIs for TB preventive treatment

Table 4. Requirements for regimen characteristics for LAIs for TB prevention

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Target population	Household contacts of people with TB, people living with HIV and other people at increased risk of TB.	All individuals recognized as being at risk of TB disease, including children, and pregnant and breastfeeding women.	TPT is currently not systematically recommended for ALL people with an increased risk of developing TB. Indication is based upon an assessment of risk of progression from infection to disease and consideration of the risk/benefit profile of TPT. The latest WHO guidelines (2024)[1] recommend TPT to: • Children aged ≥ 12 months, adolescents and adults living with HIV, • Household contacts of people with bacteriologically confirmed pulmonary TB, regardless of age, HIV status and rifampicin-susceptibility status of the index case, • Other people at risk, namely those who are initiating anti-tumour-necrosis factor treatment, receiving dialysis, preparing for an organ or haematological transplant, or who have silicosis, prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs. Current evidence does not yet support a recommendation for the systematic testing for TB infection and TPT in people whose only risk is diabetes, harmful use of alcohol, tobacco smoking, underweight or living in an area with a high prevalence of TB. Optimally, the LAI TPT would have a better safety profile and more favourable risk/benefit profile than currently available oral TPT options, justifying its wider use for prevention among populations in whom oral TPT is not currently systematically recommended.

[1] *WHO consolidated guidelines on tuberculosis. Module 1: Prevention - tuberculosis preventive treatment, second edition*. Geneva: World Health Organization, 2024 (https://iris.who.int/handle/10665/378536

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			TPT regimens based on H, HP, HR and Lfx are currently recommended in all populations at risk (there is a current restriction on the use of P during pregnancy or breastfeeding). There should be a similar expectation for the widescale use of LAI regimens regardless of age, comorbidity, pregnancy or breastfeeding status. The minimal requirements can still be satisfied if there is insufficient evidence on the safety of the drug in some populations (e.g. children, pregnant and breastfeeding women); the LAI will not be intended for use in these subgroups until sufficient evidence is available. If clinical data are not available on dosing and safety in children and pregnant and breastfeeding women, explicit plans for the generation of such evidence should be in place. Efficacy trials in these populations are not necessarily required, given that efficacy can be extrapolated from other populations. **Children**: PK and safety studies will be needed in infants, children and adolescents for optimal requirements. TB regimen developers should consider initiating paediatric studies as soon as early studies of the drug show promising efficacy and safety, allowing suitable paediatric formulations should also be developed to enable dosing in trials involving young children.[1] 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[2]. These requirements are waived by the US FDA for the orphan drug designations and the drugs for treatment of TB disease usually qualify for the orphan drug designation since TB is a rare disease in the United States of America. The EMA requires the provision of plans for paediatric studies at the conclusion of Phase 2 studies at the latest. **Pregnant and breastfeeding women**: In pregnant women at risk, TPT benefits usually outweigh the harms. In pregnant women, the drugs used in

[1] Nachman S, Ahmed A, Amanullah F, Becerra MC, Botgros R, Brigden G et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. Lancet Infect Dis. 2015;15:711–20. doi: https://doi.org/10.1016/S1473–3099(15)00007–9

[2] Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Pediatric study plans: content of and process for submitting initial pediatric study plans and amended initial pediatric study plans: guidance for industry. US Department of Health and Human Services, Food and Drug Administration; 2020 (https://www.fda.gov/media/86340/download).

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			most current TPT regimens cross the placenta, but do not appear to have harmful effects on the fetus. Formulations should be safe for use in pregnancy and during breastfeeding [1,2,3]. Studies in pregnant and breastfeeding women should be initiated early, as phase 1 and early phase 2 trial data is collected to support the inclusion of pregnant and lactating women in pre-licensure trials, including non-clinical developmental, DART and reproductive toxicology studies during phase 2b trials of promising LAI candidates. Clinical development plans should include pregnant and breastfeeding women. Pregnant and breastfeeding women share lived experiences, but there is little justification for the exclusion of breastfeeding women in research studies. The inclusion of breastfeeding women should start from the assumption of inclusion. In contrast, the exclusion of pregnant women might be supported by evidence-based rationale from developmental and reproductive toxicity studies.[4] Other considerations will be needed for special populations (e.g., people living with HIV or diabetes or other co-morbidities) even if no minimal or optimal requirements are devised explicitly for these populations.
Indication and need for testing	The LAI is indicated to treat TB infection, for at least people presumed to be infected with a rifampicin-susceptible *M. tuberculosis* strain.	The LAI is indicated to treat TB infection, regardless of whether the *M. tuberculosis* strain is presumed to be rifampicin-susceptible or rifampicin-resistant.	If LAIs contain rifamycins, the DST pattern in the presumed source case would ideally be obtained before starting a contact on TPT as a minimal requirement. When required, a single, rapid, molecular test for rifampicin resistance would be carried out. Under the optimal requirements, the LAI would ideally contain novel compound(s) to which resistance is rare in circulating *M. tuberculosis* strains or that are not known to be cross-resistant to currently used drugs. These compounds may be from amongst those in the currently recommended TB treatment or TPT regimens. DST of

[1] Miele K, Bamrah Morris S, Tepper NK. Tuberculosis in pregnancy. Obstet Gynecol. 2020;135:1444–53. doi: https://doi.org/10.1097/AOG.0000000000003890.
[2] Gupta A, Hughes MD, Garcia-Prats AJ, McIntire K, Hesseling AC. Inclusion of key populations in clinical trials of new antituberculosis treatments: Current barriers and recommendations for pregnant and lactating women, children, and HIV-infected persons. PLoS Med. 2019;16:e1002882. doi: https://doi.org/10.1371/journal.pmed.1002882.
[3] Task Force on Research Specific to Pregnant Women and Lactating Women [website]. Bethesda, MA: US Department of Health and Human Services, National Institutes of Health; 2023 (https://www.nichd.nih.gov/about/advisory/PRGLAC)
[4] Optimal and early inclusion of pregnant and lactating women in tuberculosis research: consensus statement. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			the index case would thus not be required for TPT initiation as the frequency of resistance to the new drug and the likelihood of generating resistance would both be low. As a general principle, for persons aged 5 years and older exposed to a TB case, as well as other persons at risk (excluding people living with HIV), a positive test of TB infection is recommended before starting TPT. Currently recommended tests for infection are interferon-gamma release assays (IGRA), tuberculin skin test (TST) and new antigen-based skin tests (TBST). The need to confirm infection before TPT lessens in importance as the drugs used become safer and the inconvenience in TPT delivery – including cost – is removed. Screening to exclude TB disease (symptomatic or asymptomatic) is needed to assess eligibility for TPT with LAI, for both the minimal and the optimal scenarios, to avoid the inadvertent use of TPT in people with TB disease. Screening algorithms that employ chest radiography to exclude TB disease are preferred given their higher sensitivity. Details of appropriate screening strategies must be clearly explained at the time of scale-up.
Number of encounters for LAIs administration	One		Results from surveys and FGDs highlighted limiting the number of visits to a health care centre as a top priority for people receiving preventive or curative treatment for TB.
Duration of coverage (single drug)	The duration of coverage needs to be aligned to the effective duration of the TPT regimen given as LAI		The duration of coverage that a single LAI injection will provide is an important determinant of dosing frequency and TPT duration. Given that the aim is to have only one LAI encounter the duration of coverage needs to align with the duration of the regimen to provide for an effective TPT. The LAI TPT regimen may thus require more than a single injection/encounter and therefore require trade-offs with other optimal requirements. The BREACH TB trial is evaluating a one drug (BDQ) oral TPT regimen lasting one month and, along with other ongoing studies of LAIs, will provide evidence that may inform the operationalization of this requirement.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Treatment duration	Up to one month	One instance	The current shortest duration for an oral TPT regimen recommended by WHO is one month with daily dosing. Shortening this duration would require a drug or drug combination of sufficient potency and persistence to provide a long duration of coverage, such that a relatively short period of adequate coverage would be sufficient to achieve efficacy. The **minimal target** is 1 month, during which two LAI doses are envisaged to be given. An oral lead-in may be required ahead of or concurrent with the first dose of the LAI for the purpose of testing for safety and tolerability. The **optimal target** is set to one LAI dose, with no oral lead-in.
Dosing interval flexibility	Not applicable (only one dose will be required)		For TPT, the requirement for dosing interval flexibility follows the same pharmacological principles as those detailed in the treatment section: maintaining a "forgiveness window" via a robust PK tail to accommodate programmatic delays. However, the applicability of this concept depends on the regimen model. While flexibility is essential for multi-dose prevention schedules to avoid sub-therapeutic gaps or toxic overlaps, it is less relevant for the "optimal" TPT target of a single-dose regimen. In such cases, the focus shifts from scheduling flexibility to ensuring that the single injection's PK tail is sufficiently potent and persistent to achieve a complete preventive effect without requiring a re-dosing window.
Number of component drugs	Up to two drugs		Recommended TPT regimens are currently composed of one or two drugs. This number shouldn't be exceeded in TPT LAI regimens. The minimal and optimal requirements of up to two drugs was judged to be acceptable, based on the principles of oral TPT, to maximize efficacy and durability. This also includes drugs used for lead-in, if applicable. A combination of two drugs may provide benefits over one drug alone, such as enabling a shorter duration of effective treatment. New compounds used in the regimen should have minimal cross-resistance with existing drugs used to treat TB (especially the older ones to which

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			resistance is more widespread). Any drug combination should not increase the toxicity of the individual drugs in the regimen.
Formulation & number of injections per patient encounter	Up to two injections (not co-formulated)	One injection (co-formulated)	Coformulation of drugs in a single vial may in future reduce the number of injections needed to complete a regimen. For the immediate future, we expect that one component drug would require one injection when a LAI dose is administered. For drugs that can be used for both TPT and TB treatment it may be preferable not to have a co-formulation so that the same product can be used in different clinical scenarios. On the other hand co-formulation could facilitate the administration of a regimen and is more convenient for the person taking the regimen. The formulation should provide for the maximal adult dose and one vial per patient Optimal Requirement: Ideally, there should be no or minimal adjustment to food and no need for co-medication for both the LAI and oral lead-in components. The medication for an oral lead-in would usefully be co-packaged with the LAI. Oral drugs should be available in paediatric forms (dispersible, scored tablets, palatable) and also as fixed-dose combinations. Co-packaging refers to the combined availability of all drugs needed for a regimen in the same package, whereas coformulation of LAI would mean that several drugs are included in one vial or prefilled syringe. In case the volume to be injected exceeds the minimal requirement, the dose can be given in two injections at different sites at the same encounter.
Combination with oral TB medications	Oral lead-in for no longer than two weeks	None	Given that TPT aims to treat a smaller bacterial load in the infected person than someone with TB disease, a ramping of the dose may be less important. It is likely that the adequate serum concentration levels are reached rapidly after an LAI dose. This largely depends on the LAI chemistry and delivery methods. An oral lead-in would thus only be justified to assess the safety and tolerability of the LAI compound before administering it in a long-acting form that remains in the body for months and cannot be easily removed. An oral lead-in should be as short as possible, so that the TPT duration is not prolonged. There should also be some flexibility of the oral lead-in,

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			which allows for any missed doses in a daily regimen to be taken at the end, so long as the interruption is no longer than 2-3 days.
Route of administration & injection volume	Intramuscular or subcutaneous; Upper-thigh, arm, abdomen, or gluteal Maximum injection volume: SC: <=2ml for adults (adjusted for kids) IM: <=5ml	Subcutaneous; Upper-thigh, arm, or abdomen Maximum injection volume: SC: <=1ml for adults (adjusted for kids) IM: <=3ml	In addition to volume injected, the determinants of the size and duration of any swelling after injection to be commented here. There may be a lower tolerability to have higher volumes in people who are not diseased In case the volume to be injected exceeds the minimal requirement, the dose can be given in two injections at different sites at the same encounter.
Setting of treatment administration & training requirements	Injections administered by local HCW with minimal additional training	Injections administered by local HCW without additional training or even self-administered with minimal training	For both the Minimal and Optimal requirements, it should be possible to administer the LAI at the lowest level of the health service, in the community, or a person's home. Given that most doses of oral TPT are usually taken by the unsupervised individual concerned (or their guardian), the possibility to have at least the second dose of LAI self-administered should be considered. Task-oriented training of the person administering the LAI would be envisaged.
Efficacy & effectiveness	The LAI regimen efficacy is as good as current oral TPT regimens	LAI regimen efficacy and effectiveness are both better than those of current oral TPT regimens	Currently recommended oral TPT regimens have an efficacy of about 60-90%, compared to no treatment, under trial conditions. As a minimum, the efficacy of LAI regimens should not be lower than currently recommended oral TPT regimens. Ideally, it would be superior in the main target population(s). Under programmatic conditions, adherence to oral TPT and completion of treatment are problematic and TPT effectiveness is expected to be lower than in trials. LAIs bear the promise of overcoming the commonplace interruption of oral medication and therefore they are expected to enhance effectiveness.
Safety and safety monitoring	The incidence and severity of adverse events should be no worse than those with the	The incidence and severity of adverse events should be lower than with the	The LAI formulations should not present any additional safety requirements over and above the standard injection safety requirements related to preparation, storage and administration technique. For both the minimal

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
	recommended oral TPT regimens. No more than two monitoring sessions with a health worker for drug toxicity and no laboratory monitoring needed, except in certain populations (e.g. people with pre-existing liver disease, renal disease or diabetes).	recommended oral TPT regimens. No clinical or laboratory monitoring for drug toxicity needed, except in certain populations (e.g. people with pre-existing liver disease, renal disease or diabetes).	and optimal scenarios, the target product should not require any additional medication to allay toxicity (e.g. pyridoxine). Hepatotoxicity and clinical hepatitis are serious adverse events associated with the drugs that are currently recommended for TPT, either alone or in combination. Neuropathy is a frequent adverse event with isoniazid.[1] Hypersensitivity may occur to any new or old medication. If LAI dose is incomplete the manufacturer should provide guidance on how to complete TPT with the standard of care medication. If the LAI medicine is available in oral form this may simplify continuation. Record data for any discontinuation of LAI
Drug-related tolerability	Drug-related tolerability should be comparable to oral TPT regimens. The frequency of adverse events requiring cessation after the first LAI dose should be no worse than definitive interruption of current oral TPT regimens.	Drug-related tolerability should be better than with oral TPT regimens.	Tolerability is of paramount importance. As TPT is given to individuals who are usually symptom-free, healthy and do not consider themselves to be ill, any discomfort or adverse event should be avoided.
Injection-related tolerability	The injection should only cause mild pain, redness, itching, swelling or mild induration, and discomfort should resolve after five days.	The injection should only cause mild pain, redness, itching, swelling or mild induration, and discomfort should resolve after one day..	Injection reactions should not be exacerbated with subsequent injections A person given an injection is likely to endure more discomfort than when receiving an oral dose of medication, but this needs to be balanced with the inconvenience of taking oral medication for one month or more.

[1] *WHO operational handbook on tuberculosis. Module 1: Prevention - tuberculosis preventive treatment, second edition*. Geneva, World Health Organization, 2024 (https://iris.who.int/handle/10665/378535).

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Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
DDIs	The LAI (or regimen) should have no greater amount of DDI with often co-administered drugs than the SOC treatment or a predictable DDIs of a magnitude that can be compensated.	Ability to use with other medications while maintaining safety and efficacy, without adjustment of dose or frequency and no active laboratory monitoring.	The novel drugs in the regimen should have minimal or no DDI with other drugs that are often co-administered, such as: • ART regimen(s) • drugs that are a substrate for and induce or inhibit P450 liver enzymes • proarrhythmic drugs that prolong the QT/QTc interval • oral contraceptives • antidiabetic drugs • opioid substitution • hepatitis C 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.
Propensity to develop resistance to TB medicines	Potential for the acquisition or amplification of resistance during or after LAI treatment to one or more drugs in the regimen is *comparable to or lower than* with oral TPT.	Potential for the acquisition or amplification of resistance during or after LAI treatment to one or more drugs in the regimen is *comparable to or lower than* with oral TPT. Fewer than two gene targets linked to the development of resistance. No cross-resistance with	There is no evidence so far that the use of isoniazid or rifamycins for TPT in the absence of TB disease is associated with the generation of resistance to TB drugs in a community.[1,2] However, it is possible that TPT may be inadvertently given to someone with undiagnosed TB disease. Ideally, the drug(s) used in TPT should protect each other against the emergence of resistance even in such situations. Mindful of the technical difficulties in expressing the potential for the acquisition or amplification of resistance during or after LAI treatment, some measurable markers that are known to correlate with in vitro mutations are proposed.

[1] Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerg Infect Dis. 2006;12(5):744–51.
[2] den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2016;20(8):1065–71

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
		existing drugs for single-agent LAIs	While this characteristic is primarily focused on the risk of generating drug-resistant *M. tuberculosis* strains, attention should also be given to the risk of creating resistance to other bacterial flora in the body with the use of broad-spectrum antimicrobial agents used in TB care.
Stability or shelf life	No cold-chain required. All LAI component drugs are stable for ≥2 year in climate zone 3 and 4 and freezing conditions.	No cold-chain required. All LAI component drugs are stable for ≥3 years year in climate zone 3 and 4 and freezing conditions.	Any drugs for oral lead-in should be stable to heat, humidity and light, with a shelf life ≥ 5 years under ideal conditions Consider if stable in light blocking containers and/or not sensitive to light

ART: antiretroviral therapy; CNS: central nervous system; DDI: drug–drug interaction; DOT: directly observed therapy; DS-TB: drug-susceptible TB; DTG: dolutegravir; EMA: European Medicines Agency; FDA: US Food and Drug Administration; FDC: fixed dose combination; HIV: human immunodeficiency virus; LAI: long-acting injectable; 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; TPT: TB preventive treatment; 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.

5 LAIs for the treatment of TB disease

This section outlines the minimal and optimal characteristics of an LAI-based regimen for the treatment of active TB as well as trade-offs between these characteristics.

TRPs for LAIs for the treatment of TB disease

Table 5. Requirements for regimen characteristics for LAIs for the treatment of TB disease

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Target populations	Adults and adolescents with pulmonary TB disease, including people living with HIV and people with other comorbidities, such as diabetes.	All groups, irrespective of severity and site of disease (including pulmonary and extrapulmonary disease), across the full age spectrum, including pregnant or breastfeeding women, people living with HIV and people with other comorbidities, such as diabetes.	Non-severe forms of extrapulmonary TB (EPTB), such as mild lymph node TB, pleural effusion, or peripheral joint TB, are typically managed identically to pulmonary TB because drug penetration to the site of disease is generally adequate and standard regimens are effective. Conversely, severe forms of EPTB, such as TB meningitis, pericarditis, or spinal disease, may require special approaches or regimen modifications. If clinical data are not available on dosing and safety in children, pregnant, and breastfeeding women, plans for generating evidence should be in place. However, efficacy trials in these populations are not necessarily required, as efficacy can often be extrapolated from other populations. **Children**: PK and safety studies will be needed in infants, children and adolescents for optimal requirements. TB regimen developers should consider initiating paediatric studies as soon as early studies of the drug show promising efficacy and safety, allowing the development of suitable paediatric formulations to enable dosing in trials involving young children.[1] The FDA generally requires submission of an initial paediatric study plan no later than 60 days after the end-of-Phase-2 meeting or

[1] Nachman S, Ahmed A, Amanullah F, Becerra MC, Botgros R, Brigden G et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. Lancet Infect Dis. 2015;15:711–20. doi: https://doi.org/10.1016/S1473–3099(15)00007–9

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			another date agreed upon between FDA and the sponsor[1]. These requirements are waived for the orphan drug designations and the drugs for treatment of TB disease usually qualify for the orphan drug designation since TB is a rare disease in the United States of America. The EMA requires plans for paediatric studies to be provided at the latest by the conclusion of Phase 2 studies. **Pregnant and breastfeeding women**: In pregnant women, the benefits of treatment usually outweigh the harms. 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 foetus. Formulations should be safe for pregnant women and women of reproductive age[2,3,4, 5]. Studies in pregnant and breastfeeding women should be initiated early, as phase 1 and early phase 2 trial data are collected to support the inclusion of pregnant and lactating women in pre-licensure trials, including non-clinical developmental, DART, and reproductive toxicology studies during phase 2b trials of promising LAI candidates. Clinical development plans should include pregnant and breastfeeding women. Pregnant and breastfeeding women share lived experiences, but there is little justification for the exclusion of breastfeeding women in research studies. The inclusion of breastfeeding women should start from the assumption of inclusion. In contrast, the

[1] Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Pediatric study plans: content of and process for submitting initial pediatric study plans and amended initial pediatric study plans: guidance for industry. US Department of Health and Human Services, Food and Drug Administration; 2020 (https://www.fda.gov/media/86340/download).

[2] Miele K, Bamrah Morris S, Tepper NK. Tuberculosis in pregnancy. Obstet Gynecol. 2020;135:1444–53. doi: https://doi.org/10.1097/AOG.0000000000003890.

[3] Gupta A, Hughes MD, Garcia-Prats AJ, McIntire K, Hesseling AC. Inclusion of key populations in clinical trials of new antituberculosis treatments: Current barriers and recommendations for pregnant and lactating women, children, and HIV-infected persons. PLoS Med. 2019;16:e1002882. doi: https://doi.org/10.1371/journal.pmed.1002882.

[4] Task Force on Research Specific to Pregnant Women and Lactating Women [website]. Bethesda, MA: US Department of Health and Human Services, National Institutes of Health; 2023 (https://www.nichd.nih.gov/about/advisory/PRGLAC)

[5] Amita Gupta et al., Toward Earlier Inclusion of Pregnant and Postpartum Women in Tuberculosis Drug Trials: Consensus Statements From an International Expert Panel, *Clinical Infectious Diseases*, Volume 62, Issue 6, 15 March 2016, Pages 761–769, https://doi.org/10.1093/cid/civ991

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			exclusion of pregnant women might be supported by evidence-based rationale from developmental and reproductive toxicity studies.[1]
Indication and need for testing	The regimen is indicated for patients with TB disease caused by RS *M. tuberculosis* strains.	The regimen is indicated for patients with TB disease caused by RS and RR *M. tuberculosis* strains.	**Minimal:** RS-TB as this could in principle be used for ~95% of patients globally (based on their resistance pattern) within the context of recommended drug susceptibility testing for rifampicin at the time of TB diagnosis, using WHO-recommended rapid molecular tests if the regimen includes LAIs from the rifamycin family. **Optimal:** A regimen meeting the optimal requirements could be used for virtually all patients. It could be started empirically so that treatment could begin without delay while DST to component drugs is sought. While the minimal requirement targets RS-TB for maximum global impact, initial LAI regimens may be first indicated for RR-TB. This is due to the prioritization of investigative drugs as LAIs and regulatory pathways that accelerate approvals for high-unmet-need conditions like drug-resistant tuberculosis. By utilizing novel drug classes outside the rifamycin family, LAI regimens can achieve universal applicability. Their efficacy will be independent of circulating rifampicin-resistance patterns, allowing for empirical start and reducing the diagnostic burden at the point of care.
Number of encounters for LAIs administration	Three	One	Results from surveys and FGDs highlighted the importance of limiting the number of visits to a health care centres for dosing encounters as an important priority for people receiving preventive or curative treatment for TB.
Duration of coverage	>= (2 months)	>=4 months	This is a pharmacokinetic (PK) metric. The duration of stable, clinically effective drug concentrations in serum or at the site of the disease that a single LAI injection maintains at or above the minimal inhibitory concentration (MIC) required for clinical efficacy is an important determinant of dosing frequency, treatment duration and overall PK coverage duration. Given current technologies and the properties of

[1] Optimal and early inclusion of pregnant and lactating women in tuberculosis research: consensus statement. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			candidate drugs, a single drug's duration of coverage of two or more months appears feasible. The survey and FGD outcomes also indicate a desire for 2 months of coverage from both healthcare providers and the affected community. For large-scale implementation, the number of health facility visits should be kept to a minimum. The differing durations of coverage across LAIs may complicate visit scheduling and increase the number of visits. To mitigate the complexity caused by varying coverage durations, product development should prioritize harmonized release profiles. In the absence of perfectly matched durations, clinical implementation should favour a 'synchronized encounter' model based on the shortest-acting component (e.g., a 2-monthly cycle) to ensure predictable patient follow-up and prevent the decoupling of the combination therapy, which could lead to monotherapy and subsequent resistance. The challenge of mismatched dosing is already visible in the HIV landscape, which serves as a cautionary example for TB regimen design. The experience with HIV LAIs (e.g., the 2-month cycle of cabotegravir vs. the 6-month cycle of lenacapavir) highlights the risk of dosing friction. If these two agents were required as a combination therapy (as is mandatory for TB), the patient would be forced into a "lowest common denominator" schedule. They would have to visit the clinic every 8 weeks to receive cabotegravir, essentially wasting the 6-month convenience of lenacapavir. For TB treatment, where combination therapy is a standard of care, any mismatch in duration of coverage between component drugs doesn't just increase visit frequency—it creates a dangerous window for functional monotherapy. Therefore, optimal regimens must prioritize agents that can be harmonized into a single, synchronized dosing encounter (e.g., all components administered every 4 months).
Treatment duration	<=4 months	One instance	This is a clinical metric. It refers to the total time elapsed from the first dosing encounter (including any oral lead-in) to the completion of the therapeutic course. It defines the patient's "time on treatment."

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			Targets are based on the assumption that 4-6 months of effective PK treatment coverage would be required to achieve sufficient efficacy of a regimen. If a regimen requires a period of oral lead-in, this period is counted as part of the target for treatment duration. When the treatment duration is achieved via multiple encounters, the final injection provides a 'therapeutic tail' of coverage that extends beyond the final healthcare interaction. This ensures that the patient remains protected by effective drug concentrations while transitioning into the post-treatment follow-up phase. The **minimal target** could be achieved in a variety of ways, e.g. 1 month could be achieved with a 1-month oral lead-in, followed by a single dosing instance with LAIs; 2 months could be achieved e.g. with 2 dosing encounters with LAIs with 2 months duration of coverage (3 months if additionally including a 1-month oral lead-in period). 4 months could be achieved e.g. with 3 dosing encounters with LAIs (months 0, 2 and 4) with 2 months duration of coverage. In this scenario, while the patient's clinical interaction ends at 4 months, the total effective PK coverage extends to 6 months. The **optimal target** is set to 1 instance (with several LAIs). This would require that no oral lead-in is needed and a combination of LAIs with sufficiently long duration of coverage and sufficiently high potency of the regimen, such that a period of effective PK coverage would be adequate to achieve sufficient efficacy.
Dosing interval flexibility	Dosing interval +/- 2 week from the scheduled dose	Dosing interval +/- 4 weeks from the scheduled dose	The product should maintain therapeutic drug concentrations over an extended period following a single injection, with a pharmacokinetic profile characterized by a potential gradual rise to peak concentration and a prolonged decline ("PK tail"). This slow-release profile of LAIs should enable a dosing interval flexibility of ±2 to 4 weeks around the target re-dosing point without compromising efficacy or safety. The formulation should provide sufficient dosing interval flexibility — a period during which suboptimal dosing (either delayed or early) does

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			not lead to significant drops below the minimum effective concentration or increase the risk of drug resistance or dose overlap, thereby increasing the risk of toxicity. This flexibility is critical to accommodate programmatic realities (variability in patient follow-up and health system capacity) and enhance patient adherence, particularly in settings with limited healthcare access. Dosing flexibility shifts the burden of "perfect timing" away from the patient and the provider. It allows the program to accommodate flexible dosing encounter schedules with multidrug regimens without jeopardizing the patient's cure.
Number of component drugs	3-4 drugs throughout the regimen (possibly a decrease in the number of component drugs in the maintenance phase of treatment).		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 [REF 2023 TRPs]. Conversely, it is desirable to limit the number of component drugs in a LAI regimen to minimize the number of injections and safety risks, and to facilitate coformulation if possible. Current regimens recommended for DS-TB (HRZE or HPMZ) and MDR/RR-TB (BPaLM or BPaLC) are effective four-drug regimens, and that the BPaLM regimen without moxifloxacin is an effective three-drug regimen (BPaL) for pre-XDR-TB in non-severe cases. 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. While three to four drugs may be required during the intensive phase of treatment, two drugs may be sufficient during the maintenance phase to achieve adequate efficacy, as evident from 2HRZE/4HR regimen.
Formulation & number of injections per	3-4 separate injections (one with each of 3-4 drugs)	1-2 injections (with each injection containing two or more co-formulated drugs)	Coformulation of drugs in a single vial may, in the future, reduce the number of injections needed to complete a regimen. For the immediate future, we expect that one component drug would require

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
patient encounter			one injection when a LAI dose is administered. Where multiple LAIs are used within a treatment regimen, staggered or harmonized dosing schedules may be needed to simplify programmatic implementation. Ideally, there should be no or minimal adjustment to food and no need for co-medication for both the LAI and oral lead-in components. If an oral lead-in is required, the oral medication would usefully be co-packaged with the LAI. Oral drugs should be available in paediatric forms (dispersible, scored tablets, palatable) and also fixed-dose combinations. Co-packaging refers to the combined availability of all-drugs needed for a regimen in the same package whereas coformulation of LAI would mean that several drugs are included in one vial or prefilled syringe.
Combination with oral TB medications	If required, an oral lead-in will be given for no longer than **one month**;	No oral lead-in	While fully LAI-based regimens offer the most transformative potential, hybrid models represent an essential transitional step. They enable the immediate use of LAI technology as it matures, providing clinicians with a 'modular' approach to TB care that can be tailored to the patient's resistance profile and the health system's capacity. These hybrid models may depend on the LAI availability and their PK profile and clinical objective: Safety and PK stabilization (same medicines but different formulations) when the oral version of the LAI drug is used as a temporary bridge with the purpose of a safety lead-in that allows for immediate discontinuation if systemic reaction or acute toxicity occurs or addresses the lag time of some LAI chemistries that take time to reach steady-state therapeutic levels. Regimen optimization and pill-burden reduction when high potency of existing medicines is combined with the convenience of LAIs (e.g., if only 2 drugs of the 4-component regimen are available in LAI form). Once the bacillary burden is lowered and the patient feels better (the point where adherence traditionally drops), the regimen switches to

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			100% LAI. Hybrid regimens can reduce the complexity of treatment by converting a 10-pill-a-day regimen into a 2-pill-a-day regimen plus LAI. For some drugs with poor bioavailability or high GI toxicity the LAI route can be a viable way to achieve effective PK levels.
Route of administration & injection volume	Intramuscular or subcutaneous; Upper-thigh, arm, abdomen, or gluteal Maximum injection volume: SC: <=2ml for adults (adjusted for kids) IM: <=5ml	Subcutaneous; Upper-thigh; arm, or abdomen Maximum injection volume: SC: <=1ml for adults (adjusted for kids) IM: <=3ml	The choice between subcutaneous (SC) and intramuscular (IM) administration is often dictated by the drug's formulation (e.g., oil-based vs. aqueous) and the desired release profile. IM typically allows for faster onset and slightly larger volumes, but requires deeper penetration and specific anatomical sites (gluteal or deltoid, etc). SC is often preferred by patients and can potentially be used for self-administration in the future. However, SC tissue has a lower capacity for large volumes and may be prone to local injection site reactions. High volumes are often cited by healthcare providers as a barrier to implementation due to the increased time required for administration and the increased risk of pain and discomfort. In some settings there may be cultural sensitivities in relation to gluteal as the site of injection. On the other hand TB is frequently a disease of poverty and malnutrition and large muscle groups may be preferable. This creates a specific physiological challenge for LAI administration since the malnourished patients often have significant muscle wasting and minimal subcutaneous fat. This reduces the "reservoir" capacity for LAI deposits.
Setting of treatment administration & training requirements	Injections administered by local HCW with Minimal additional training	Injections administered by local HCW without additional training or even self-administered with minimal training	The desirable TB treatment setting is community- or primary care-based, enabling patient-centred, decentralized care, supported by appropriate training of healthcare providers and community workers to ensure safe, effective, and equitable treatment delivery. For treatment of drug-resistant TB or severely ill or complex cases, specialized outpatient or inpatient services are warranted.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Efficacy & effectiveness	The LAI regimen efficacy is *as good as* the comparator (SOC) regimens	The LAI regimen efficacy and effectiveness are *both better* than the comparator (SOC) regimens	The current standard regimens for the treatment of RS-TB and most types of RR-TB have an efficacy of about 90% under trial conditions. The effectiveness of recommended all-oral regimens is decreased under programmatic conditions for a variety of reasons, some notable being adherence challenges and care discontinuation. Since such challenges are expected to be reduced with the use of LAIs, the "efficacy-effectiveness-gap" is also expected to be reduced for LAI-based regimens. Thus, under the optimal requirements, the expectation would be *better effectiveness* than current comparator regimens.
Safety and safety monitoring	The incidence and severity of adverse events should be *equal to or lower than* those with the comparator (SOC) regimens. No more than monthly clinical and laboratory monitoring for drug toxicity is 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 comparator (SOC) regimens. 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[1]. 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[2], the Study 31 (2HPMZ/2HPM)[3], and the PaMZ Phase 2B trial[4]. Among participants receiving the 4-month isoniazid, rifapentine, moxifloxacin and pyrazinamide regimen in Study 31, 19% experienced Grade 3 or higher adverse events[3]. The LAI formulations should not present any additional safety requirements over and above the standard injection safety requirements related to preparation, storage and administration technique.

[1] Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf. 2006;5:231–49. doi: https://doi.org/10.1517/14740338.5.2.231.

[2] Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med. 2014;371:1577–87. doi: https://doi.org/10.1056/NEJMoa1407426

[3] Dorman SE, Nahid P, Kurbatova EV, Phillips PPJ, Bryant K, Dooley KE et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. N Engl J Med. 2021;384:1705–18. doi: https://doi.org/10.1056/NEJMoa2033400

[4] Dawson R, Diacon AH, Everitt D, van Niekerk C, Donald PR, Burger DA et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. Lancet. 2015;385:1738–47. doi: https://doi.org/10.1016/S0140–6736(14)62002-X

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Drug-related tolerability	*Tolerability* should be *comparable to that of* the SOC.	*Tolerability* should be *better than that of* the SOC.	The survey findings reveal that while systemic drug-related tolerability is a concern, it does not significantly deter stakeholder interest in long-acting injectables (LAIs). A high majority of participants, including those with prior experience of systemic side effects during TB treatment, maintained a positive outlook on transitioning to LAIs. This suggests that the benefits of reduced pill burden and enhanced adherence are often perceived to outweigh the risks of drug-related adverse events. However, the "non-reversible" nature of systemic effects remains a pivotal factor. The survey data indicates that interest in LAIs is sensitive to the duration of side effects; stakeholders expressed a specific concern regarding scenarios where systemic adverse events might take longer to resolve than with oral medications.
Injection-related tolerability	The injection should only cause mild pain, redness, itching, swelling or mild induration, and discomfort should resolve after five days.	The injection should only cause mild pain, redness, itching, swelling or mild induration, and discomfort should resolve after one day.	While the minimal target allows for a five-day resolution period, the optimal target seeks resolution within a single day. However, feedback from surveys and focus group discussions suggests that the duration of mild symptoms is less critical than the severity of the pain itself. Stakeholders indicate a greater "appetite" for mild, lingering symptoms (extending 2–3 days) if it means avoiding severe injection-site reactions that could interfere with daily functioning. Ultimately, the tolerability of Long-Acting Injectables (LAIs) is evaluated by its impact on a patient's quality of life compared to the management of oral drug adverse events. For many, the brief localized discomfort of an injection is preferable to the systemic side effects or the complex scheduling often required to minimize symptoms associated with daily oral regimens. Therefore, the goal is to ensure that injection-site reactions remain localized and transient, providing a net benefit in terms of both adherence and daily lived experience.
DDI	The LAI (or regimen) should have no greater amount of DDI with often co-administered drugs than the SOC treatment or a	Ability to use with other medications while maintaining safety and efficacy, without adjustment of dose or	The prolonged systemic presence and non-retrievable nature of LAIs mean that DDIs are not temporary—they are "locked in" for the duration of the PK profile. Therefore, the regimen must allow for the safe introduction of or transition to other medications without the risk of metabolic interference or cumulative toxicity.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
	predictable DDIs of a magnitude that can be compensated. If predictable adjustments need to be made to the drugs for the other (non-TB) condition, this may be acceptable.	frequency and no active laboratory monitoring.	The novel drugs in the regimen should have minimal or no DDI with other drugs that are often co-administered with TB treatment (e.g. ART or HIV prevention, either with LAI or oral drugs). HIV medicines may include drugs that are substrates of P450 or other metabolizing enzymes (e.g. dolutegravir, cabotegravir, 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 LAI for TB treatment or they must be compatible with current oral ART (e.g., dolutegravir) and LAI-HIV PrEP/Treatment (e.g., cabotegravir, lenacapavir). Given 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 the safety of concomitant use. Regulatory guidance on QT/QTc prolongation by non-antiarrhythmic drugs is available[1]. Potential toxic effects of accompanying drugs should also be investigated.
Propensity to develop resistance to TB medicines	Potential for the acquisition or amplification of resistance during or after TB treatment to one or more drugs in the regimen is *comparable to* the SOC.	Potential for the acquisition or amplification of resistance during or after TB treatment to one or more drugs in the regimen is *lower than* with the SOC.	Drug resistance observed during TB treatment 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 for 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 treatment support, 2.1% acquired resistance during or after treatment

[1] Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs. US Department of Health and Human Services, Food and Drug Administration; 2012 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinicalevaluation-qtqtc-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-0)

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			to one or more drugs in the regimen[1], whereas another study found no acquisition of drug resistance (0/768)[2] (4).
Stability or shelf life	No cold-chain required. All LAI component drugs are stable for ≥2 years in climate zone 3 and 4 and freezing conditions.	No cold-chain required. All LAI component drugs are stable for ≥3 years in climate zone 3 and 4 and freezing conditions.	Any drugs for oral lead-in should be stable to heat, humidity and light, with a shelf life ≥ 5 years Consider if stable in light blocking containers and/or not sensitive to light

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; LAI: long-acting injectable; 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

[1] Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney GB et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med. 1994;330:1179–84. doi: https://doi.org/10.1056/NEJM199404283301702

[2] Dorman SE, Nahid P, Kurbatova EV, Phillips PPJ, Bryant K, Dooley KE et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. N Engl J Med. 2021;384:1705–18. doi: https://doi.org/10.1056/NEJMoa2033400

6 Trade-offs between characteristics

We acknowledge that during the development of LAI-based regimens, difficult decisions may need to be made as optimizing one characteristic is often at odds with optimizing another.

The TRPs detailed in this document describe requirements for various characteristics of LAI-based regimens for TB treatment and prevention, 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. Regimen developers may therefore have to decide to prioritize one characteristic over another.

Injection volume vs number of dosing instances

A central trade-off in development of the LAI formulation concerns the relationship between injection volume and the number of dosing instances required to achieve adequate therapeutic coverage.

A **single, high-payload injection** can provide extended duration of coverage and reduce the total number of encounters. However, achieving prolonged exposure typically requires either higher drug concentration, larger injection volume, or both. Increasing injection volume is associated with worsened injection-site tolerability. Mechanical distension of muscle or subcutaneous tissue may lead to intense pain, persistent pressure sensation, swelling, and general discomfort. Larger volumes also increase the risk of localized tissue reactions, including sterile abscesses, granulomas, and palpable nodules that may persist for weeks. In addition, higher total drug payloads amplify the inherent irreversibility of LAIs: unlike oral therapy, the injected drug cannot be withdrawn if systemic toxicity occurs, potentially prolonging adverse effects.

An alternative strategy is to use **several smaller injections** or lower-volume administrations. Distributing the total payload reduces mechanical strain at each injection site and may decrease the incidence and severity of local adverse events. Smaller depots can also support a more gradual pharmacokinetic profile, potentially improving tolerability. However, this approach increases the number of injections per encounter or the total number of encounters, thereby diminishing some of the core programmatic and adherence advantages of LAIs. Minimizing encounters has been noted as a highly desirable feature of LAI-based regimens in surveys of potential recipients of LAIs.

The acceptable balance depends on predefined minimal requirements for injection volume and tolerability. While fewer dosing instances are desirable for adherence and operational simplicity, the injection volume must not exceed thresholds that result in intolerable pain or unacceptable local reactions.

Injection volume is influenced by multiple factors, including the active compound, required dose, formulation chemistry, and release characteristics. Importantly, the maximum feasible injection volume is route-dependent. Subcutaneous administration generally accommodates smaller volumes than intramuscular administration. Therefore, a strategic preference for subcutaneous delivery—for example,

to enable decentralization or potential self-administration—may necessitate adjustments in drug concentration, total dose per injection, or dosing frequency.

Combination with oral TB medications vs. exclusively LAI regimen

Another key strategic decision in LAI regimen design is whether to implement an oral lead-in phase or pursue an exclusively injectable regimen from the outset.

An exclusively LAI-based approach maximizes simplicity. It minimizes ongoing pill burden, reduces daily adherence demands, and limits repeated interaction with the health system. From a patient perspective, receiving an injection and returning to normal activities without continued daily dosing is attractive and may reduce stigma and treatment fatigue.

However, an oral lead-in may provide an important safety advantage. Because oral therapy can be discontinued immediately, it allows early action when drug-related hypersensitivity, intolerance, or systemic adverse effects occur. In contrast, once a long-acting injection formulation is administered, it cannot be removed. This reversibility is particularly relevant for compounds with known toxicity risks or limited post-marketing safety data.

An oral lead-in may also serve a strategic role in regimen structuring. In regimens requiring prolonged total coverage, an initial oral phase could reduce the number of required LAI injections, potentially enabling a single LAI encounter. This may improve acceptability and reduce the risk of treatment interruption if patients do not return for subsequent injections—particularly once they become asymptomatic but may still harbour viable bacilli and remain at risk of relapse or resistance development.

Alternatively, an LAI–oral hybrid model (concurrent or phased use of LAIs and oral drugs) partially compromises the conceptual simplicity of a fully injectable regimen. Nonetheless, it offers practical advantages. It can substantially reduce total pill burden while ensuring inclusion of a sufficient number of effective drugs in multidrug regimens, especially where not enough agents are yet available in LAI formulation. Additionally, hybrid approaches may facilitate gradual implementation, allowing patients and healthcare providers to gain familiarity with LAIs and mitigating apprehension associated with exclusive reliance on long-acting injectables.

Efficacy vs tolerability in TB preventive treatment (TPT)

In TPT, the acceptable balance between efficacy and tolerability differs fundamentally from that in TB disease. Because TPT is typically offered to individuals who feel well and do not perceive themselves as ill, tolerance for toxicity, injection-related pain, or procedural inconvenience is inherently low.

LAI regimens for TPT must, at a minimum, demonstrate efficacy comparable to current standard-of-care oral regimens. However, pursuing marginal gains in efficacy at the expense of increased systemic toxicity, larger injection volumes, greater pain, or reduced convenience may not be acceptable from a

patient or programmatic perspective. In this context, incremental improvements in protective efficacy may not justify a deterioration in safety profile or user experience.

Accordingly, for TPT, tolerability, injection-related comfort, and simplicity are not secondary attributes but central determinants of overall value. Optimizing efficacy beyond established standards must not compromise the safety, acceptability, and risk–benefit balance required for TPT in otherwise healthy populations.

Number of drugs in continuation phase

In treatment regimens that include an intensive and continuation phase, the total number of drugs maintained during the continuation phase presents a strategic trade-off. Reducing the number of component drugs may simplify administration, decrease cumulative toxicity, and lower injection burden. However, maintaining multiple active agents throughout treatment strengthens protection against resistance amplification and may improve robustness of cure, particularly in patients with high bacillary burden or cavitary disease. Decisions regarding drug number in the continuation phase must therefore balance regimen simplicity and tolerability against microbiological security and resistance prevention.

Formulation chemistry and reversibility

The choice of LAI formulation platform introduces additional trade-offs related to reversibility. Certain technologies—such as removable implants or in situ forming systems—may permit physical removal of the drug depot in cases of severe adverse events or intolerance. This offers an important safety advantage, particularly for compounds with uncertain long-term tolerability.

In contrast, conventional intramuscular depot injections cannot be removed once administered. Drug release continues for the full intended coverage period, limiting options for mitigating systemic toxicity. While intramuscular formulations may be operationally simpler or more scalable, they inherently sacrifice reversibility. Selection of formulation chemistry must therefore consider the balance between implementation feasibility, safety assurance, and risk management.

7 Cross-cutting aspects

While the TPPs indicate the attributes to be considered at the *developmental* stage, these should not be dissociated from the factors to be considered at the *implementation* stage in the framework of overall TB-oriented activities. The TRPs detailed in this document present a series of characteristics considered essential for LAI-based 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. This section discusses each of these aspects.

Efficacy, effectiveness, and trial design considerations for TB regimens

The central value proposition of LAIs is biological forgiveness. By shifting the burden of adherence from the patient (daily pill-taking) to the drug delivery system, LAIs eliminate the risk of adherence-related failures, where missed daily doses lead to sub-therapeutic drug levels and resistance. However, missing an LAI dose is more consequential given that it covers for a longer period of time. This tension is most acute in active TB treatment, where resistance is a direct threat, but remains critical in TPT unless a "one-shot" regimen goal is achieved.

In clinical trial designs for LAIs, the forgiveness-versus-retention issue necessitates a shift toward pragmatic and implementation-focused trial protocols. For TB treatment trials, the consequences of missing an LAI dose during the period where drug levels slowly decline requires makes it more important to track patients carefully to prevent the emergence of drug resistance.

For prevention trials, where participants are healthy and the harm of dropping out is less immediate, the design must incorporate acceptability and preference endpoints. Researchers must determine if the physical burden of an injection outweighs the convenience of fewer visits.

In both contexts, the trial design must transition from measuring pure biological efficacy to measuring real-world effectiveness, specifically accounting for whether the health system can maintain adherence without the intensive, artificial incentives typically found in a clinical study environment.

Trial designs should allow for switches to oral regimens if for any reason a patient cannot continue an LAI-based regimen.

One question is whether existing phase 3 evidence from oral drugs that are already licensed for the same indication as an LAI could supplant large-scale clinical trials for the same medication formulated as an LAI on the basis of PK studies showing bioequivalence. This can fast-track the clinical use of LAI counterparts of oral medicines. This faster route may be justified on public health grounds (e.g., the slow scale-up of global recommendations on TPT). Drug regulators are increasingly open to this idea so long as

- The LAI formulation is pharmaceutically and pharmacokinetically comparable to the oral one
- Safety is adequately characterized for the new route
- No new risks (local toxicity, excipient issues, immunogenicity) are introduced

The regulators may require a phase 1 safety + PK study, possibly a phase 2 dose-finding or safety study to explore the performance of the LAI, although efficacy data may not be required, unless PK is substantially different. Such experience, if successful, can provide a pathway for other anti-TB medicines that are being tested in trials in oral form and subsequently become available in LAI formulation.

Overall treatment burden

LAIs should strive to reduce the negative experience of treatment. The evaluation of trials of LAIs for TPT should not focus solely on severe AEs or laboratory findings, neglecting other elements of treatment burden that matter to patients, such as quality of life, tolerability, and mild-to-moderate AEs that may affect adherence to and acceptability of TPT. For this purpose, there is a need to solicit patient, community and stakeholder input to include patient-reported outcomes (PRO) alongside other outcomes, to ensure relevance and improve treatment uptake. A suitable metric to capture the different dimensions of treatment burden in both regimens that include LAIs and those without needs to be derived. Studies that are focused on real-world and the implementation context would be more suitable to capture these aspects of care (ref to GEG for TPT).[1]

Scalability, equitable access and transparent pricing

The price and the associated resources required to use an LAI-containing regimen should be set against considerations of equity, non-discrimination and transparency, with the goal of affordable access for all, ensuring that vulnerable and marginalized groups do not bear disproportionate costs. 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. Scalability needs to be built into the development of LAIs from the very start, as the intervention needs to work on a large scale with good geographical access in order for it to make a difference to global TB prevention and care.

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[2].. Quality of medicines can be assured through WHO prequalification or similar assessment by the WHO Listed Authority (WLA)[3]. 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.

[1] Guidance on evidence generation on new regimens for tuberculosis preventive treatment. Geneva: World Health Organization; 2025 https://iris.who.int/server/api/core/bitstreams/123452b9-660e-4477-89b5-3b2a9ef434ba/content

[2] Guidelines Review Committee [website]. Geneva: World Health Organization; 2023 (https://www.who.int/groups/guidelines-review-committee).

[3] Evaluating and publicly designating regulatory authorities as WHO listed authorities. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240023444)

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[1] and WHA69.23[2]. 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.

In the case of TPT, the uptake of which still depends on programmatic efforts of demand creation, pricing should not present an additional barrier to scale-up. Lessons from recent experience with scaling up of the 3-month regimen of weekly isoniazid and rifapentine should be considered fully for further information[3].

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

[1] Follow up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (WHA66.22). Geneva: World Health Assembly; 2013 (https://apps.who.int/gb/ebwha/pdf_files/WHA66-REC1/WHA66_2013_REC1_complete.pdf).

[2] Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (WHA69.23). Geneva: World Health Assembly; 2016 (https://apps.who.int/gb/ebwha/pdf_files/WHA69-REC1/A69_2016_REC1-en.pdf#page=1)

[3] An Activist's Guide to Rifapentine for the Treatment of TB Infection. Treatment Action Group [Internet]. [cited 2024 Nov 22]. Available from: https://www.treatmentactiongroup.org/publication/an-activists-guide-to-rifapentine-for-the-treatment-of-tb-infection/

Cost considerations

Purpose and scope

This section draws on existing economic modelling studies to inform cost targets for long-acting injectable (LAI) TB regimens for treatment and prevention. The analysis includes WHO-commissioned models for previous target product profile exercises, research by key modelling groups known to WHO for TB economic evaluation, and recently published models examining regimen characteristics relevant to LAI development. Where LAI-specific models were available, these were included directly. Where such models were unavailable, relevant studies were reviewed to inform estimates of the potential economic value of LAI formulations.

TB preventive treatment

No studies have yet addressed the cost-effectiveness of LAI-based TB preventive treatment (TPT) regimens. We therefore reviewed existing cost-effectiveness models for oral TPT to gain insights into how LAI-based regimens may affect outcomes and cost. Nsengiyumva et al. (2022) conducted a cost-effectiveness analysis using bottom-up micro-costing in Brazil and South Africa, comparing the WHO TPT target product profiles to six-month isoniazid (6H, drug cost of $3.70). Cost-neutral drug cost thresholds, defined as the maximum drug prices that would result in no additional cost relative to the standard of care, were $26 in Brazil and $27 in South Africa for a 3-month regimen, and $53 in Brazil and $142 in South Africa for a 1-month regimen. Primary savings resulted from fewer follow-up visits and higher completion rates. Single-dose LAI-based TPT regimens would add additional value by eliminating adherence monitoring and ensuring completion, which was not reflected in these oral regimen models and thus, cost-neutral prices would be expected to be higher than these values. Ryckman et al. (2023) analysed the scale-up of TPT using 3HP (a 12-week regimen of weekly isoniazid and rifapentine) across 29 high-incidence countries. Contact investigation was a major cost driver, accounting for 39-70% of costs by age group, and would remain unchanged for LAI regimens. However, costs for visits, monitoring, and adverse events during TPT (estimated at $39 in Brazil and $32 in South Africa per person for 6H, reducing to $16 and $11, respectively, for a 1-month oral regimen) could be further reduced with LAI formulations that ensure completion through a single or fewer administrations.

Mafirakureva et al. (2023) studied paediatric TPT with integrated case-finding and contact management in nine sub-Saharan African countries, using real-world data from 146 sites. TPT completion rates varied widely, from 33% to 93% at baseline, and improved to 83% to 99% with the intervention. This variation in completion rates was a key factor in the differences in cost-effectiveness across settings. The finding that poor completion reduced cost-effectiveness underscores the main value of LAI formulations, which can guarantee treatment completion through fewer administrations.

Treatment of TB disease

Two modelling studies provide evidence for LAI treatment regimens. Ryckman et al. (2024) used a mathematical cohort model to assess the effects of a hypothetical oral pan-TB LAI regimen in India, the Philippines, and South Africa over a 10-year time horizon. The model also evaluated a single-dose LAI

version of such a regimen, aligning with optimal targets in the pan-TB TRP. The LAI-based regimen increased initial cure rates from 69-71% to 82%. Compared to the standard of care, pan-TB LAI reduced mortality by 58-63% and transmission by 33-39%. These improvements were driven mainly by the elimination of non-adherence and treatment discontinuation. The model identified cost-neutral price thresholds for pan-TB LAI, with HRZE for rifampicin-susceptible TB and BPaL[M] for rifampicin-resistant TB as comparators. From a health system perspective, thresholds for pan-TB LAI were $160 in India, $210 in the Philippines, and $310 in South Africa. From a societal perspective, including patient-borne costs, thresholds increased to $200, $290, and $390, respectively. These figures provide reasonable upper bounds for the cost-neutral pricing of an LAI-based regimen, assuming perfect adherence and single-dose administration.

Zheng et al. (2026) used a microsimulation model to examine LAI treatment of people living with HIV and drug-susceptible TB in South Africa. The model compared a two-month oral lead-in followed by a single LAI injection to a 6-month daily oral regimen, using both a 24-month and a lifetime time horizon. The LAI approach reduced treatment disengagement from 20.9% to 12.9% over 6 months, and TB mortality from 21.3% to 16.6% over 24 months and from 24.5% to 19.9% over a lifetime. With the LAI regimen priced at $199.8 versus $50.4 for the standard of care, the incremental cost-effectiveness ratio was $2,230 per year of life saved over 24 months and $520 per year of life saved over a lifetime, both below the opportunity cost-based threshold of $3,000 per year of life saved. At 24 months, the cost-effective price ceiling for the LAI regimen was $200. These results indicate that LAI treatment could be particularly valuable where treatment disengagement is high, although applicability to HIV-negative populations would require further research.

Key considerations

At their introduction, LAI-based regimens are expected to be costlier than equivalent oral treatments, given that they will employ a novel technology. However, some of these development costs are expected to be offset by savings from the smaller amount of active pharmaceutical ingredient needed to deliver the total dose as an LAI. From the programmatic perspective, LAIs are also expected to lower the costs to both the individual on treatment and the health services given that there will be fewer encounters needed to complete treatment or to follow up in case of interruption. Although evidence remains limited, current evidence suggests that LAI formulations can be cost-effective or cost-saving at prices above those of current oral regimens, with thresholds that depend on country income, health system costs, and baseline treatment completion rates. The economic case for LAI regimens is based on their potential to address two main cost drivers in TB care: suboptimal treatment completion and healthcare delivery costs associated with prolonged oral regimens that require multiple clinic visits for monitoring and adherence support. Additional benefits, such as fewer adverse events or eliminating the need for facility visits for injection, may further reduce costs. However, important evidence gaps remain. No LAI-specific TPT economic models currently exist, and LAI modelling is very limited and has not yet been explored for use in community screening contexts. Efforts are underway to address these gaps. Further research is needed on parameters where costs remain uncertain, including the price of LAI formulations, cold-chain and storage requirements, the number of encounters and injections needed, injection-delivery infrastructure, and training requirements.

In addition, future economic models could further explore key LAI characteristics such as duration of protection, dosing frequency, and oral lead-in requirements.

8 References

TBD

9 Annexes

Annex 1: List of 'Scientific TRP Development Group' (TDG) members

Role	Last name	First name	Institution
Member	Churchyard	Gavin	Aurum
Member	Davies	Gerry	Liverpool University
Member	Dooley	Kelly	VUMC
Member	Fox	Greg	U Sydney
Member	Hesseling	Anneke	SUN
Member	Kendall	Emily	Johns Hopkins
Member	Kityo	Cissy	Joint Clinical Research Centre in Uganda
Member	Nuermberger	Eric	Johns Hopkins University School of Medicine
Member	Owen	Andrew	University of Liverpool, CELT
Member	Salazar	Nicole	Johns Hopkins University School of Medicine
Member	Svensson	Elin	Uppsala University
Member	Ashesh	Ashna	Civil Society Taskforce
Member	McConnell	Erin	TAG
Member	Angami	Ketho	
Member	Faisal	Sobia	Deputy General Manager Technical & Training (TB), Greenstar Social Marketing (G) Pakistan
Member	Gler	Maria Tarcela (Maricel)	Makati Medical Center
Member	Lange	Christoph	Borstel Institute
Member	Meintjes	Graeme	University of Cape Town
Member	Campbell	Michael	CHAI
Member	Ndjeka	Norbert	NTP RSA
Member	**Urvashi**	Singh	NTP India
Member	Sekkade	Moorine	MOH Uganda
Member	Zhao	Yanlin	NTP China
Member	Cavaleri	Marco	EMA
Member	Semete	Boitumelo	SAPHRA
Member	Bizzini	Alain	SwissMedic
Member	Ningyi	Wei	National Institutes for Food and Drug Control (NIFDC)
Alternative member	Mattoo	Sanjay	NTP India
Technical resource person	Kim	Chaelin	LSHTM
Technical resource person	McQuaid	Finn	LSHTM

Observer	Brigden	Grania	Global Fund
Observer	Flood	Debra	BMGF
Observer	Lienhardt	Christian	IRD
Observer	Scott	Cherise	UNITAID
Observer	Perrin	Christophe	MSF
Observer	Holtzman	David	GMRI
Observer	Spiegelman	Mel	TB Alliance
Observer	Sun	Eugene	TB Alliance
Observer	Wells	Charles	GMRI
Observer	Waning	Brenda	GDF
Observer	Chauhan	Sandeep	WHO / RNTCP

Annex 2: Report on Community Perspectives on Long-Acting Injectables for Tuberculosis: Mixed Methods Analysis

Prepared by: Erin McConnell (TAG) with Nora West (Consultant) and Chaelin Kim (Consultant, LSHTM); reviewed by: Mike Frick (TAG)

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1. Background and rationale

Long-acting technologies (LATs), including long-acting injectable (LAI) treatments, represent a potential gamechanger for treating many diseases. LAIs for tuberculosis (TB) prevention and treatment (Ammerman et al., 2022; Kaushik et al., 2019; Kim et al., 2022; Vermeulen et al., 2025), could offer an alternative to current standard oral regimens that require daily dosing over weeks or months. However, despite the promise of LAIs, historical community experiences and concerns with injectables for TB which must be addressed in the context of new technologies to ensure maximal impact (Almeida et al., 2021). Community and stakeholder input on the ideal characteristics of any new intervention or technology, particularly LAIs to prevent and treat TB, is critical to their successful introduction (Chavez-Rimache et al., 2023). It is imperative to ensure that new treatment approaches meet the needs and mitigate concerns of patients, healthcare providers, and health systems.

The overall aim of this study was to gather community perspectives on the preferred characteristics of LAIs for TB and factors that may affect community acceptance and uptake such as health facility preferences, route of administration, side effects, drug interactions, and timing. In addition, the study collected community impressions and existing awareness of LAIs for TB treatment, including lingering negative associations related to injectable aminoglycoside agents that will need to be addressed during development of other injectables. This information is intended to inform an addendum to WHO target regimen profiles (TRPs) for treatment and prevention of TB focused on LAIs and help drug developers design LAIs that are acceptable to people affected by TB.

2. Study Design

The study utilized a mixed-methods approach to understand community perceptions around LAIs. In phase I, an online survey was developed to assess community perceptions and acceptance of long acting injectables for TB. In phase II, four regionally organized focus group discussions were conducted to probe survey findings and generate qualitative data to inform the development of the WHO TRPs for LAIs for TB, as well as to identify further areas for investigation in advance of LAI introduction.

Phase I: Community Survey

An online survey (administered via Google forms) was developed and disseminated to collect anonymous data on preferences for and acceptability of LAIs for TB prevention and treatment. Survey questions were written to align with and build off the WHO-led survey of TB service providers conducted in early 2025 (Table 1, Survey 1). The survey was designed and reviewed in English, then translated into French, Russian, and Spanish for dissemination. Survey recruitment was conducted via email and listservs to civil society and community partners and organizations affiliated with TAG, as well as their

community partners and networks. Recruitment was supplemented with purposive snowball sampling through regional networks and direct outreach to community representatives serving marginalized and hard to reach population groups. The online community survey was open for participation in June 2025 and resulted in 208 completed surveys from all WHO regions and 45 countries (Table 1, Survey 2).

Eligibility

a. Adults 18 and older
b. Individuals living in a high-TB burden country
c. Individuals living in high-TB burden communities

Sample Size

Up to 200 participants

Phase II: Focus Group Discussions (FGDs)

After analyzing survey data, focus group discussions were organized to further explore Phase I findings and better understand how LAI preferences were being considered among community respondents. Separate focus group discussions were held for participants in four WHO-defined regional groupings: African Region (AFRO), Region of the Americas (AMRO), Western Pacific and South-East Asia Regions (WPRO, SEARO), and European and Eastern Mediterranean Regions (EURO, EMRO). A FGD facilitation guide was developed to further explore preferences and concerns for LAIs identified from the Phase I survey. Participants were consented via Google Forms in advance.

Eligibility

a. Adults 18 and older
b. Individuals living in a high-TB burden country who previously participated in the Phase 1 survey
c. English language proficiency

Recruitment

Recruitment to join the survey was conducted via email, and only individuals demonstrating proficient English and who had indicated willingness in the survey (Phase I) to be contacted for a focus group were contacted. Targeted outreach was used for regions with limited potential participants (e.g., Eastern Europe and Central Asia, Region of the Americas).

Sample size

Up to 10 participants per focus group (n=up to 40 in total)

Limitations

The analysis of phases 1 and 2 faced inherent limitations:

- *Geographic Scope:* Despite disseminating the survey broadly and conducting purposive outreach within TB community networks to ensure global representation, some regions and contexts are underrepresented in the data (South America, Francophone Africa, Middle East and North Africa).
- *Language Barriers:* The survey was available in English, French, Russian, and Spanish, limiting responses to those proficient in these languages. The focus groups were conducted exclusively in English, limiting participation to those proficient in English from each region.
- *Selection Bias:* Our sampling strategy focused on community groups, networks, and individuals already engaged in existing regional or global TB networks. Both the survey and the focus groups were conducted electronically, accessible only to people with internet access. The focus group was conducted to accommodate Eastern Time (GMT – 5), which may have influenced who was available to participate.
- *Gender Bias:* Despite recruiting broadly from survey respondents to ensure equitable gender representation in focus groups, male participants were underrepresented in the FGDs. Across both the survey and the focus groups, gender minorities were not meaningfully represented.
- *Age Bias:* The survey and focus group eligibility began at 18 years of age, and younger populations that may benefit from LAIs were un-represented in survey findings.

3. Data Analysis

Survey

The analysis of survey data employed descriptive statistics and visual representations to examine preferences across stakeholder groups. Participant characteristics were summarized using descriptive statistics for each variable type. Categorical variables, including demographic characteristics (gender, age groups, education level, employment), were analyzed for frequencies and percentages with 95% confidence intervals. We stratified key demographic subgroups using pre-specified categories for stakeholder affiliation, geographical region, and previous experience with TB treatment and/or TB injections.

The results from the TAG-led community survey (Survey 2, Table 1) were combined, where possible, with responses from the related WHO-led survey targeting NTP managers, civil society members, and healthcare workers (Survey 1, Table 1). Both surveys queried trade-off and preference considerations, with Survey 2 building upon the questions in Survey 1 to gain a deeper understanding of community perceptions around LAIs. For all questions where the answer choices were identical between surveys 1 and 2, the data were analyzed and reported together.

Focus Group Discussions

Focus group transcripts were analyzed using a modified framework analysis (Gale et al., 2013). Focus group discussions were transcribed, deidentified, and analytically coded in ATLAS.ti Software (ATLAS, 2016) and charted into thematic categories, situated within three a priori chosen categories of interest: (1) LAI treatment characteristic preferences, (2) barriers and facilitators to LAI acceptance, and (3) community-specific considerations for implementation. Findings were initially summarized by region, and once thematically charted, findings were further compared across regions. When present, regional differences are noted in the results. Representative quotes from the focus groups are presented with narrative text. Specific thematic areas highlighted follow the overarching areas of inquiry in focus group conversations. All participants were assigned pseudonyms, so any names included do not reflect real names. This observational, non-intervention-based study was reviewed and deemed exempt by the WCG IRB (IRB Protocol#: 20252075).

4. Results

Survey Demographics

The community survey closed with 208 completed submissions representing a diversity of countries, geographic regions, target populations, knowledge of LAIs, and experience with TB treatment.

Respondents from civil society made up the largest share of stakeholder affiliation, (46%, n=95), followed by individuals with TB experience (29%, n= 60), clinician/healthcare workers (24%, n=50), and researchers (1%, n=3). Respondents came from 45 countries from all six WHO regions (See: Table 1, Survey 2). There was broad age representation, with near equal respondents aged 35 – 44 (28%, n=59) and 45 – 54 (27%, n=57), followed by 26 – 34 (22%, n=46), 55 – 64 (11%, n=23), 18 – 25 (7% n=15), and 65+ (4%, n=8). Gender representation was split between female (51%, n=107) and male (47%, n=98) respondents, with gender minorities making up 1.4% (n=3) of all respondents.

Around half of all respondents (53%, n=110) reported existing awareness of LAIs for TB. Given the history of negative associations around injectable aminoglycosides for drug-resistant TB treatment, respondents were asked about previous experience with TB treatment and injectables for TB: 38% (n=79) of respondents had previous experience with TB treatment *or* TB preventive treatment. Of those, 45% (n=21 of 79) had experience taking injectables as part of their TB regimens.

Table 1. Survey Participant Demographics

Category	**Name**	**Survey 1:**	**Survey 2: Community**	**Total**

		NTPs, CSOs and Healthcare Workers (led by WHO)	**Survey (led by TAG)**	
Primary Role	Civil society	26 (25%)	95 (46%)	121 (39%)
	Clinician/health worker	26 (25%)	50 (24%)	76 (25%)
	Person with TB experience	0 (0%)	60 (29%)	60 (19%)
	Multilateral Organisation or NGO	18 (18%)	0 (0%)	18 (6%)
	National TB Program staff	16 (16%)	0 (0%)	16 (5%)
	Laboratory	11 (11%)	0 (0%)	11 (4%)
	Researcher	5 (5%)	3 (1%)	8 (3%)
WHO Region	Africa (AFRO)	11 (11%)	91 (44%)	102 (33%)
	Europe (EURO)	27 (26%)	49 (24%)	76 (25%)
	South-East Asia (SEARO)	17 (17%)	30 (14%)	47 (15%)
	Western Pacific (WPRO)	34 (33%)	6 (3%)	40 (13%)
	Americas (AMRO)	3 (3%)	30 (14%)	33 (11%)
	Eastern Mediterranean (EMRO)	0 (0%)	2 (1%)	2 (1%)

	Global	10 (10%)	0 (0%)	10 (3%)
	Overall Total	**102 (100%)**	**208 (100%)**	**310 (100%)**

Surveys detailed here include the community and civil society focused survey (Survey 2) described in the text above, as well as a parallel survey focused on NTPs and Clinicians (Survey 1). When questions aligned, data was analyzed collectively to understand preferences across the larger TB community.

Focus Group Demographics

Table 2. Focus Group Participant Demographics

	Mean age range	Gender
Africa (AFRO) (n=4)	55 – 64	Male (n=1)
		Female (n=3)
Western Pacific and South-East Asia (WPRO, SEARO)(n=5)	35 – 44	Male (n=1)
		Female (n=4)
Americas (AMRO)(n=3)	35 – 44	Male (n=1)
		Female (n=2)
Europe and Eastern Mediterranean (EURO, EMRO)(n=2)	45 – 54	Male (n=0)
		Female (n=2)

Four focus groups were conducted with community representatives who had participated in the Phase I community survey. Participants were selected to balance lived experiences and demographics across each focus group region. Focus group topics include: LAIs for children, preferred location for treatment administration, trade off concerns between LAIs and oral regimens, among other topics. Each focus group had two to five participants, with a median age range of 35 – 44 across all groups (Table 2). Male

participants made up 21% (n=3) of all participants, compared to 79% (n=11) female participants. No participants from gender minorities participated in the focus groups.

LAI treatment acceptability

Overall acceptability of injectables for TB prevention and/or treatment

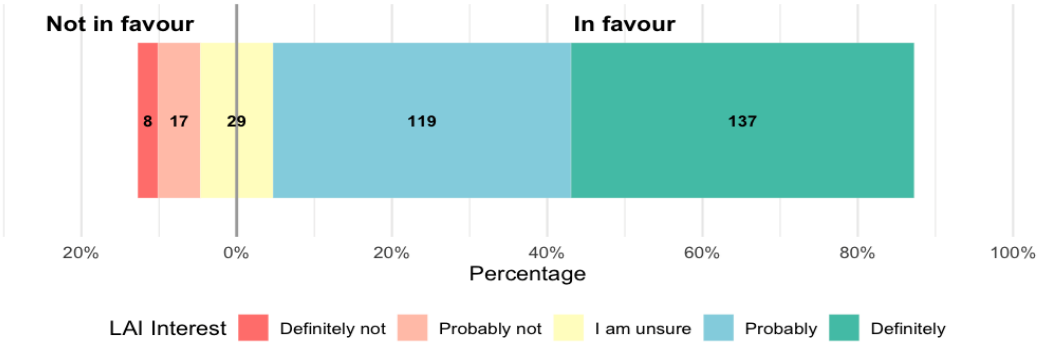

Figure 1. Interest in LAI for TB adoption (Surveys 1 and 2 combined)

Survey respondents and focus group participants were largely supportive of long acting injectables for TB, with 82% (n=256) of all survey respondents reporting net favorable interest in LAIs for TB (Figure 1). An additional 9% (n=29) indicated a neutral or undecided position, and 8% (n=25) reported net unfavorable interest. Among civil society and persons with TB experience, there was a slight decrease in favorable interest in LAIs for TB as compared to other respondent groups (Figure 2). [Describe what you're seeing in the graph that backs this up — as you did for the discussion of Figure 1.] This difference may be attributable to differences between program and implementation considerations and experiential considerations of TB-affected communities.

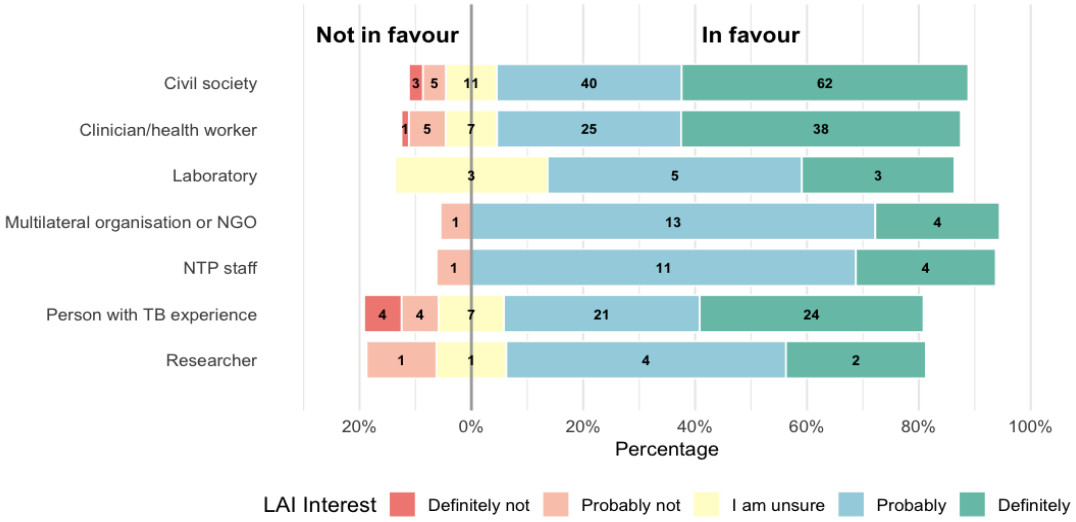

Figure 2. Interest in LAI for TB adoption by primary associations and/or identification (Surveys 1 and 2 combined)

Acceptability of LAIs followed similar patterns across regions; with some variability between regions most respondents reported a favorable interest in LAIs (Figure 3).

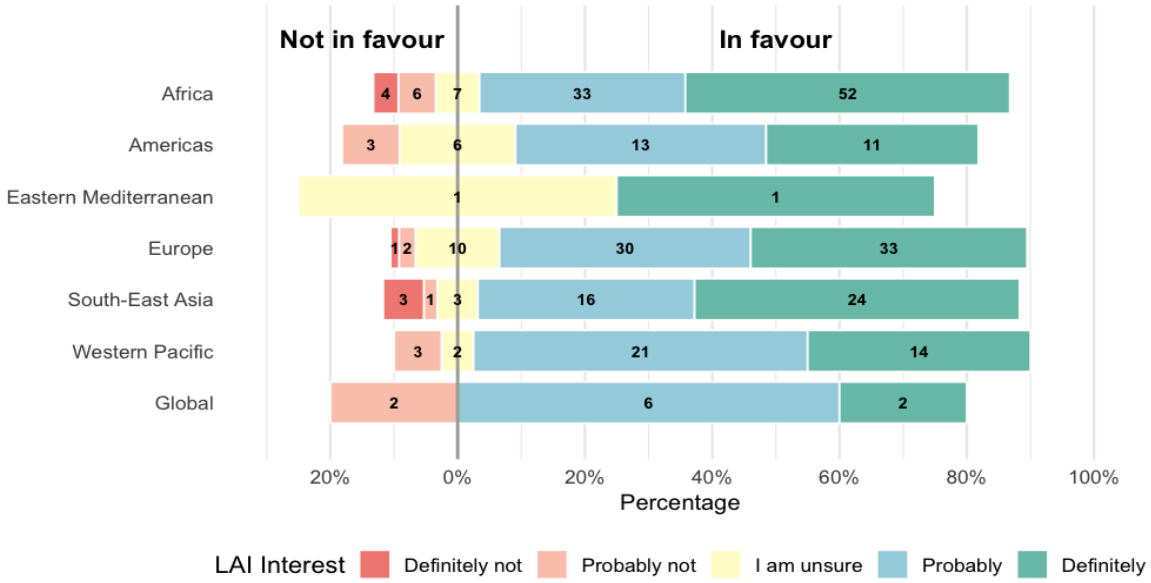

Figure 3. Interest in adopting LAIs for TB by WHO Region (Surveys 1 and 2 combined)

Within the focus groups, acceptability of injections in general varied by region, with participants from the WHO African and the Americas regions more likely to endorse LAIs overall, often citing pill burden for both other comorbid conditions and TB itself. However, important caveats for certain groups (e.g., urban vs. rural) influenced overall perceptions and acceptability of LAIs in each region.

> *"I think this [LAIs] will be a great milestone because most of the time, people have complained of having to swallow a lot of pills once they have TB. So, if the injections are there, they are receiving them once every three months or every two months. I think that can also be a relief [from] swallowing a lot of pills. And this has also affected the adherence to [TB] treatment because people will reluctantly not take the pills if they don't have food. But if it is an injection, sometimes people will not directly think of getting food now, uh, because they will say the injection, I can get the injection, then find food, because the injection will be acting slowly as compared to the pills, which I cannot swallow on an empty stomach." —African Region Participant*

> *"So, in general, it depends. It depends on the situation because, of course, I fully support the point of view of the previous speaker that, normally, injections are painful. Yeah? But at the same time, well, for instance, when there is the alternative, well, now I'm speaking about myself. If I have the alternative, well, for instance, of having one injection instead of having uh, um, well, 20 pills. Well, for instance, I would definitely prefer having this, uh, injection because for me, it's*

> *more convenient. That's again, uh, depending on people. — European and Eastern Mediterranean Regions Participant*

Participants in the WHO AFRO region did not bring up multi-drug resistant (MDR-TB), but did note historical negative memories of anti-TB injectables for MDR-TB treatment (i.e., aminoglycoside agents) causing severe symptoms including hearing loss. Participants from other regions had discussions around existing historical memories of MDR-TB injection frequency and side effects, though some participants stated this may be less of a concern for younger generations.

> *"At the same time, if coming back to those times when people with TB didn't have any opportunity to choose while having TB treatment. They had only the choice of having injections, and at that particular time, the injections were painful, and at the same time, they had lots of adverse effects. And now, uh, if, um, thinking retrospectively, um, if the let me say so that new generation, I mean, of people with TB, um, have the experience of communicating with people with TB who had bad consequences of treating a TB with injections, it might potentially influence their decision. And, well, we should always keep this thing in mind." — European and Eastern Mediterranean Regions Participant*

The impact of historical negative experiences with anti-TB injectables bears out in survey results. Respondents with prior injection experience in TB treatment reported higher opposition to and lower acceptance of LAIs for TB. Of 21 people with prior injection experience, 52% (n=11) expressed they definitely or probably would *not* receive an LAI for TB as compared to 13% (n=25) of the 187 people who had no prior experience with injectables (Figure 4). The higher opposition among respondents with prior injection experience underscores the potential challenges of lingering negative association around historic TB injectables when introducing LAIs.

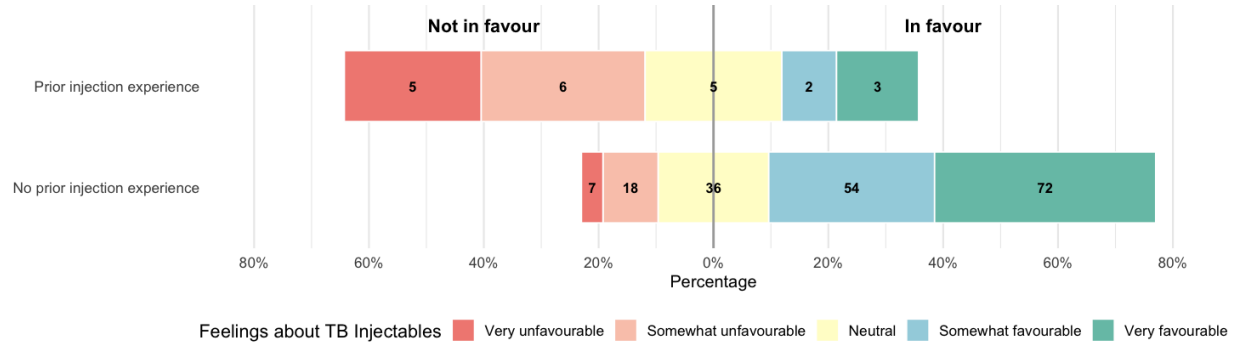

Figure 4. Perception of LAIs for TB by prior injection experience in TB treatment

Differences in acceptability among men and women

Focus group participants discussed how the acceptability of LAIs may differ among men and women, with some participants raising concerns about men's willingness to get an LAI injection in the buttocks versus the arm. Considerations around the age of men receiving LAIs — with older men potentially being less comfortable — were also described.

> *"Uh, men with the ladies [females administering injections]. And, of course, at that point, they have lost weight, so their clothes kind of fall off, uh, uh, when they they they they they can't keep holding to it, uh, or the pain of the injection. So, uh, it's to me, it's those two issues, uh, the concerns, the part of the body. Uh, they would prefer the arms like other vaccines. That would be very comfortable." — African Region Participant*

Some focus group participants noted their perception that women are more engaged with the health system in their region (for various reasons, including work burden and lifetime interactions with the health system — e.g., women come for other types of services like pre-natal care). These participants expressed belief that women may therefore be more likely to be interested in an LAI. However, this dynamic is highly influenced by cultural or contextual factors that shape gendered access to care — factors which vary between regions with different effects on LAI acceptability and access in each context.

Given the underrepresentation of males in the focus groups and male-specific concerns raised, further exploration of LAI acceptability by gender is warranted.

Adult acceptability of injectables for TB prevention and/or treatment for children

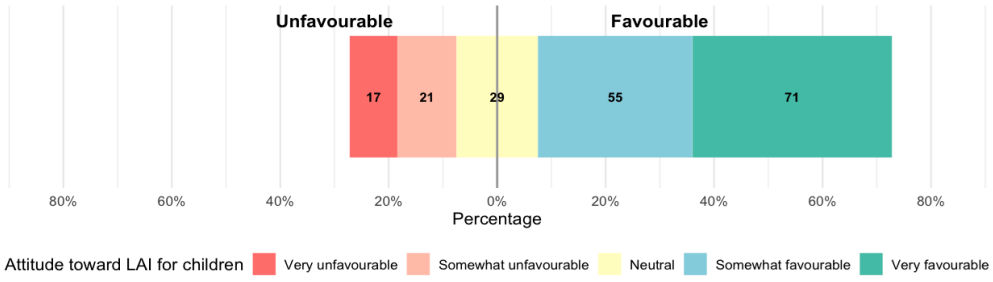

Figure 5. Adult or parental favorability of long-acting injectables for treatment or prevention of TB in children

The community survey explored adult or parental willingness to adopt LAIs for TB treatment and prevention in children. Overall, a majority (65%, n=126) of respondents felt favorably towards *their child* being treated with LAIs (Figure 5). When stratified by prior experience with injectables in TB, those with prior experience reported higher unfavourability towards LAIs for TB (35% of responses) compared with TK% unfavourability among respondents without prior injectables experience (Figure 6). This suggests that the negative perception of historical anti-TB injectables within the TB community may influence overall acceptability of LAIs, particularly in communities with a greater burden of DR-TB.

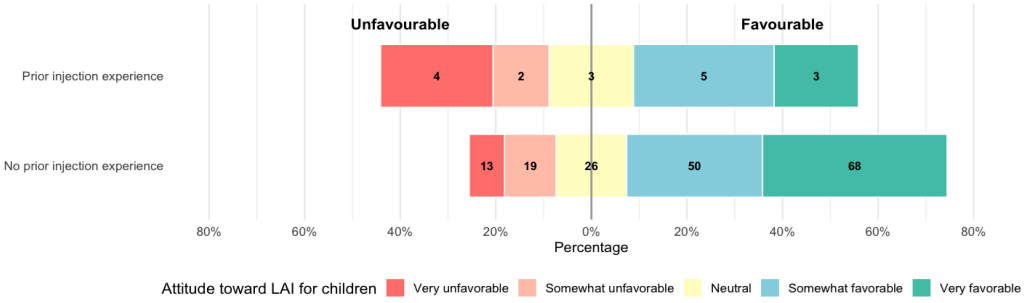

Figure 6. Adult or parental favorability for of long-acting injectables for treatment or prevention of TB in children by prior respondent experience with injections for TB treatment

In focus group discussions, participant feelings about the acceptability of LAIs for children were largely favorable. Participants expressed that it is challenging to deal with pain and injection site reactions for children of any age. Most participants acknowledged that younger children do not like injections, and some participants said that it can be hard for older children to accept a vaccine. At the same time, participants described the difficulty for parents in administering oral medications and ensuring the full dose is taken, making LAIs largely acceptable for treatment or prevention of TB in children.

> *"But if, um, I do know that my kids might not like injections, but they would get them, um, because it would be easier. And especially because of what I would have to do here, which would be crushing pills, um, you know, and I think the options I would have that that, uh, people in my country have for treating their kids, there's just not many of them. So, I would definitely be interested in injectables because crushing pills is just not great. It's not accurate." — European and Eastern Mediterranean Regions Participant*

Some participants also spoke about how children, particularly younger children, may dislike injections in the moment, administering an injection is faster and shorter in duration than giving pills daily.

> *"And if there is an, uh, an injection for treating TB, it will be great, I think, because it will be, okay, just a few quiet minutes of crying and screaming, some yelling. That's right. But you will be sure that they receive those in the dose, and on time." —Western Pacific and South East Asian Region Participant*

Trade-offs

Unique preference scenarios were designed and included in the survey to understand and explore personal preferences and stakeholder priorities around different LAI characteristics. Seven trade-off scenarios were examined in the phase I surveys:

1. Standard of care (6-month oral regimen) versus LAI regimen without co-formulation (3-month regimen, with one-month oral lead-in, followed by 4 shots monthly for two months)
2. Standard of care versus LAI regimen with co-formulation (two shots monthly for two months)
3. Coverage duration versus number of injections, i.e., fewer injections monthly versus more injections on a bi-monthly schedule
4. Subcutaneous injections monthly versus intramuscular injections bi-monthly

5. Injections at local clinics monthly versus at central hospitals bi-monthly
6. A single injection appointment for continuation phase vs two monthly injection appointments
7. TB preventive treatment standard of care (1-month oral regimen) versus a single LAI injection(s) appointment

Survey findings on trade-offs were explored discussed in greater detail in focus groups. When asked about trade-offs (e.g., longer oral-lead in, fewer total injections, and frequency), many focus group participants raised questions about the efficacy of treatments. This suggests that treatment efficacy is of high concern for people being treated for TB and is central to assessing individual preferences for potential LAIs regardless of their characteristics.

Table 3. Combined Treatment Preference Summary from Surveys 1 and 2

Treatment Preference Scenario	**Option A Preferred** n (%)	**Neutral** n (%)	**Option B Preferred** n (%)
TB treatment			
A: 6-month daily oral (standard of care) B: 3-month (1-month oral lead-in + 4 monthly injections for 2 months)	61 (20%)	34 (11%)	215 (69%)
A: 6-month daily oral (standard of care) B: 3-month (1-month oral lead-in + 2 monthly co-formulated injections for 2 months)	44 (14%)	17 (6%)	249 (80%)
A: 4-month (3 monthly injections) B: 3-month (6 injections given on months 1 and 3)	141 (46%)	50 (16%)	119 (38%)
A: 4-month (3 subcutaneous monthly injections) B: 3-month (3 intramuscular injections given on months 1 and 3)	81 (26%)	31 (10%)	198 (64%)
A: 4-month (monthly injections at local clinic visits) B: 3-month (injections at district hospital visits on months 1 and 3)	108 (35%)	36 (12%)	166 (53%)
A: 3-month (1-month oral lead-in + 2 monthly injections)	141 (45%)	36 (12%)	133 (43%)

B: 3-month (2-month oral lead-in + 1 injection visit)			
TB preventive treatment			
A: 1-month oral prevention (standard of care) B: Single prevention injection given at 1 visit	46 (15%)	18 (6%)	246 (79%)

Standards of Care versus LAIs

Comparing a 6-month daily oral regimen (standard of care TB treatment) to a 3-month LAI regimen with 1-month oral lead-in with four monthly injections for two months (no co-formulation), 69% of all respondents preferred the LAI option while only 20% of respondents preferred the standard oral regimen. This suggests strong support for an LAI regimen that shortens overall treatment timelines and reduces pill burden. When a 3-month co-formulated LAI regimen with one-month oral lead-in with two monthly co-formulated injections for two months) was compared to the standard of care, preference for the LAI regimen rose 11-points to 80%. The large increase in support for the co-formulated LAI regimen indicates community and other stakeholder interest in minimizing overall number of injections alongside reducing treatment times and pill burdens.

Queried about coverage duration versus number of injections (i.e., fewer injections monthly versus more injections on a bi-monthly schedule), 45% of respondents preferred a longer treatment duration with fewer injections (e.g., a 4-month regimen with three monthly injections) versus 38% of respondents preferring a shorter duration with more injections (a 3-month regimen with 6 injections on months 1 and 3) (Figure 7). Preference varied across stakeholders, but clinicians/healthcare workers and civil society respondents favored fewer injections with longer treatment duration, suggesting a higher priority among advocates and healthcare providers for reducing the number of injections per visit, aligned with findings from other trade-offs (see above).

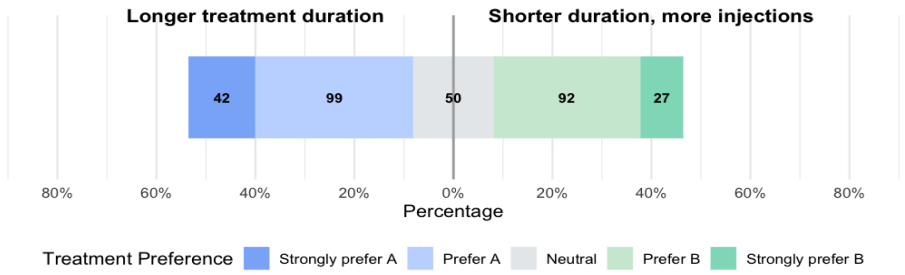

Figure 7. Preference for longer duration of treatment coverage with fewer injections vs shorter duration with more injections

The findings from the three scenarios described above suggest that reducing the total number of injections and the time in treatment are high priorities for TB stakeholders, with reducing the total number of injections representing a key aim for acceptability of LAI regimens. Further exploration of the trade-off between number of injections and time in treatment is required to identify the ideal balance between each parameter.

Aligned with the findings from the TB treatment preferences, respondents indicated a strong preference for a single LAI injection for TPT (79%) over a 1-month oral regimen (15%). An option which showcases the strong potential LAIs have for TPT.

Options

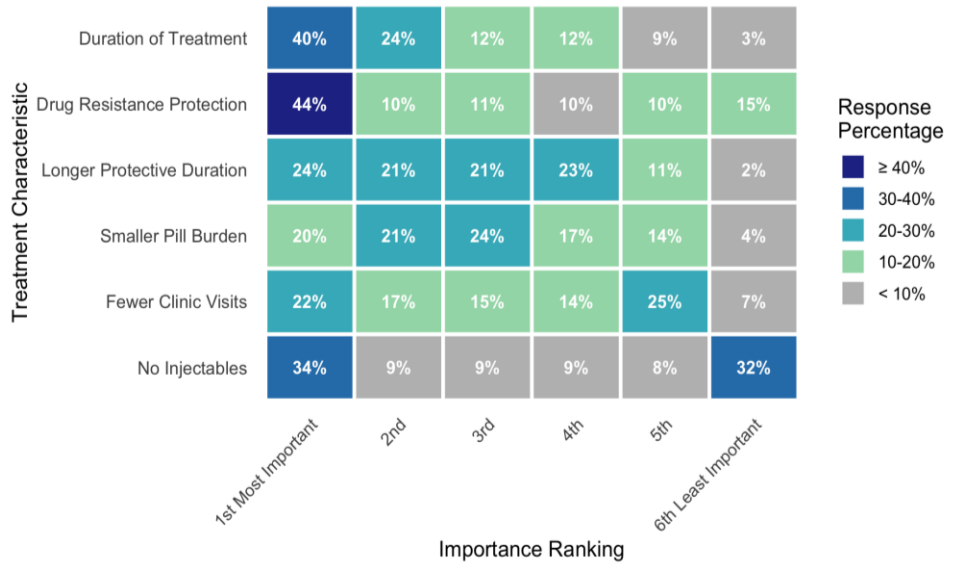

Figure 8. Prioritization and preferences of LAT treatment characteristics in overall acceptability and uptake of LATs

When directly queried about which LAT characteristics were of highest priority, community survey respondents reported that protection against drug-resistance was the most important (44%), followed by duration of treatment (40%), with longer protective duration, fewer clinic visits, and smaller pill burden as secondary priorities (Figure 8). There was a near equal split between "most important" and "least important" that long-acting technologies do not feature injectables. This is in line with earlier analysis that revealed the impact of negative history of injectables in TB on LAI acceptance while also underscoring an appetite for LAT in general.

Focus group participants stressed that options and information were most critical to successful implementation of any LAIs. Across regions, participants described how healthcare workers were likely to influence their choice, noting that it was likely a healthcare worker (per their role) had determined a specific course of treatment prior to discussing with the individual. In an expanding landscape of TB treatment and prevention options, a common request was that there be clear information on trade-offs and that individual decisions could be made, whether for adults, children, or other sub-groups.

> *"One thing, like, I really want for other people who have had TB or have TB is just options. And, um, so, you know, if we're viewing this as another option, I think that's a great way to do it. And, um, the other thing is, of course, you know, please remember children, and please remember people who are pregnant. Um, these are populations that always get left out. I feel very strongly about it, obviously." — Americas Region Participant*

Stigma

The impact of new LAI regimens on stigma was described across focus groups. One common theme was that LAI regimens that result in fewer visits to a health center could mean being seen at health centers collecting pills less frequently.

> *"A patient will go to the medical department for injections. How to say — not so often. It means that the risk of receiving stigma and discrimination from medical staff, people, or somebody from his environment [community]. That is why less visits, risk of meeting somebody who will stigmatize him." — European and Eastern Mediterranean Regions Participant*

Other participants raised that reducing or eliminating the duration of taking oral medication in the home or work could reduce family and community-based stigma. However, the nuances of this dynamic between regions were not explored in depth in the focus groups. Further investigation into the potential impact of LAIs on stigma is required.

> *"It gives them the right to privacy, and getting injections gives them space to do other chores as well as to reduce the cost of frequent visits to the facility. So that also, uh, uh, gives them time to manage their households. So, most of the women here will prefer injections because they provide that privacy and respect and dignity, and no one can stigmatize them or blame them" — African Region Participant*

Intramuscular vs. Subcutaneous Injections

When preference for injection site — intramuscular or subcutaneous — was explored, 64% of respondents preferred the intramuscular option (3-month treatment with three intramuscular injections given bi-monthly) over subcutaneous (4-month treatment with three subcutaneous injections given monthly). However, as the intramuscular option featured both a shorter treatment duration and fewer injections, it is difficult to draw conclusions specific to subcutaneous versus intramuscular injection preferences (Figure 9). The community survey asked respondents to independently rank their preferences for models of long-acting technologies, and when queried on technology type specifically, respondents preferred subcutaneous injectables over intramuscular (Figure 10). The preference for subcutaneous injectables when considered outside of hypothetical treatment time and number of injections but intramuscular when it is associated with shorter treatment and fewer injectables suggests that duration of treatment and number of clinic visits are of higher importance in determining LAI preferences than the specific injection site.

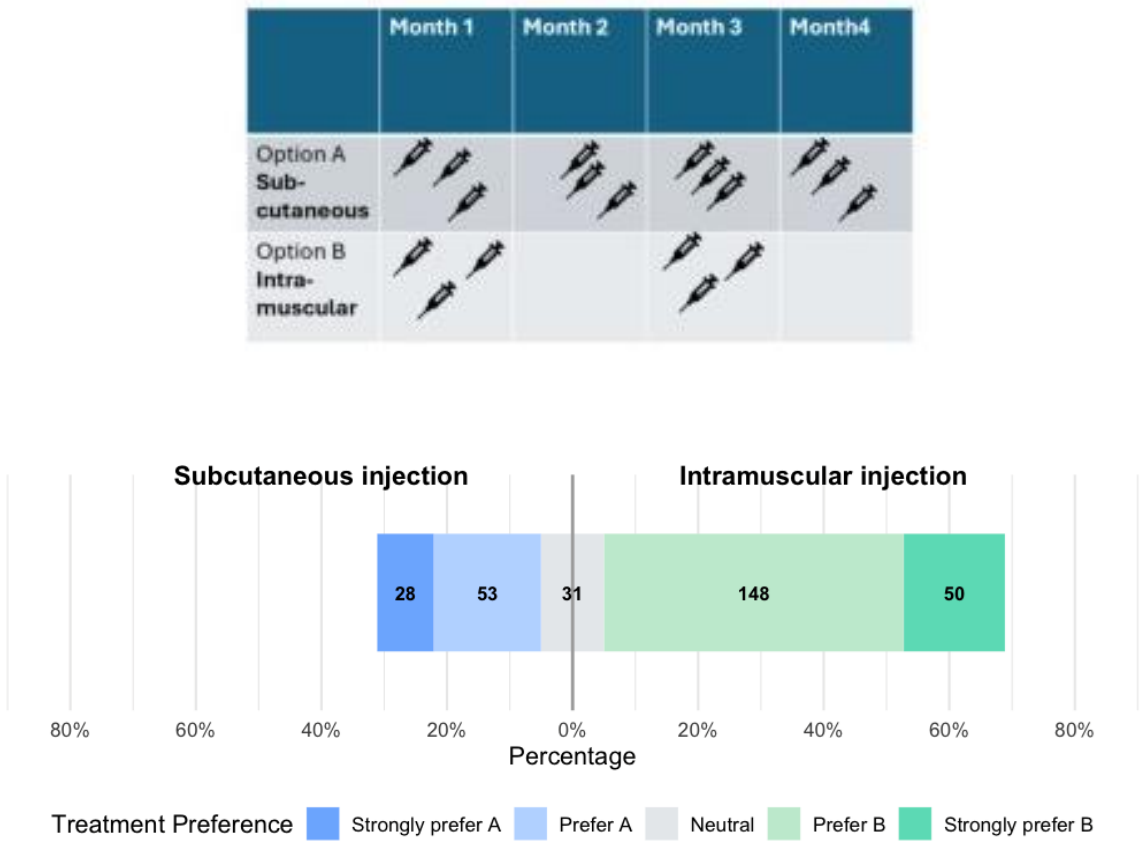

Figure 9. Preference for subcutaneous injections with monthly visits versus intramuscular injection with bi-monthly visits (Survey 2).

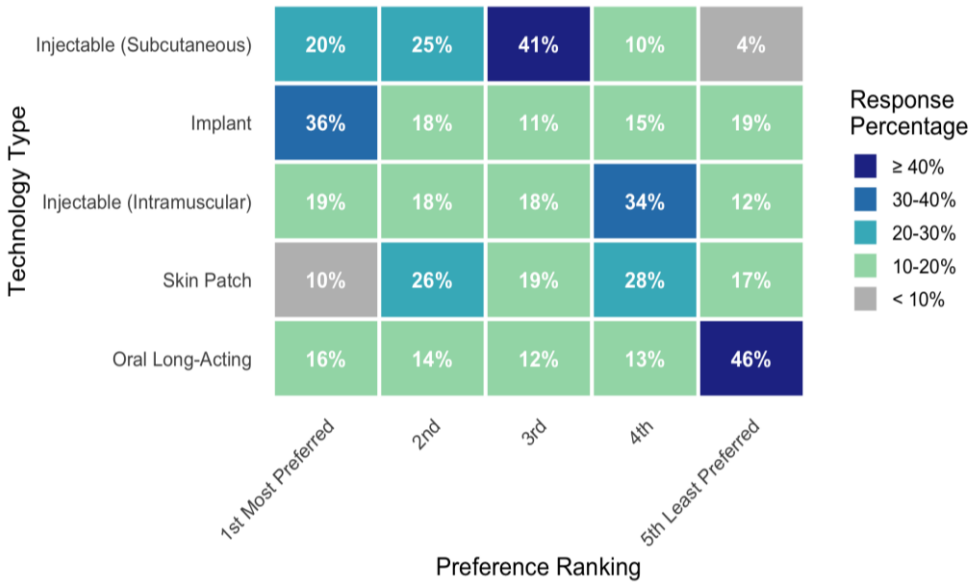

Figure 10. Preference rankings for long-acting technologies for TB.

When injection sites were raised in focus groups, participant responses were primarily focused on minimizing pain associated with injections:

"Less painful? Every time is better." — European and Eastern Mediterranean Regions Participant.

Others described how the duration of the pain may not be unfamiliar to people, but the severity of pain and how long the pain lasts is the most important consideration. This is in line with survey findings that suggest the highest priority for affected communities in assessing injections is not the *type* of injection, but the side effects of injection and by extension the severity of pain from administration. Focus group participants suggested that the associated pain of LAI treatment will have an outsized impact on acceptability.

> *"It depends on how painful. If it's the that is derived from the then penetrating the muscle, then that one, they can easily bear because they are used to it…but if it is a pain from the drug getting into the muscles and the pain persists, after the administration, then they might prefer to go back to the pills." — African Region Participant*

Location of LAI Treatment

When queried between receiving LAI treatment at a local clinic monthly (4-month regimen) versus at central district hospitals bi-monthly (3-month regimen), 54% of respondents preferred the district hospitals (Figure 11). However, the query did not isolate location of treatment from considerations about preferences for number of visits, visit rhythm (i.e., monthly vs. bimonthly), or overall regimen length. As such, respondent preference for the district hospital in the scenario described (Figure 11) may

reflect interest in a shorter treatment duration, in less frequent clinical visits, and/or in receiving treatment at a district hospital over a local clinic.

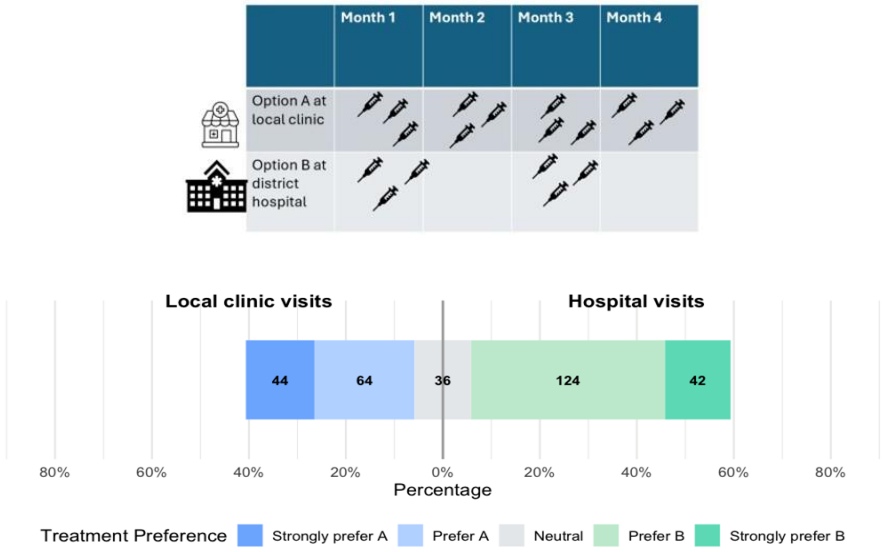

Figure 11. Preference for receiving LAIs for TB in local clinics on a monthly schedule vs regional hospitals on a bimonthly schedule, regardless of injection type (Surveys 1 + 2)

When community survey respondents were asked to rank preferences for where they would want to receive LAI treatment *independent* of number of visits or injections required, 51% of respondents preferred local clinics compared to 14% preferring central district hospitals (Figure 12). This suggests that when LAI regimen–agnostic, respondents prefer receiving care closer to their communities (e.g., at local clinics).

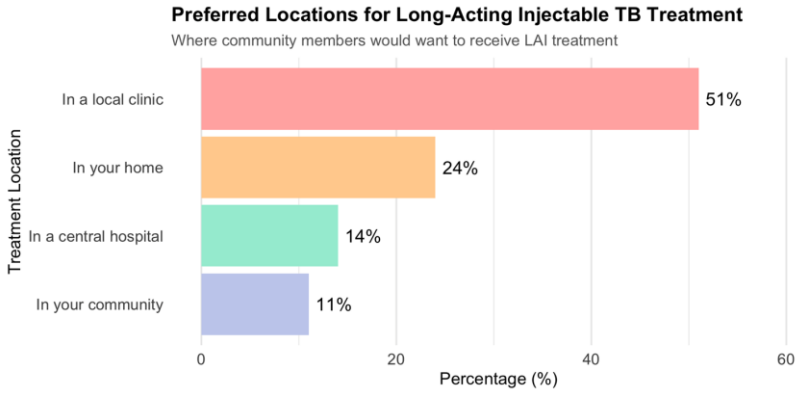

Figure 12. Overall preference for location of LAI treatment regardless of injection type and treatment schedule.

Despite this strong preference for receiving care closer to home (Figure 12), when considerations like regimen duration and number of visits are included (Figure 11), respondents prioritized shorter treatment durations or fewer clinic visits over a central location of care (e.g., local clinics). This finding is supported by the rankings of LAI characteristic priorities (Figure 8), in which "Duration of Treatment" and "Fewer Clinic Visits" were high priority for respondents. When queried about how often they'd be willing to visit their treatment provider regardless of location, the majority (70%) preferred monthly visits, with 20% indicating a willingness to go once a week, and 10% willing to go bi-weekly; bi-monthly options were not queried (Figure 13). Taken together, these findings indicate that patients are willing to accept less convenient locations in exchange for shorter treatment durations and fewer total visits.

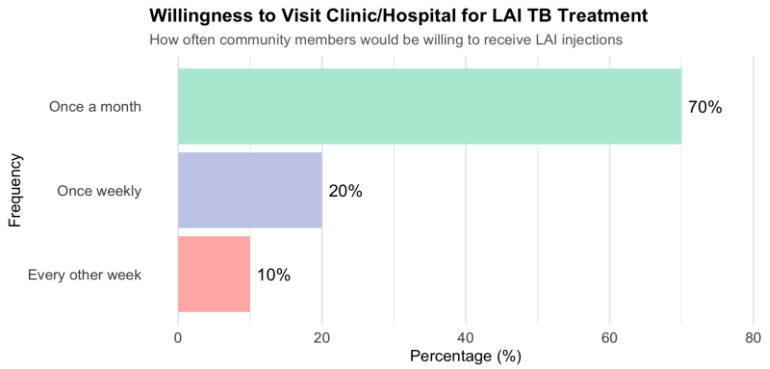

Figure 13. Preference and/or willingness for timing of required clinical visits for LAI treatment, regardless of treatment location.

Focus group participants expressed mixed feelings about the best location for LAI treatment (e.g. health center, hospital, community location, home-based). Some participants noted that a community location would minimize travel costs. Others described how in their respective health systems, LAIs at community clinics is an unlikely option as all TB care is administered through a pre-existing, fixed TB clinic system. Some participants from the Americas, European, and Eastern Mediterranean Regions raised a preference for oral regimens with video DOT over an LAI regimen as they felt oral regimens can be more convenient than taking time away from work, childcare, and other responsibilities for LAI treatment. This suggests that personal conveniences will be a consideration in LAI acceptance and how easily LAIs can be integrated into existing routines or structures. Participants did not raise interest in DOT for self-administration of LAIs, but this should be explored in greater detail in future studies.

> *"That's actually a lot and big, it's kind of a pain. If I could take the pills by myself and on a, you know, DOT, you know, if they can watch me take it, and I can do it from my home, video DOT is way more convenient. For me personally, and I know a lot of working people, having a doctor's appointment every month would be a pain. So, if for me, it would be the treatment I can take at home versus the treatment I have to go in for, and however it would be." — European and Eastern Mediterranean Regions Participant*

LAI Treatment Side Effects

Within focus groups, the side effects of LAIs compared to pill-based TB treatment or prevention were raised by participants as an important consideration. If side effects are too severe, there were concerns that after one injection or one series of injections, someone might not return for additional injections.

> *"If the side effect is [bad], then people might not have a repeat [come to] a repeat visit if the injection is over a period of time. We have had that problem with TB, with side effects when people can't work properly…so they stop [treatment] immediately because they don't want to be sicker than they are [due to side effects]." — African Region Participant*

Other discussions around side effects included timing of an injection vs. taking a pill, which could influence when side effects are experienced, and there may be less control of this with an LAI administration.

> *"I was on pills. And I could kind of take them at a time, like, right after work, and then I would have the side effects, like, at night. And so I could time that a little bit better once I figured out what was going on. Whereas, you know, if you're on the clinic schedule or whatever and going back to work, you might not have that option. Like, if you have a morning appointment or whatever, that's all they have available." — Americas Region Participant*

The discussion of side effects also focused on ensuring that patients have information to make an informed choice about what will work best for their lives (e.g., pills vs. injection vs. a combination), and whether or how easy it would be to switch to a pill-only based regimen if LAI side effects were too significant. Participants raised considerations as to how much agency individuals on LAIs will have to control their side effects, timing, and even mode of treatment (e.g., switching from LAI to oral), and the impact on acceptability.

> *"People then, after they are taking the long-acting injectable, don't feel comfortable and want to change the mode of transmission from the injection to taking the pills, or the other way around. Is that possible for people to do that?" — Asia-Pacific Region Participant*

5. Summary

Taken together, the findings from the survey(s) and the focus group discussions underscore strong existing interest and support in LAIs for treatment of TB. Support is consistent across all groups engaged in the TB field including TB affected communities, healthcare workers, NTPs, and civil society. While the history of anti-TB injectables still influences community perceptions of LAIs, support for LAIs is found even among those with prior experience in TB injectables.

Overall, community respondents favor shorter treatment durations, fewer injections, minimal associated pain in the design of LAIs, and personal modesty during treatment (i.e., resistance to injections in the buttocks or other culturally-sensitive areas of the body), with less importance placed on the route of administration or location of treatment. There is particularly strong interest in LAIs for TB prevention, demonstrating the strong potential of future LAIs to overcome adherence concerns associated with existing oral TPT regimens.

The insights gleaned from the focus groups reveal that while LAIs represent a promising alternative to daily oral regimens, the acceptability, implementation, and success of LAIs will depend on careful consideration of diverse community needs, preferences, and contextual factors that differ across regions. While participants from the African and Americas regions demonstrated strong support for LAIs and recognized their promise in reducing daily pill burden and improving adherence, the support was not unconditional. In line with survey findings, participants highlighted key concerns and historical experiences with injectable TB treatments, particularly for multidrug-resistant TB.

Several key themes emerged as critical to LAI acceptance and implementation. Side effects stand out as a pivotal concern that could determine whether patients continue with LAI treatment. Participants emphasized the need for clear information about potential adverse effects and the flexibility to switch between treatment modalities if needed. Second, stigma mitigation was identified as a potential benefit of LAIs, as fewer clinic visits could reduce visibility within communities and healthcare settings; however, this must be balanced against the logistical challenges of attending clinics for injections.

These findings highlight the critical trade-offs that must be addressed in LAI development and implementation to support community acceptability and uptake. Early consideration and inclusion of community perspectives and voices in the LAI development pathway are critical to ensuring that future LAIs carry the potential to meaningfully meet the needs of TB affected communities. LAIs hold significant promise as an innovation that could improve treatment adherence and reduce pill burden, but their success requires a nuanced, person-centered implementation approach.

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Annex 3: Overview of results of the WHO public comment process

TBD

Annex 4: Consensus meeting agenda

TBD

Annex 5. Summary of Declarations of interest and management of conflicts

MEETING	**Technical expert group to update the Target Regimen Profiles (TRPs) for long-acting injectable (LAI) regimens for tuberculosis (TB) treatment and TB preventive treatment (TPT).**		
DOI ASSESSMENT PERIOD	2024-25	**DATE OF FINAL NOTE FOR THE RECORD:**	29.09.2025
PROPOSED GROUP COMPOSITION	**Churchyard Gavin** (Aurum), **Davies Rhys Geraint** (Liverpool University), **Dooley Kelly** (VUMC), **Fox Greg** (University of Sydney), **Hesseling Anneke** (SUN), **Kendall Emily** (Johns Hopkins University), **Kityo Cissy** (Joint Clinical Research Centre in Uganda), **Nuermberger Eric** (Johns Hopkins University School of Medicine), **Owen Andrew** (University of Liverpool, CELT), **Salazar Nicole** (Johns Hopkins University School of Medicine), **Svensson Elin** (Uppsala University), **Ashesh Ashna** (Civil Society Taskforce), **Erin McConnell** (TAG), **Faisal Sobia** (Deputy General Manager Technical & Training (TB), Greenstar Social Marketing (G) Pakistan), **Gler Maria Tarcela** (Maricel) (Makati Medical Center), **Lange Christoph** (Borstel Institute), **Meintjes Graeme** (University of Cape Town), **Campbell Michael** (CHAI), **Ndjeka Norbert** (NTP RSA), **Sekkade Moorine** (MOH Uganda), **Zhao Y**anlin (NTP China), **Cavaleri Marco** (EMA), **Semete Boitumelo** (SAPHRA), **Bizzini Alain** (SwissMedic), **Angami, Ketho** CSO / patient perspective, India), **Mattoo, Sanjay** (NTP, India), **Ningyi, Wei** (National Institutes for Food and Drug Control, China).		
NUMBER OF PARTICIPATING EXPERTS	27	**NUMBER OF EXPERTS WITH DECLARED INTERESTS:**	10

BACKGROUND AND ASSESSMENT PROCESS	The WHO Global Programme on Tuberculosis and Lung Health (GTB) will convene a Technical Expert Group meeting to update the Target Regimen Profiles (TRPs) for long-acting injectable (LAI) regimens for tuberculosis (TB) treatment and TB preventive treatment (TPT). These TRPs are developed to reflect the latest scientific advancements and to ensure alignment with the practical needs of end-users. The updated profiles aim to guide the development of LAI regimens with performance and operational characteristics suitable for implementation across diverse settings. Twenty-seven experts with a wide range of technical and programmatic expertise have been invited to participate, including representatives from academia, research institutions, product development partnerships, civil society, and national TB programmes. All invited experts have completed and submitted their Declaration of Interest (DoI) and Confidentiality Undertaking forms. On review of the completed DoIs, the following 10 experts declared interests that required further consideration: 1. Ashesh Ashna 2. Churchyard Gavin 3. Fox Greg 4. Hesseling Anneke 5. Kendall Emily 6. Mentjies Graeme 7. Nuermberger Eric 8. Svensson Elin 9. Davies Rhys Geraint 10. Gler Maria Tarcela

2. EXPERTS WITH POTENTIAL CONFLICT OF INTEREST	
1	
EXPERT NAME	**Ashesh Ashna**
CONFLICT DISCLOSED	**(5b) Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work** Ashna Ashesh is a steering committee member of the ReLAY track of FAST-TB. ReLAY's focus is on helping prioritize clinical research that aligns with the global realities of TB care and accelerating the introduction of more effective regimens that dramatically improve outcomes for TB patients.
ASSESSMENT	The disclosed conflict supports a broader TB research strategy, not specifically linked to LAIs or any product that is under review.
CONCLUSION	No significant conflict of interest.
2	

EXPERT NAME	**Churchyard Gavin**
CONFLICT DISCLOSED	**(1b) Consulting, including service as a technical or other advisor** The expert has received an honorarium (1,500 USD) as a member of the Janssen advisory board on long-acting injectables for TPT. This has now ceased. **(2a) Research support, including grants, collaborations, sponsorships, and other funding** The expert has received salary support from the NIH/DAIDS ACTG, approximately 13,500 USD, until the USG funding cut. While this support has now ceased, the research activities are still ongoing. **(6e) Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence**? G. Churchyard disclosed that he is supporting Janssen in developing a protocol, as a protocol co-chair, to evaluate long-acting bedaquiline (ongoing activity). This is expected to be submitted to the NIH/DAIDS/ACTG for approval, and if approved, the project will start in Q3 2026.
ASSESSMENT	Although previous funding has ended, the ongoing collaboration with Janssen represents a direct involvement in a commercial LAI product, which is currently under review and thus represents a potential perception of conflict.
CONCLUSION	Dr. Churchyard may participate as a member of the TRP with observer status~~,~~ due to the active protocol development role. He should refrain from participating in the decision-making processes on TRP characteristics.
3	

EXPERT NAME	**Hesseling Anneke**
CONFLICT DISCLOSED	**(1b) Consulting, including service as a technical or other advisor** Technical advisor for GlaxoSmithKline (GSK) on the ganfeberole clinical development plan, once-off. **(2a) Research support, including grants, collaborations, sponsorships, and other funding**: Stellenbosch University receives 750,000 USD for several investigator-initiated research studies, including with the NIH IMPAACT network, TBTC UNITAID. The support is ongoing.
ASSESSMENT	Dr Anneke Hesseling is an academic at Stellenbosch University, a leading teaching and academic institution in South Africa. The university receives annual grants for several investigator-initiated research studies, including from the NIH IMPAACT network, TBTC, UNITAID, BMRC/Wellcome Trust, and the South African MRC. These studies focus on therapeutic trials and diagnostics in childhood TB, and although these subgroups may be discussed, this is not a key focus of this Technical Advisory Group. Ganfeberole trial, Phase 2, is focused on early bactericidal activity of Oral GSK3036656 in Combination with Delamanid or Bedaquiline, Delamanid in Combination with Bedaquiline, or Standard of Care in Male and Female Participants Aged 18 to 65 Years. She had only a time involvement which has ended. This study is not directly linked to the primary focus of TRPs of LAIs.
CONCLUSION	No significant competing interests were identified as the disclosure is not in conflict with the scope of the work being undertaken by the technical expert group for TRPs.
4	

EXPERT NAME	**Fox Greg**
CONFLICT DISCLOSED	**2b. Non-monetary support valued at more than US $1000 overall (include equipment,** **facilities, research assistants, paid travel to meetings, etc.)** Dr Greg Fox received in-kind contribution of $30,000 from Sanofi Pharmaceuticals for the medications to support the research project (clinical trial). There was no personal benefit and no financial contribution. The trial has now finished.
ASSESSMENT	The disclosed in-kind contribution of $30,000 from Sanofi Phamaceuticals, provided for a clinical trial on Rifapentine, which is not a subject of the TRP update and the support is no longer active.
CONCLUSION	No significant conflict of interest.
5	
EXPERT NAME	**Kendall Emily**
CONFLICT DISCLOSED	**(2a) Research support, including grants, collaborations, sponsorships, and other funding** She is currently involved in research activities funded by the Gates Foundation and the U.S. National Institutes of Health. As Principal Investigator for the Gates Foundation, she leads grants on: i) modeling resistance risks and diagnostic needs for a pan-TB regimen; ii) supporting a cohort study to understand the true burden of TB among people with trace Xpert Ultra management and guide their clinical management. For the NIH, she is the PI on projects investigating; i) the prevalence and incidence of TB among people with trace Ultra results during community-wide screening; ii) the implementation and effective of two different approaches to mass digital chest X-ray screening for TB in Uganda. The expert is a co-investigator in modeling roles on NIH grants studying a variety of new TB diagnostics (the R2D2 project) and studying active case-finding for recurrent TB after successful completion of initial treatment. The amount of funding has not been disclosed.
ASSESSMENT	The disclosed funding is for research that is non-commercial and not related to LAIs.
CONCLUSION	No significant conflict of interest.
6	

EXPERT NAME	**Meintjes Graeme**
CONFLICT DISCLOSED	**(1b) Consulting, including service as a technical or other advisor** He received an honorarium of $5,000 for his service as an independent consultant; this has now ceased. He also served as an independent consultant for Gates MRI without financial compensation; this has also ceased.
ASSESSMENT	The disclosed funding has ended and was unrelated to LAIs.
CONCLUSION	No significant conflict of interest.
7	
EXPERT NAME	**Svensson Elin**
CONFLICT DISCLOSED	**(2a) Research support, including grants, collaborations, sponsorships, and other funding** The research unit has received funding of €60 K, one-time from Jansen pharmaceuticals and $200,000 /ongoing from TB Alliance.
ASSESSMENT	-Dr. Svensson received one-time funding (€60,000) from Janssen Pharmaceuticals to support a research project focused on improving QT correction methods in TB patients and developing a new type of pharmacometric model for TB outcomes. This funding was used to cover the salary of one of her students. -She also receives ongoing funding ($200,000) from the TB Alliance for pharmacometrics analyses related to the IMPAACT-TB Alliance pediatric study of pretomanid and for assisting with population pharmacokinetic modeling of TBAJ-876 to inform the design of a drug-drug interaction study. This support is being used to cover a PhD student's salary. Both activities are conducted within Dr. Svensson's research unit and are directly related to her academic work. There are no personal or financial interests that could compromise her objectivity in contributing to the review of long-acting injectables (LAIs). The disclosed relationships do not represent a significant competing interest.
CONCLUSION	No significant competing interests were identified as the disclosure is not in conflict with the scope of the work being undertaken by the technical expert group for TRPs.
8	

EXPERT NAME	**Nuermberger Eric**
CONFLICT DISCLOSED	**(1b) Consulting, including service as a technical or other advisor** He served on an advisory board for Janssen on two occasions, once in 2021 and once in 2024, receiving a total of $8,175. In each case, he served as a consultant in a virtual advisory board meeting to evaluate clinical practice and unmet needs in the treatment and prevention of tuberculosis and provided feedback and advice regarding interpretation of preclinical data, clinical trial designs and target product profiles. **(2 a) Research support, including grants, collaborations, sponsorships, and other funding** In 2022, he received research support from Janssen, and in 2024 from the Gates Medical Research Institute. In addition, he is currently receiving support from the TB Alliance, the amount not specified. He served as PI for these research grants and contracts awarded to John Hopkins University. **(4 a) Patents, trademarks, or copyrights (including pending applications)** The expert is an inventor on a patent application for long-acting injectable formulations of diarylquinoline drugs for treatment and prevention of tuberculosis.
ASSESSMENT	Dr. Nuermberger's 2024 advisory role with Janssen, a developer of LAIs, represents a recent and directly relevant financial relationship. Although the advisory role now ended, its timing and compensation raise concerns, as the advisory work aligns closely with the TRP meeting's focus. Additionally, he is listed as an inventor on a patent application for long-acting injectable formulation diarylquinoline drugs for treatment and prevention of tuberculosis, a topic that is the subject of the TRP meeting.
CONCLUSION	Given the direct relevance of both the recent financial relationship and the intellectual property interest to the TRP meeting's topic, Dr. Nuermberger will be part of the group as an observer.
9	

EXPERT NAME	**Davies Rhys Geraint**
CONFLICT DISCLOSED	**(2 a) Research support, including grants, collaborations, sponsorships, and other funding** In 2024, Gerry Davies is a co-investigator on a research grant funded by ViiV Healthcare, awarded to the University of Liverpool Department of Pharmacology, totaling £374,574. He receives no personal salary or other benefits from this grant. The study focuses on the pharmacokinetic interaction between high-dose rifampicin and dolutegravir. **(6e) Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?** 2011–2017: Academic coordinator of PreDiCT-TB consortium (EU-funded, public funding only; no direct funding from industry for him or his institution). Since 2017: Academic partner in PanACEA clinical trials consortium (no pharmaceutical funding to him neither for his institutions). Since 2020: Academic partner in UNITE4TB consortium (EU-funded with industry partners; no direct funding from industry). Attended GSK and Janssen advisory meetings with no payment or benefits received.
ASSESSMENT	Gerry Davies' involvement in publicly funded consortia and his role as a co-investigator on a ViiV Healthcare funded grant, without receiving personal financial benefits, indicates no direct financial conflict of interest. His advisory meeting participation was unpaid.
CONCLUSION	No significant competing interests
10	

EXPERT NAME	**Gler Maria Tarcela**
CONFLICT DISCLOSED	(1b) Consulting, including service as a technical or other advisor (2a) Research support, including grants, collaborations, sponsorships, and other funding Gler Maria Tarcela received research support of USD 2,000 Gates MRI for a qualitative study describing three patient scenarios related to potential long-acting injectables for TB treatment.
ASSESSMENT	Although the topic is relevant to the TRP, the amount received is considered insignificant.
CONCLUSION	No significant competing interests.