Report of the technical consultation on innovative clinical trial designs for evaluating new TB preventive treatments

Virtual meeting,

15-17 September 2021

Report of the technical consultation on innovative clinical trial designs for evaluating new TB preventive treatments: virtual meeting, 15-17 September 2021

ISBN 978-92-4-004715-0 (electronic version)
ISBN 978-92-4-004716-7 (print version)

Suggested citation. Report of the technical consultation on innovative clinical trial designs for evaluating new TB preventive treatments: virtual meeting, 15-17 September 2021. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Contents

Acknowledgements

The meeting report was drafted by Saskia den Boon, with contributions from Dennis Falzon and Matteo Zignol, under the overall guidance of Tereza Kasaeva, Director of the WHO Global Tuberculosis Programme. WHO acknowledges with gratitude the contributions of participants in this consultation and the administrative personnel who made this meeting possible and productive. Yohhei Hamada and Molebogeng (Lele) Rangaka, both from the Institute for Global Health and the Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL), drafted the concept note and helped organize the meeting. Elena Pallari and Genevieve Wills, both also from the MRC Clinical Trials Unit at UCL, served as meeting rapporteurs. The report was circulated to all participants for review ahead of finalization.

Abbreviations

1HP	1 month of daily rifapentine plus isoniazid
3HP	3 months of weekly rifapentine plus isoniazid
6H	6 months of daily isoniazid
9H	9 months of daily isoniazid
AIR	averted infections ratio
BCG	bacille Calmette–Guérin
COVID-19	coronavirus disease 2019
GRADE	Grading of Recommendations Assessment, Development and Evaluations
GTB	Global Tuberculosis Programme
IGRA	interferon-γ release assay
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials network
IMPAACT4TB	Increasing Market and Public health outcomes through scaling up Affordable Access models for short Course preventive therapy for TB
IPT	isoniazid preventive treatment
PrEP	pre-exposure prophylaxis
MDR-TB	multidrug-resistant tuberculosis
MRC	Medical Research Council
RCT	randomized controlled trial
SATVI	South African Tuberculosis Vaccine Initiative
TB	tuberculosis
TPT	tuberculosis preventive treatment
TST	tuberculin skin test
UCL	University College London
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

Executive summary

The World Health Organization (WHO) Global Tuberculosis Programme, in collaboration with University College London and other partners, convened a virtual technical consultation from 15 to 17 September 2021 that focused on innovative clinical trial designs that could be used for evaluating new tuberculosis (TB) preventive treatments (TPTs). The objectives of the meeting were to identify and summarize challenges in designing future TPT trials and to explore innovative designs that could facilitate advances in biomedical TB preventive interventions and would complement similar developments in other fields relevant to TB prevention. Discussions were organized in four main sessions.

Session 1: Models of delivery

Although TPT is an effective intervention, its uptake has been poor. The barriers along the cascade of care for TB prevention have been well characterized and studied in recent years. In addition to these barriers, there are a lack of prioritization by providers, programmes and governments, and a lack of financing, as well as limited access to diagnostics and anti-TB medicines, and there are also patient-related factors. Efforts to scale up TPT have also been adversely impacted by mitigation measures for coronavirus disease 2019 (COVID-19), and they need to be accelerated as part of recovery in the postpandemic phase.

Pragmatic clinical trials can evaluate strategies to overcome some of the well-known barriers to TPT implementation. This first session of the meeting described how trials can become person-centred by researching whether offering choices improves the uptake of an intervention; patient-level barriers, motivators and behaviours before and during TPT; the reasons why people might refuse or stop TPT; and patients' costs in accessing health care. Developing interventions with patients, providers and other stakeholders and using methods that address an individual's context, as well as implementing different rounds of testing, are likely to increase acceptability and uptake.

When trials are conducted in multiple countries and in a variety of settings (e.g. including rural and urban settings), insights can be obtained about which proposed solutions might be generalizable to other settings and which ones might not be. It is crucial that research findings are shared with national or provincial TB programmes and that sustainable funding is made available to scale up interventions that are shown to work.

Session 2: Estimating the benefits and harms of TPT

The context of research on TPT is changing, along with the populations prioritized for TPT. These changes will have an impact on the design of future trials. For example, the prospect of new TB vaccines and the expanding number of TPT regimens mean that for future trials more than one option will be available for the standard of care for participants. For HIV prevention trials, which face a similar diversity of comparator groups, the Joint United Nations Programme on HIV/AIDS and WHO's Global HIV, Hepatitis and Sexually Transmitted Infections Programme have issued a statement emphasizing that the standard of preventive care should be upheld in trials of HIV prevention and that participants must be provided with

preventive interventions that reflect guidance from WHO. A similar statement might be desirable for TB trials. It might also be desirable to explore what the minimum preventive package should entail.

To promote the uptake of TPT, greater value should be placed on its community-level benefits. While some trials of TB screening and prevention have been able to show the community-level impact on TB incidence, these outcomes are often not measured in trials, and the impact on the transmissibility of TB is often insufficiently acknowledged. Nevertheless, while TPT benefits communities as well as individuals, the risks are solely borne by individuals. Trials usually report on benefits (e.g. efficacy) and risks (e.g. adverse events) separately and leave the risk–benefit assessment to external groups, such as guideline development groups. Conducting risk–benefit analyses of outcomes within trials would allow the superiority of a treatment to be shown in its totality by comparing it with a composite outcome of efficacy data, safety data and other factors that are anticipated to make the experimental treatment superior to the standard treatment. The composite outcome is created by scoring or ranking combinations of outcomes in terms of their overall desirability, which can be based on stakeholders' preferences and incorporate patient-important outcomes.

Session 3: Trial design and analytical approaches

Part 3A: Biomarkers and the spectrum of TB

Innovations in the identification of biomarkers to monitor treatment response and cure offer the possibility of developing innovative designs for trials of treatment for TB disease. For innovation in TPT trials, we most urgently need biomarkers as surrogate end points for disease that can assess who will progress from TB infection to TB disease and also identify those who would benefit from TPT. Identifying biomarkers that after successful treatment of infection return to the levels observed in people who are not infected would allow for efficient trial design and smaller sample sizes. Promising biomarkers, including transcriptomic biomarkers in blood and immunogenetic predictors of TB disease and incipient TB, have been and are being evaluated in TPT trials.

A biomarker that can accurately identify patients on different stages of the TB spectrum, from infection to disease, could be used for a stratified medicine approach in which patients are grouped based on their risk of disease or response to therapy. This could mean that different treatments may be tested for TB infection, incipient TB, subclinical TB without symptoms, TB disease with symptoms and quiescent or controlled TB (e.g. treating incipient or subclinical TB with a shorter TPT-like regimen instead of a full TB treatment regimen, or with a regimen for TB disease but for a shorter duration). If proven effective, stratification would bring obvious benefits, given that the one-size-fits-all principle is not suited to a condition that covers a spectrum of pathologies. These benefits would extend to the conduct of clinical trials, where there could be benefits to subgroups of patients that are masked by the unstratified results of a clinical trial.

Part 3B: Eligibility criteria and selection of trial populations

The optimal target population for TPT – and thus for inclusion in a clinical trial of TPT – is one with the highest risk of TB disease. However, the tests currently used to diagnose TB infection are imperfect, and no tests exist that predict progression from infection to clinical disease. The individuals at highest risk can be identified through a combination of clinical and epidemiological factors (e.g. close contacts of someone with TB, those who are HIV-positive) and tests such as the interferon-γ release assay and the tuberculin skin test. There is hope that tests for transcriptomic signatures conducted at the point of care will further improve the accurate identification of high-risk people, which has the potential to reduce the sample size of trials. In the meantime, eligibility criteria should include consideration of whether participants need to be tested for TB infection, and test imperfections must be explicitly considered when designing and powering noninferiority trials.

Part 3C: Dealing with few TB events

This session focused on novel methods that can be used to address problems arising from the small number of TB events, particularly in trials with a noninferiority design in which the risk of a control event that is lower than assumed can quickly lead to a loss of power. A new summary measure that has been useful in HIV prevention trials was discussed: the averted infections ratio (AIR). The AIR is the ratio of the number of infections averted in the experimental arm to the number of infections averted in the control arm. This concept may have application for TPT trials in addressing the problem of rare events.

Other solutions were proposed to deal with the low number of events in trials using a noninferiority design, including deciding at the design stage whether the noninferiority margin should be expressed as an absolute or a relative risk, and reviewing the noninferiority margin at the interim analysis to determine whether the risk among the controls has been correctly estimated. The power-stabilizing noninferiority frontier, a curve defining the most appropriate noninferiority margin for each possible value of the control event risk, was introduced as a prespecified approach for adapting the margin. This metric might also help define margins for high- and low-risk groups.

Session 4: Trial populations