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

Virtual meeting,
15-17 September 2021
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Acknowledgements

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### Abbreviations

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

Part 4A: Strategies for determining individual- and population-level efficacy and safety in different risk groups

Innovative strategies and study designs are needed to determine individual- and population-level efficacy and safety in different risk groups, including those for whom TPT is not systematically recommended owing to a lack of evidence. This could, for example, be done by using basket trial designs in which cohorts of patients are recruited to different “baskets”. For baskets that lack power, perhaps owing to difficulty in recruiting, additional information can be borrowed from other groups (i.e. from within the trial or from other trials) or based on expert opinion. The basket design aims to draw conclusions about the efficacy of the treatment within each subgroup of the trial.
An alternative way of estimating the efficacy and safety of TPT in different risk groups is by extrapolation and decision analytic modelling that looks at quality-adjusted life-years resulting from alternative courses of action (i.e. providing or not providing TPT) for various risk and age groups. However, modelling may not provide sufficient evidence to make recommendations about which risk groups should receive TPT, especially in situations in which persons have not only an increased risk of developing TB but also a potential increased risk of developing adverse reactions to TPT.

Part 4B: Special populations

This session addressed trial designs that could be used for special populations, including people with diabetes, household contacts of people with drug-resistant TB, children and pregnant women. Each of these groups poses specific challenges to designing trials. For people with diabetes, the trial population typically consists of older patients with comorbidities and comedication that could lead to drug–drug interactions and the challenges of distinguishing adverse events from TPT from the effects of diabetes (e.g. peripheral neuropathy). For this population there are no recommendations for systematic testing for TB infection and for TPT, so the control group in a trial of people with diabetes does not need to receive TPT, particularly because there is often not enough information about the efficacy of a treatment in this population and its possible harms.

For contacts of patients with drug-resistant TB, the antibiogram of the presumed source case is best determined directly because it cannot be reliably inferred from the prevalent drug-susceptibility patterns derived from community surveys. A high proportion of contacts may have coprevalent TB rather than incident TB. These considerations have implications for the selection and dosing of anti-TB medicines, including for the control group. Integrating pharmacokinetic studies and an evaluation of biomarkers to look at disease progression into trial designs could support research in this specific population.

For children, the risk of disease progression is high and disease progression is fast, which may offer the possibility of shorter follow-up duration. However, careful consideration of trial end points (i.e. the definition of TB disease) is required because children have different disease pathogenesis, which is often paucibacillary and has a wide disease spectrum.

For pregnant women, gestational age matters, and safety outcomes should be addressed for both a woman and her fetus; additionally, there may not be an established standard of care. It could be interesting to use risk–benefit analyses to assess efficacy and safety in special populations in addition to the planned trial outcomes.
Background

The landscape of tuberculosis (TB) prevention is changing fast. In 2018, a high-level meeting of the United Nations General Assembly was dedicated to TB and set ambitious targets for increasing the delivery of TB preventive treatment (TPT) (1). World Health Organization (WHO) guidelines published in 2018 and updated in 2020 expanded the target groups for TPT to all household contacts of people with TB regardless of their age or whether they were HIV-positive (2). Shorter rifapentine-based regimens, including 3-month weekly rifapentine plus isoniazid (3HP) and 1-month daily rifapentine plus isoniazid (1HP), now feature as alternatives to 6 or 9 months of daily isoniazid (6H or 9H). Also of relevance to TB prevention, WHO has recently updated its guidance on TB infection prevention and control and on the systematic screening for TB (3-5). WHO has also published frameworks for evaluating new tests to diagnose TB infection and for evaluating future tests to predict progression from TB infection to TB disease (6-9).

In 2020, WHO published target product profiles for TPT that defined minimum and optimal targets that new regimens should achieve (10). The optimal characteristics of new regimens include a shorter duration (≤2 weeks), superior efficacy and better safety than the current regimens. Long-acting formulations for use in TPT are also desirable (11). Research on TPT needs to accelerate to develop regimens that meet these targets.

In parallel, research on alternative host-directed biomedical interventions to prevent the development of TB disease continues to evolve. During the past few years, trial results raised hopes that there will be an effective, scalable TB vaccine in the near future. The M72/AS01E candidate vaccine showed 51.3% efficacy in preventing TB disease in HIV-negative adults infected with TB, and revaccination of adolescents with bacille Calmette–Guérin (BCG) reduced the rate of sustained QuantiFERON-TB Gold (Qiagen, Germantown, MD, USA) in-tube assay conversion with an efficacy of 45.4% (12, 13). Other host-directed therapies such as metformin, that reduce the deleterious inflammation associated with immune pathology and enhance the antimycobacterial activity of immune cells, are gaining interest for use in preventing TB in people with diabetes (14). A 2019 systematic review of observational studies showed a lower risk of TB disease in people with diabetes who were taking metformin, but this association has not been formally tested in clinical trials (15). TPT in the preventive care pathway has to be evaluated within a rapidly changing landscape in technology, modalities for prevention and public health approaches, all aimed at achieving the same ends. This requires new evaluation frameworks and normative guidance to address methodological challenges.

The WHO Global Tuberculosis Programme (GTB), in collaboration with University College London (UCL) and other partners, convened a virtual technical consultation from 15 to 17 September 2021 that focused on innovative clinical trial designs for evaluating new TB preventive treatments (Annex 1). 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. The list of participants is reported in Annex 2.
Introduction

After a welcome by Dr Saskia den Boon (WHO GTB), Dr Tereza Kasaeva (Director, WHO GTB) opened the meeting.

WHO activities on TPT and meeting objectives

Saskia den Boon, GTB, WHO, Switzerland

Dr den Boon spoke about the technical consultation on innovative designs for TB clinical trials for developing new TB treatments that was organized by WHO in 2020 and for which WHO produced a position statement (16, 17). That meeting highlighted advances in pharmacokinetic and pharmacodynamic modelling and biomarkers that had contributed to the development of adaptive and seamless trial designs, making the process of developing effective and safe treatment regimens shorter and more efficient. The current meeting was convened to explore whether similar innovations and advancements could also improve trial design and analyses for TPT regimens. She explained that the meeting could also learn from developments in other fields, such as postexposure prophylaxis for HIV, that may have comparable characteristics to trials for TPT. Dr den Boon also presented the declarations of interest of the meeting participants (Annex 3).

Session 1: Models of delivery

Introduction

Chairs: Thu Anh Nguyen, Woolcock Institute of Medical Research, Viet Nam, and The University of Sydney, Australia, and Susan Swindells, University of Nebraska Medical Center, USA

Professor Swindells introduced the session by emphasizing that TPT is effective, but the uptake is poor. Trials can address barriers to the implementation of TPT for all steps along the cascade of care for TB prevention including (i) identifying those who are eligible for TPT and linking them to care, (ii) testing for TB infection, (iii) providing medical evaluations to exclude TB disease, and (iv) ensuring initiation and completion of TPT. However, several areas need to be addressed to enhance the implementation of TPT including the lack of (i) prioritization by providers, programmes and governments; (ii) access to diagnostics and anti-TB medicines; (iii) financing and (iv) understanding of patients’ perspectives. The need for research in these areas was identified in 2019 during a WHO consultation organized in collaboration with McGill University (18, 19).

Dr Nguyen then introduced the questions for the session and the speakers.

Questions for the session

- Which types of trials are needed to address the challenges of implementing TPT?
- How can we address patient-important outcomes in trials?
- How can trials address gaps in the delivery of TPT?
- Which implementation challenges are not being addressed in clinical trials?
**Addressing TPT needs with trials**

**Gavin Churchyard, Aurum Institute for Health Research, South Africa**

Professor Churchyard highlighted research gaps in barriers to implementation, the cascade of prevention and for specific risk groups, and indicated where trials could provide evidence (17, 18). He then explained that WHO uses the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework to rate the certainty of evidence used to inform recommendations. The grading of the certainty of evidence is influenced by a trial’s design: the highest quality evidence is from well-conducted randomized controlled trials (RCTs), while observational studies can provide epidemiological data and identify gaps in the TPT cascade. Professor Churchyard then discussed different study designs (e.g. observational studies, RCTs, phase IV/pragmatic trials, phased implementation and cluster-randomized studies) and used examples to illustrate which types of evidence can be collected with each of these designs. He gave examples of the PHOENIx feasibility study (20), the DOLPHIN trial (21), the BRIEF TB trial (22), the One-to-Three trial (starting in August 2022), WHIP3TB trial (23), the CORTIS trial (24), the THRIO study (25) and three trials that are evaluating treatment for TB infection in contacts of patients with drug-resistant TB: the TB-CHAMP (26), VQUIN MDR (27) and PHOENIx studies (https://clinicaltrials.gov/ct2/show/NCT03568383). He then used examples of several community-wide studies to show that mass TB screening that is simultaneously linked to treatment for TB infection or disease reduces TB burden (28-32). He reiterated the importance of conducting further research to address barriers to implementation in the TPT cascade and gaps specific to certain high-risk populations. He emphasized the importance of trials in generating high-quality evidence to inform policy and practice for TPT.

**Opt-out studies**

**Christopher Hoffmann, Johns Hopkins University School of Medicine, USA**

Dr Hoffmann proposed a model of TPT delivery with service delivery on one side (i.e. policies, guidelines, payers, national programmes, health systems, care settings, health care workers) and service uptake on the other (i.e. patients, including their belief system, expectations, experiences, medication tolerability and relationships; and social institutions and community). Once policy has been set and supplies made available, the critical aspect for TPT delivery and uptake is at the clinician–patient level. Clinicians need to be able to effectively integrate TPT assessment, prescribing and patient education within other time-constrained clinical tasks. Another bottlenecks to TPT implementation is a lack of confidence by the provider in reliably ruling out TB, with concerns about inducing drug-resistant TB by inadvertently giving TPT to patients who need TB treatment (33-37). Because algorithms are often complex and cannot provide certainty (e.g. certainty that TB has been ruled out), the health care provider faces a high cognitive load and decision fatigue when shifting from the default position of no TPT to providing TPT.

Choice architecture is an implementation strategy that can help clinicians overcome this cognitive load; it aims to make the medically preferred choice the easiest one and the default option for busy clinicians. It shifts decision-making from who should receive TPT to who should not receive it. While this is a subtle difference, it can make dramatic changes in
service delivery. In a study in South Africa, choice architecture was operationalized in three steps: (i) those who should not receive TPT were identified, (ii) clinicians were advised to accept medical uncertainty, and (iii) implementation was assisted through the use of work aids and an electronic system to check prescriptions (38). As part of IMPAACT4TB, (Increasing Market and Public health outcomes through scaling up Affordable Access models for short Course preventive therapy for TB) a similar study in Malawi, Mozambique and Zimbabwe, known as Choice Architecture for TPT, (https://clinicaltrials.gov/ct2/show/NCT04466293) aims to test a feasible, low-resource strategy to achieve levels of TPT delivery that are substantially higher than routine. Furthermore, the Prevent TB: Choice Architecture for TPT Delivery trial (https://clinicaltrials.gov/ct2/show/NCT04466488) is a cluster-randomized trial that allows for additional primary data to be collected to assess a clinician’s cognitive load. Thus, these studies aim to determine whether reducing cognitive load, such as through using choice architecture, aids in the delivery of TPT.

Opt4TPT study: optimizing the delivery cascade for TPT among people living with HIV: a multicountry programme evaluation

Violet Chihota, Aurum Institute for Health Research, South Africa

Dr Chihota discussed the challenges that arise in moving from evidence to delivery at scale and often result in long delays in shifting from discovery to implementation. These issues raise questions about how to reach implementation goals in low- and middle-income countries. The Opt4TPT study (https://www.impaact4tb.org/opt4tpt-study/) uses multidisciplinary approaches and systematically applies them to understand the delivery of TPT in countries introducing new regimens.

The aim of the Opt4TPT study is to generate knowledge to improve the uptake and scale up of TPT among people living with HIV. The study consists of two parts. The first is a prospective cohort that studies patient-level factors through qualitative analysis, including assessing patients’ costs to access care. The second part analyses health care systems to understand providers’ attitudes towards prescribing through direct observation and semistructured self-administered questionnaires. The aim is to make recommendations about how to optimize TPT delivery. The study is ongoing in Ethiopia, South Africa and Zimbabwe. In each country, two sites are implementing 3HP and one site is implementing isoniazid preventive treatment (IPT).

The primary objective of the study is to quantify the TPT continuum, from treatment initiation to completion, among people living with HIV who are eligible for TPT and to understand better what is happening from the time when people initiate treatment until they complete it. The second objective is to identify key characteristics of the health system and providers, including models of care used in TPT prescribing, from the patient’s and clinician’s perspectives. Secondary objectives are to describe reasons why people refuse, discontinue or complete TPT; to describe the incidence of adverse events, comparing individuals on TPT to those on antiretroviral treatment who are not receiving TPT; and to evaluate the medium-term economic benefit of TPT. The study also aims to assess whether TPT implementation complies with local guidelines, provider-level barriers and facilitators to
TPT delivery, and to compare TPT delivery within differentiated care models for people living with HIV. The exploratory objectives are, first, to measure the incidence of TB disease and all-cause mortality among individuals enrolled into the study and to assess associated factors, focusing on those related to TB and TPT use; and, second, to measure resistance to anti-TB medicines among patients with TB, stratified by TPT status (i.e. on TPT, completed TPT, no history of TPT). Factors that will be considered in the study include patients’ journeys, beliefs and costs, as well as adverse events and clinic-level factors, such as providers’ attitudes. Several nested qualitative and costing studies are also being conducted, with the ultimate aim of providing recommendations on optimizing the delivery of TPT.

Reducing the gap between policy and practice: example of the ACT4 study – enhancing the public health impact of the diagnosis and treatment of TB infection

Thu Anh Nguyen, Woolcock Institute of Medical Research, Viet Nam, and The University of Sydney, Australia

Dr Nguyen discussed the ACT4 study, which aims to evaluate the effectiveness of a standardized public health evaluation to increase the number of people starting TPT among household contacts of patients with pulmonary TB (39). The multicountry study was designed as a pragmatic cluster-randomized study; in Viet Nam it was conducted in two areas: a city and a rural area.

Key aspects that contributed to the successful implementation of TPT were (i) testing for TB infection, which provided evidence of infection and acted as the key to convince people of the need for treatment; (ii) screening household contacts while the index patient was in the process of initiating treatment; (iii) using a one-stop-shop model of care, which was appreciated by contacts; (iv) implementing health education and encouraging household contacts to be screened for TB infection; (v) providing logistical support to districts and ensuring frequent face-to-face supervisory visits for clinicians; (vi) including leadership boards, TB doctors, radiology technicians and paediatricians in training for TB clinic staff at district sites; (vii) having health care providers with good counselling skills, (viii) changing the terminology used from TB prophylaxis to treatment of TB infection; (ix) developing incentive systems based on health insurance payments, which motivated staff to provide TPT; (x) using integrated monitoring and in-service training, which allowed the intervention to be sustained.

After the trial concluded, key steps to support scale up were identified and presented to stakeholders at the national and provincial levels to encourage their interest and commitment. Cost components and potential funding sources were identified, and a cost calculator was developed to support scale up. The findings of the study also led to the prioritization of provinces for TPT scale up, based on their burden of TB.

Dr Nguyen explained how the researchers negotiated with stakeholders to obtain funding for provincial programmes to scale up the intervention and how they worked with health insurance providers in Viet Nam to develop reimbursement mechanisms for the TPT programme. Ensuring that the financial incentives were in place for the system and staff, based on hospital financing mechanisms, was considered essential for the sustainability of the programme.
Professor Cattamanchi introduced the 3HP Options trial, a pragmatic, hybrid randomized trial assessing the implementation and effectiveness of different strategies for delivering the 3HP regimen (40). The primary objective is to compare the acceptance and completion rates of 3HP under three delivery strategies: facilitated directly observed therapy, facilitated self-administered therapy and allowing the patient to choose between the two using a standardized decision aid (40). The hypotheses are that the proportion of people living with HIV who accept and complete the 3HP regimen can exceed 80% in settings with a high burden of HIV/TB coinfection and the proportion that accepts and completes the regimen will be highest among people living with HIV who are randomized to the informed-choice arm, in which patients choose their delivery strategy. Secondary objectives focus on costs, cost–effectiveness, implementation outcomes and adverse events, as well determining the cumulative 16-month incidence of TB disease in each study arm. The three delivery strategies are facilitated, meaning that they are intended to target barriers to 3HP completion. Both the observed and self-administered arms involve pretreatment counselling to provide information about the risks and benefits of TPT. They also include streamlined clinic visits, dosing reminders, adverse event monitoring, travel cost reimbursement and adherence documentation.

The 3HP delivery strategies are based on implementation science and behavioural theory that acknowledges that behaviour is determined by capability, motivation and opportunity (41). Other important concepts are informed choice and shared decision-making, which grew out of initial formative work and a hypothetical trial that identified eight key factors influencing decisions about the choice of strategy: time, job obligations, stigma, side effects, connection to the health worker, ease of travel, autonomy and cost.

Professor Cattamanchi explained that the researchers were interested in using digital adherence technologies and wished to adapt them to the local context for 3HP using human-centred design methods. Early design work showed strong dislike of electronic pillboxes, which patients found highly stigmatizing. Therefore, an adapted version was implemented, using local fabrics along with a card insert describing how to take the medicine, a toll-free number to call to confirm dosing and a motivational message.

Dr Semitala provided some preliminary results. By 1 September 2021, 33% of eligible participants were enrolled in the trial. Interim analysis shows that 3HP is highly acceptable, and there has been a 93% completion rate. Key findings from qualitative interviews showed that patient acceptance and completion of 3HP are impacted by process factors, such as having adequate information about 3HP provided at enrolment, a supportive clinic environment, weekly dosing and a choice between strategies. Contextual factors impacting patient acceptance and completion of 3HP were support from family or significant others, disclosure to family or significant others, knowledge of the lack of side effects among friends or contacts also receiving TPT and the impact of the coronavirus disease 2019 (COVID-19) pandemic.
In summary, the 3HP Options trial is evaluating delivery strategies that target key barriers to 3HP uptake and completion. The strategies were informed by behavioural theory and principles of human-centred design. The trial design and its execution make this a highly pragmatic study.

Discussion

The discussion started with a question about which elements need to be emphasized to make a stronger public health case for TPT. It was suggested that to build a value proposition for TPT, a package of evidence needs to be assembled that demonstrates the effectiveness of the treatment, its safety, and its acceptability and feasibility. Additionally, cost-effectiveness and budget information are essential to ensure sustainable funding.

Offering a choice of treatment or treatment delivery mechanism accommodates personal preferences and might help implementation. In the 3HP Options trial, the acceptability of the pillbox was evaluated by offering participants different options and interviewing them about their opinions. The potential implications of stigma associated with TPT should be considered.

Co-developing interventions with patients, providers and other stakeholders is likely to increase acceptability and uptake. This strategy requires different rounds of testing using different methods of human-centred design.

Other incentives, such as the one used in Viet Nam – where the provincial budget for the TB programme gave a cash incentive to health workers when a household contact completed treatment – were also considered to be interesting. In Viet Nam, it was crucial that health insurance complemented these treatment enablers by covering the cost of diagnosing TB infection and providing TPT.

The one-stop-shop employed in the ACT4 trial was designed in such a way that TB patients and their family members could go to one place in the hospital where contacts could all be screened for TB disease and TB infection. For chest radiography, they had to go to another department in the same hospital. When the whole family goes to the hospital together for TB services, it saves time and travel costs, and it increases the feeling of safety.

The discussion then turned to the tuberculin skin test (TST). While researchers in Viet Nam had initially thought this might be a barrier to TPT implementation (i.e. it requires two visits, there are occasional stock-outs of reagent), it actually appeared to enhance uptake since it showed people evidence of TB infection, thus increasing their motivation to start and complete TPT.
Session 2: Estimating the benefits and harms of TPT

Introduction

Chairs: Richard Chaisson, Johns Hopkins University School of Medicine and Bloomberg School of Public Health, USA, and Lele Rangaka, Institute for Global Health and the Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL), United Kingdom

Professor Chaisson explained that the session would expand the scope of the discussion to consider more than the traditional end points in clinical trials of TPT to explore both individual and societal aspects of TPT. For TPT, the risks are borne by individuals, but the benefits accrue largely to the community. Dr Rangaka added that the main motivation for the session was to show that the context for research on TPT is changing, along with the priority populations for TPT. The interpretation of risks and possible harms and ways in which populations are engaged will frame future trials.

Questions for the session

• Is TB incidence the best primary outcome? Can we incorporate patient-important outcomes and, if so, how?
• How can we better evaluate the balance between benefits and harms within trials?
• What are the key ethical considerations for TPT trials?

Benefits and harms for individuals versus communities

Guy Marks, University of New South Wales Sydney, Australia

Professor Marks reasoned that screening and prevention of noncommunicable diseases benefit the individual, but for communicable diseases, the benefits extend far beyond the individual. The ACT3 study was a cluster-randomized controlled trial for TB disease conducted in the southernmost province in Viet Nam, which has a population of just over 1 million and a high prevalence and incidence of TB (42). Sixty clusters were randomized to the intervention (i.e. active screening for TB disease for all resident adults for 4 years) and 60 clusters were randomized to standard passive case detection. This latter group was screened for TB disease only in the final year of the study.

In the final year, there was a 44% reduction in TB prevalence in the intervention group compared with the control group. Additionally, the benefits extended far beyond the individuals who were screened and treated for TB. For example, a post hoc analysis of children born between 5 and 14 years before the study was conducted found that the prevalence of TB infection was 4% in the intervention cluster compared with 8% in the control cluster – that is, there was a 50% reduction among the children despite them not receiving the intervention. In addition, it was thought that many cases of TB were prevented because of the active identification of people with TB infection, followed by administering TPT to those who were eligible.
In summary, there are three types of benefits from interventions for infectious diseases. The first benefit accrues only to the individual, for example, when optimal critical care is provided to COVID-19 patients. The second accrues only to the community including the health services, for example, when those who have COVID-19 isolate and when the population wears masks. The third benefit accrues to both the individual and the community, for example, through vaccination. These considerations are important when evaluating the benefits and harms of TPT, including ethical considerations.

Applying a risk–benefit analysis to outcomes in TB clinical trials
So Yeon Kim, Frontier Science Foundation, USA

Dr Kim discussed applying risk–benefit analyses to TB trials, which are defined as using a systematic approach to examine safety and efficacy jointly (43). In noninferiority studies, there is an implicit assumption that there is a benefit from the intervention (e.g. fewer adverse events, improved tolerability) that offsets a small loss in efficacy compared with the standard of care. However, 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 (43). Furthermore, the noninferiority margin is often based on a subjective assessment and is often controversial. As an alternative, Dr Kim suggested that it is possible to show the superiority of a treatment in its totality by comparing it using a composite outcome of efficacy data, safety data and potentially 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. This composite outcome can be based on stakeholders’ preferences and can incorporate patient-important outcomes.

This approach was used in the BRIEF TB trial (22), a noninferiority trial comparing 1HP with 9H. The primary outcome in the original study was a binary composite of TB disease and death from TB or death from an unknown cause (any versus none). A composite risk–benefit scoring system of six categories was developed, combining measures of efficacy (i.e. TB, no TB) and safety (i.e. grade ≤2, grade 3, grade 4), with death as a seventh category. Clinical TB investigators were asked to assign scores to the seven categories. BRIEF TB participants were scored based on their experience during the trial, and study arms were compared in a post hoc analysis using this risk–benefit outcome, with superiority assumed in the trial design.

Future work could incorporate other factors, such as quality of life and patients’ preferences, and capture a greater complexity of events, such as a more refined scale of adverse events or the total number of adverse events experienced by an individual.

Power and sample size considerations should be no less rigorous than when designing trials that consider efficacy and safety outcomes separately. Ideally, the outcome distributions should be informed by data gathered from similar populations using data collection methods that are identical to those that will be used in the planned study. The proportion of participants expected to fall into each outcome category has implications for power. Simulations can be used to select a sample size that will allow the study to detect meaningful differences with high power by utilizing existing data sets and combining them with assumptions about the experimental treatment (e.g. mechanisms of action, preclinical
and early clinical data). Statistical power is not usually increased by using the risk–benefit outcome compared with a noninferiority trial that balances risks and benefits.

Ongoing studies can be used to elicit patients’ preferences for future RCTs that have similar objectives and are conducted in similar populations, and these trials can include the risk–benefit analysis as a secondary objective to gain experience using the outcome and learn its properties.

In summary, if well-designed, a risk–benefit analysis may allow researchers to compare study arms using a superiority trial design. The risk–benefit analysis uses an overall outcome that considers the totality of participants’ experiences, including clinical benefit and adverse events. It can be easily extended to outcomes from several domains and related individuals (e.g. mother–child dyads). Gaining acceptability for risk–benefit analyses as primary outcome measures could be challenging, but including the risk–benefit analysis as a secondary objective adds value and builds an understanding of its operating characteristics.

**Ethics of preventive treatment trials**

*Rieke van der Graaf, University of Utrecht, Netherlands*

Dr van der Graaf has applied research ethics guidance that was recently published for trials of HIV prevention to TB prevention. She highlighted the eight ethical principles of clinical research and emphasized that all are relevant to research on TPT; the research must have (i) social value, (ii) scientific validity, (iii) unbiased selection of participants, (iv) a favourable risk–benefit ratio, (v) independent review, and include (vi) informed consent, (vii) respect for human participants and (viii) collaborative partnerships (44, 45). She then highlighted three areas to discuss in more depth: (i) the need for additional and new TB prevention methods, (ii) the standards for prevention and (iii) the delivery of TPT to populations who live in social contexts of vulnerability.

There is a clear need for new methods to prevent TB, including better vaccines and TPT that includes shorter regimens and has better safety profiles. However, TB prevention trials are challenging because the events investigated (e.g. TB disease or death) are rare, which translates to a need for large trials to obtain the required power. Ensuring strong collaboration between all relevant stakeholders can move this area forward.

Compared with interventions to prevent HIV, the package of interventions that prevent TB is relatively limited and includes, in addition to TPT, TB infection prevention and control strategies and BCG vaccination for infants. The possibility of new vaccines and the expansion of treatment options for TPT mean that for future trials more than one option is available for the control (standard of care) arm of the trial. The Joint United Nations Programme on HIV/AIDS (UNAIDS) 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. The challenge remains to define the standard of preventive care that should be provided to all trial participants in both the intervention and control groups.

Those who are at high risk of TB infection or disease, or both, are likely to benefit most from
TPT, but these people are often also in need of special ethical protections because they are considered vulnerable populations owing to their social, political or economic context. Researchers and their sponsors should be mindful of the need to collaborate with communities and appropriate civil society stakeholders to incorporate relevant input and ensure community support.

Developing specific ethical guidance for trials of TPT might help to prevent unnecessary delays in designing, approving and conducting such trials, and may also strengthen protection for trial participants (46).

Discussion

The presentations in this session raised the issue of whether combined risk–benefit outcome measures can provide a way to rigorously assess questions of social value and be incorporated in the design of studies. These measures may be able to deliver evidence for the sections on values and preferences and equity of the GRADE framework, which WHO uses to review evidence for recommendations. The session also emphasized the importance of ensuring community engagement and developing collaborative partnerships.

Dr Kim explained that she works closely with the AIDS Clinical Trials Group and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) networks to bring patients’ perspectives into trials. In addition, input on risks and benefits can also be incorporated from other stakeholders, such as policymakers. She advised using the risk–benefit approach for secondary outcomes in trials to gain experience and understand better how this strategy works and which factors affect power. In noninferiority trials, researchers are willing to accept slightly worse efficacy to gain a benefit in other areas, and this is reflected in the noninferiority margin, which is implicitly based on value judgements; these value judgements could be based on more rigorous methodology. Quantitative benefit–harm assessments were proposed as an approach that explicitly takes into account patients’ preferences (47, 48).

The point was raised that death is generally undervalued as an outcome, particularly in young and healthy people who are the target of TPT efforts. Especially when a composite outcome combining disease and death is used, which is often done to limit sample size, death is weighted similarly to disease despite that the seriousness of these two end points differs. The discussion then centred around methods for assigning a relative value to the outcome of death. In Dr Kim’s experience, clinicians indicate that death is not always considered the worst possible outcome and when scoring different disease states, they were able to propose disease states as a trade-off with death. Discrete choice experiments, which have been used by social scientists to elicit patients’ preferences, can incorporate probabilities of events, including death, and the results from these can be used to determine trade-offs. A counter-argument was raised: because it is known that TPT prevents TB disease and death from TB, that no longer needs to be proved and that is why noninferiority trials are conducted.

It was re-emphasized that when analysing trials, TB is often treated as a noncommunicable disease and that its transmissibility is often insufficiently acknowledged in trials. Trial
end points have to reflect better that preventing an episode of TB in one person prevents disease and death in others. For example, the Bethel study (29) showed dramatic declines in TB incidence in control households as well as in intervention households, and this could be attributed to the intervention, similar to the community-level benefit from the Viet Nam study presented by Dr Marks.

Session 3: Trial design and analytical approaches

Introduction

Chair: Angela Crook, MRC Clinical Trials Unit at UCL, United Kingdom, and Dick Menzies, McGill University, Canada

Professor Crook explained that the session would focus on TPT trial design and analysis, as well as issues around the limitations of existing diagnostic tests, the lack of biomarkers and trial entry criteria. Part 3A would review promising biomarkers across the spectrum of TB disease and consider the use of a stratified medicine approach for TPT trial design. Part 3B would focus on eligibility criteria and selecting trial populations, given the limitations of current diagnostics and the imprecision of the tests as well as the lack of a gold standard. Part 3C would discuss novel methods that can be used to address problems arising from the small number of TB events, focusing on noninferiority issues, and introduce a new summary measure: the averted infections ratio (AIR), which has been successfully used in HIV prevention trials.

Questions for the session

- Is there a role for surrogate markers and end points for preventive efficacy in TB prevention trials?
- Are there promising biomarkers in the pipeline, and what are their characteristics?
  - Are there biomarkers for end points?
  - Are there biomarkers for selecting populations who are likely to benefit most from TPT?
- How can we evaluate these markers in TB prevention trials?
- How can patients be selected for trials, considering the limitations of current tests used to identify those at highest risk for developing TB disease?
- Can novel designs or statistical measures help new TB prevention trials so they are conducted more efficiently and reliably?

Part 3A: Biomarkers and the spectrum of TB

Promising biomarkers and their utility in TPT trials

Morten Ruhwald, FIND, Switzerland

Dr Ruhwald discussed the spectrum of TB as a continuum of stages, from no infection to TB infection to incipient TB to subclinical TB without symptoms and to TB disease with symptoms (49). Currently, no tests can assess who will progress from TB infection to TB
disease or identify those who would benefit from TPT. Biomarkers that predict clinical outcomes are needed to detect phenotypes associated with progression or later disease, and these could potentially be used as end points for shorter and smaller trials of TPT, as well as biomarkers that identify the individuals at highest risk for these outcomes, which could identify at-risk individuals to aid in patient selection for clinical trials.

Current diagnostics are of limited use in identifying incipient, subclinical or minimal disease. However, new tests and tools are in the pipeline that may allow better elucidation of the area between incipient and subclinical disease. These include new chest X-ray technologies that use artificial intelligence to deliver segment-specific objective scoring, masks that capture aerosols and bacteria in exhaled air, identification of transcriptomic signatures in host blood and immunology markers.

Evaluating biomarkers in TB prevention trials: example of the CORTIS trial

*Thomas Scriba, South African Tuberculosis Vaccine Initiative (SATVI), University of Cape Town South Africa*

Professor Scriba described the CORTIS trial, which aimed to use a transcriptomic biomarker in blood to identify those with early TB, allowing someone with a positive signature to receive an early intervention (24). The study was conducted in five communities in South Africa. Participants with the RISK11 signature were randomized to 3HP or to a control arm consisting of observation only. In addition, a random selection of patients who were negative for RISK11 was assigned to the observation arm.

RISK11 scores were correlated with the spectrum of disease, and higher scores were associated with advanced disease. Of all participants with TB disease identified at baseline, 82% had no clinical symptoms. RISK11 did not meet the minimum target product profile criteria for a triage test for asymptomatic disease because the area under the curve was 0.7, but it performed much better for symptomatic disease, with the area under the curve = 0.97. RISK11 had good prognostic potential for incident TB in the subsequent 6–9 months; it did not meet the WHO target product profile criteria for a test for incipient TB over a longer period, during which both sensitivity and specificity were reduced.

Results of longitudinal follow up of some participants in the CORTIS trial looked at how stable the signature was and found that among those who were negative for RISK11 at baseline, 13–14% converted to positive, but most of those cases returned to negative, so the signature seemed to be only transiently positive. Most, but not all, of those who started with a positive signature and received 3HP in the trial returned to a negative signature and remained negative. However, most of those who were initially positive for the RISK11 signature and who did not receive 3HP, also returned to a negative result and remained negative. It is possible that transcriptomic signatures in this study were affected by respiratory viral infections, leading to a transient, false-positive RISK11 score.

Blood biomarkers reveal the spectrum of *Mycobacterium tuberculosis* infection and disease to some degree and can identify those at risk for progression who can benefit from early intervention. 3HP was not efficacious in the CORTIS trial in a high-incidence setting where most participants were positive by interferon-γ release assay (IGRA). It was not possible to
say whether this was due to reinfection, because 3HP was not sterilizing *M. tuberculosis* or because RISK11 is not a suitable signature for predicting who will benefit from TPT.

**Immunogenetic predictors of active and incipient TB**

Timothy Sterling, Vanderbilt Institute for Global Health, USA

Professor Sterling presented preliminary data from the Regional Prospective Observational Research for TB (RePORT) Brazil study that will evaluate immunogenetic predictors of TB disease and incipient TB, and he discussed the implications for TB prevention trials. Follow up of 24 months was completed in June 2021. Patients with culture-confirmed pulmonary TB were in cohort A (n = 1055) and close contacts of these people were in cohort B (n = 1835).

In cohort B, 25 progressed to incident TB disease (5 [0.5%] of those who were IGRA-negative, 16 [4.5%] of those who did not receive TPT, 3 [1.1%] of those who started but did not complete TPT, and 1 [0.6%] of those who completed TPT), with a median time to progression of 10 months. Of those who progressed, 12 (48%) were confirmed by culture or GeneXpert assay (Cepheid, Sunnyvale, CA, USA), and 19 (76%) had pulmonary TB. Incident cases occurred sporadically throughout follow up, and there was no clustering during the first months after exposure. The risk of progression to TB was similar to that reported in previous studies, and it was higher in those who were IGRA-positive compared with those who were IGRA-negative. Treatment of TB infection significantly reduced the risk of progression to TB. Additional analyses are planned of whole blood transcriptomic signatures, innate and acquired immune responses, and genetic associations.

The optimal target population for TPT and for inclusion in a clinical trial of TPT is those who are at highest risk of TB disease. These individuals could be identified through a combination of clinical and epidemiological factors (e.g. close contacts of someone with TB and those who are HIV-positive) and tests such as IGRA and for transcriptomic signatures, which should ideally be conducted at the point of care. If such identification of high-risk people is successful, then it could reduce the sample size of trials.

**Stratified medicine trial designs and the spectrum of TB**

Payam Nahid, University of California, San Francisco, USA

Professor Nahid argued that bringing the principles of stratified medicine to TB care requires a paradigm shift in care objectives. Stratified medicine – that is, grouping patients based on their risk of disease or response to therapy by using diagnostic tests – is patient-centred, can reduce treatment duration (which impacts toxicity, costs, and resource and health system usage), can enhance cure rates for severest forms of TB and is an alternative to the current one-size-fits-all approach in TB treatment (50).

Points to consider when thinking about stratified medicine for the spectrum of *M. tuberculosis* infection that includes latent, incipient, subclinical and quiescent or controlled TB include the following.
Are the partitions across the spectrum distinct in terms of the strata for severity, risk, or being hard to treat and for clearing the pathogen and achieving durable cure?

Which anti-TB medicines and regimens are optimal for treating the incipient and subclinical forms of TB?

Are the mechanisms of action of the medicines needed to treat TB infection the same across the spectrum, given the different physiological states of *M. tuberculosis* infection?

In cases in which there is a higher burden of bacteria, as is presumed to be the case in the incipient and subclinical states, which anti-TB medicines should be combined, given that the susceptibility status of the infecting strain cannot be known with certainty?

Is there a role for host-directed and adjunctive therapy to disrupt the transition between TB infection and disease, or to clear the pathogen? Such therapies are effective even in the presence of antimicrobial resistance.

Which molecular markers, immunological responses and protein biomarkers are reliable enough to diagnose and to define when TB infection or incipient TB has been successfully treated?

Do children and adults require the same treatments and durations of treatment for TB infection? Do the treatments and durations differ for participants with HIV or diabetes?

Should long-acting or extended-release formulations be favoured in TPT to provide more consistent antibiotic exposure, given that treatment adherence is expected to be low in asymptomatic individuals?

Professor Nahid proposed several priority steps to be taken to help address the questions raised. First, ensuring that data are shared is essential to permit integrated analyses of data from the individual-patient level. Second, it is essential to test regimens of interest in animal models, such as in murine studies that mimic the TB infection spectrum. Third, end points and outcomes of interest for subclinical and incipient TB must be defined and standardized, including developing consensus on biosignatures or biomarkers. This would allow for the development of stratified medicine trials that explore the same regimen with different durations based on biomarkers and the best end points.

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.

**Discussion**

The discussion initially centred around the RISK11 signature, which seemed dynamic in treated and untreated people who were positive for RISK11. There were individuals in the CORTIS trial who were negative for RISK11 at baseline but then developed TB disease, and there were also symptomatic individuals who were RISK11-positive but did not develop TB disease (51). In addition, a group that was RISK11-positive and had viral pathogens was
identified. As a result, it was hypothesized that RISK11 might be a nonspecific marker of pulmonary infection or an indication of a sick versus healthy condition. A participant then asked whether a simpler test might be preferable, such as an assay for C-reactive protein. C-reactive protein has not been studied extensively as a marker of incident TB, but it is not a bad marker and does not perform much worse than transcriptomic signatures (it is now recommended for use by WHO for TB screening in people with HIV) (4). It was agreed that because specificity issues with these transcriptomic signatures limit their application, there is a need to look for more-specific markers.

Questions were also raised about the spectrum of disease and the potential for individualized treatment. Participants noted that TPT, and particularly regimens containing rifamycins, might be effective in treating incipient TB, even though this was not observed in the CORTIS trial (24). A study by the International Union Against Tuberculosis from 1982 that included about 24 000 participants showed that IPT was efficacious among asymptomatic persons with untreated TB diagnosed on chest X-ray, that is, those with with subclinical TB (52). In addition, a trial conducted by the US Public Health Service during 1955–1957 showed that children with asymptomatic primary TB improved when treated with isoniazid: approximately 7% of the children had pulmonary infiltrates and 15–20% had hilar lymphadenopathy (53). In addition, in the Bethel trial, in which household contacts were screened by chest X-ray, people with asymptomatic disease benefited from TPT (29). The intervention resulted in a 69% overall reduction in risk of TB.

Following this discussion, it was proposed that the incipient and subclinical stages could be treated with regimens that are closer to TPT than those used for TB disease. However, the CORTIS RISK11 score identified a range of patients in different stages across the TB spectrum, making it difficult to use this biomarker for treatment decisions (e.g. deciding whether to use a treatment regimen for TB disease but for a shorter duration or to use a TPT regimen such as 1HP). Furthermore, many parameters vary across the spectrum, including exposure, treatment adherence, the physiological state of the bacteria and its microenvironment. In addition, there is the issue of community transmission and the risks of infection and reinfection, which in many settings (e.g. South Africa) are much higher than in others (e.g. Brazil). Thus, the epidemiology of TB in different settings translates to different risks and might partly explain differences in the efficacy of TPT. The use of the RISK11 score in the work in Brazil will be interesting because reinfection occurs less often.

Identifying biomarkers that after successful treatment of infection return to the levels observed in people who are not infected would allow for the design of much more efficient trials, that is, those with smaller sample sizes. Because such a biomarker has not been identified, other follow-up measures, end points and outcomes are required to define whether treatment was successful. However, it was acknowledged that it is not currently known whether treatment returns people to a sterilized state. The challenges caused by the lack of surrogate markers and intermediate markers for TB remain. The indirect host-dependent markers and nonspecific markers that are currently available offer no information about the presence of the pathogen. Data sharing and data integration across research groups and trials could help identify new biomarkers.
Part 3B: Eligibility criteria and selection of trial populations

Eligibility and inclusion criteria: challenges
Jason Stout, Duke University Medical Center, USA

Professor Stout explained that noninferiority trials for TPT face two challenges that may compromise their ability to detect an inferior regimen. First, the current tests used to diagnose TB infection are imperfect (e.g. the specificity of the TST is an issue in populations that have been vaccinated with BCG), and the outcome of interest (TB disease) occurs at relatively low rates, even in high-risk populations. For example, in the PREVENT TB trial that included more than 7000 participants, there were only 22 TB events (54). In addition, in a similarly sized trial of rifampicin monotherapy as TPT, there were only 17 people with TB disease (55).

Prompted by an early presentation of the BRIEF TB study (22), which showed that 1HP was noninferior to 9H, a mathematical model of a two-arm TB infection study comparing an experimental arm to a control arm was designed. A simulation of 10 000 trials was conducted using different enrolment strategies: (i) enrolling everyone otherwise eligible (no test), (ii) enrolling those with a positive TST, (iii) enrolling those with a positive IGRA, (iv) enrolling those with a positive TST, or (v) enrolling participants irrespective of their TST result if they came from a high-prevalence area (similar to the BRIEF TB study). The assumptions were that the control regimen was 80% effective, the experimental regimen was 50% effective and 5% of participants with TB infection would get TB disease if not treated. The sensitivity of TST and IGRA was assumed to be 60%, the specificity of TST to be 70% and the specificity of IGRA to be 98%. Noninferiority was declared if the upper bound (97.5% confidence interval) of the difference in incidence of TB disease between the experimental and control arms was smaller than the noninferiority margin (at an absolute 0.75% margin, but a 1.25% margin was explored in a sensitivity analysis).

The results of the modelling showed that using an IGRA, the most specific test possible, optimizes the likelihood of detecting an inferior regimen. Enrolling participants with negative tests, even in high-incidence areas, increases the likelihood of falsely declaring noninferiority. It was concluded that these imperfections must be explicitly taken into account when designing and powering noninferiority trials.

Eligibility and inclusion criteria: example of the BRIEF TB trial
Amita Gupta, Johns Hopkins Bloomberg School of Public Health, USA

Professor Gupta explained that preventing TB with IPT is effective, but uptake has been poor globally. 3HP is also effective in both HIV-positive and HIV-negative people, but an even shorter treatment could be transformative and allow for substantial scale up and improved uptake of TPT (56, 57).

The BRIEF TB trial examined whether 1HP was noninferior to 9H for preventing TB in people with HIV infection (22). It included 3000 HIV-positive people aged ≥13 years with no evidence of TB disease who had either TST reactivity ≥5 mm or a positive IGRA or lived in an area with a high burden of TB (defined as TB prevalence ≥60/100 000 population). At baseline, 87% of participants had CD4 counts >250 cells/mm³, 21% had a positive skin test
and 97% were from settings with a high burden of TB. Treatment completion was 97% in the 1HP arm and 90% in the 9H arm ($P < 0.001$).

The study found that 1HP is noninferior to 9H for preventing TB, TB death or death from an unknown cause in HIV-positive adults and adolescents. The rates of TB were higher in those with a positive TST, positive IGRA or CD4 counts ≤250 cells/mm$^3$. The safety of the regimens was good and similar in both study arms, with more haematological toxicity with 1HP and more liver and neurotoxicity with 9H. Completion of treatment was excellent in both study arms, but better with 1HP. Overall, 1HP provides a highly effective, ultra-short-course regimen for preventing TB in people with HIV and could contribute to improvements in the global control of TB; its use should be studied in other high-risk groups.

Discussion

Discussion initially focused on the studies that showed a high incidence of TB in risk groups such as people living with HIV and household contacts of people with TB, even if the TST or IGRA results were negative. A participant mentioned that it has been shown that there is a high incidence of TB among household contacts and people living with HIV even if they are negative by IGRA or TST ($58$). Furthermore, when the benefit is considered to outweigh the risks, TPT should be delivered to high-risk populations even if they do not have evidence of TB infection by an immune-based test ($2$).

There are big differences across studies in how a high TB-burden setting is defined and how people most at risk of progressing to TB are identified. However, these definitions and inclusion criteria impact how trials are designed. A systematic review found that a positive test for TB infection helps to define a group that is at higher risk of TB disease, but epidemiological or clinical risk factors also help identify populations that would benefit from TPT, such as close contacts of people with TB and people living with HIV ($59$).

Also discussed were the uncertainties about the relative contributions to TB transmission of the degree of exposure and infectious load. For example, it is not clear how people exposed multiple times or who are exposed to bacillary loads that vary by hundreds or thousands of times differ in their long-term risk of developing TB. The background TB rate in the country of origin is often used as a proxy for such risks. However, it is challenging to derive workable cut-offs for the categories high risk and high TB burden when referring to someone’s country of origin or residence. For most individuals with a positive test and a recent risk factor, the timing of their infection cannot be known with certainty. It is clear that most progression occurs soon after infection, but there is no way to measure this. A study in the 1960s showed that infectious load was associated with risk of disease and household context by comparing household contacts of smear-positive source cases with smear-negative source cases ($60$). Interestingly, there is work in an animal model (i.e. rabbit) that showed exposure to multiple small doses resulted in more extensive disease than exposure to a single dose similar in size to the multiple doses ($61$).

A discussion ensued on whether a different duration of TPT should be considered for people living with HIV who present to the health services with very low CD4 counts (<100 cells/mm$^3$). For this group, 1 month of prevention might be too short because they will still be at risk after that, considering that their CD4 counts will remain low. In the REALITY study
run by Professor Gibb, even limited exposure to isoniazid had a big effect in people with very low CD4 counts, leading to the conclusion that preventive therapy in this specific population works and that even 3 months of isoniazid was significantly better than none in this population (62). WHO recommends 36 months of IPT in people with HIV who are in settings with high TB transmission (see https://who.tuberculosis.recmap.org/recommendation/f8503f42-66ec-4085-992d-53b736d284b6).

Part 3C: Dealing with few TB events

Averted infections ratio: an example from pre-exposure prophylaxis for HIV

David Dunn, MRC Clinical Trials Unit at UCL, United Kingdom

Professor Dunn introduced a new tool: the AIR; it may be especially useful in noninferiority trials when event numbers are low (63). The AIR has been used in trials of pre-exposure prophylaxis (PrEP) for HIV. In that setting, when emtricitabine–tenofovir was compared with placebo it showed high efficacy in preventing HIV infection among adherent participants (approximately 95%) (64). As a result, following this trial it was no longer ethical to conduct studies to compare new medicines for PrEP with a placebo arm, and emtricitabine–tenofovir became the standard for the active control arm. In the subsequent DISCOVER trial (65), HIV incidence was much lower than expected. As a result it was impossible to know whether both study treatments (intervention and comparator) were effective or neither treatment was effective because the population was not at substantial risk.

Professor Dunn then discussed a hypothetical example that compared active control trials with identical observed outcomes, but with different event rates in a placebo arm. Although the rate ratio remained the same, knowledge of the event rate in the placebo arm changed how the results of the trial are viewed. Thus, in HIV prevention, valid interpretation of an active control trial must consider the HIV incidence rate that would have been observed in a hypothetical placebo group – that is, the counterfactual incidence.

Therefore, there is a need for a metric that incorporates this counterfactual incidence. Averted infections are defined as the number of infections that are averted by using a specific medicine compared with no intervention. The proposed measure is the AIR. The numerator is the number of infections averted in the experimental arm and the denominator is the number of infections that are averted in the control arm (64). The AIR measures the proportion of infections that would be averted by using the experimental medicine rather than the control medicine. An AIR equal to 1 implies that the two medicines are equally effective; an AIR <1 means that the new medicine is less effective; and an AIR >1 indicates that the new medicine is more effective.

The major challenge in using the AIR is estimating the counterfactual incidence. Several groups are actively researching how best to estimate this parameter, including by using a run-in period, registration cohort, local epidemiological surveillance or by inference from tests on baseline samples for recent infection. Alternatively, the AIR can be estimated via its counterfactual effectiveness (i.e. a control arm versus a hypothetical placebo), including by using meta-analysis of previous trials comparing an active control to a placebo or by
measuring adherence within trials and inferring effectiveness from meta-regression or pharmacokinetic and pharmacodynamic models (66).

There are strong parallels between PrEP and TPT, and the AIR can be directly applied to TPT. The differences are that efficacy is higher for PrEP than for TPT, the end points are more clear-cut in PrEP trials and estimating the counterfactual parameter may be more challenging in TPT trials.

Noninferiority trials of TPT
Ian White, MRC Clinical Trials Unit at UCL, United Kingdom

Professor White showed that when using a binary outcome, either an absolute (risk difference) or a relative (risk ratio) noninferiority margin can be defined. This choice affects the sample size for the trial, especially when the margin is quite substantial on the relative risk scale (67). This issue does not arise in a superiority trial because the null hypothesis is no difference (the risk ratio = 1 and the risk difference = 0), so both measures of relative or absolute risk can be used. A possible solution for noninferiority trials is to consider clinical decisions at the design stage to determine on which scale the margin should be expressed. This is more important for time-to-event outcomes because often the noninferiority margin is expressed on the hazard ratio scale, which is like a risk ratio and, therefore, gives a substantially larger sample size (67).

Another issue arises if the trial design is based on an incorrect control risk. This has implications for the original noninferiority margin because the power may be too low or the margin may be implausibly large, potentially leading to different interpretations depending on whether the absolute or relative noninferiority margin is chosen. To counteract this, investigators could review the margin at the interim analysis in light of the estimated control risk or they could prespecify a procedure for adapting the margin, for example, by using a power-stabilizing noninferiority frontier (67).

A third issue is that if different subgroups of patients have different TB incidences, it is questionable whether the same noninferiority margin is appropriate for all of them. Using a noninferiority frontier may be helpful to enable different margins to be specified for high- and low-risk groups.

Professor White concluded that the scale for the noninferiority margin must be chosen carefully. The risk difference scale is commonly used, but it may not make sense if the control risk is different than expected or for subgroups with different risks. It is important not to lose power with time-to-event outcomes. The margin could be adapted to reflect the observed instances of other benefits, and a risk–benefit analysis could be considered for superiority, as mentioned by Dr Kim.

Discussion
Professor White was asked about the implications for sample size of using the power-stabilizing frontier, whether there is an appetite for using it and if it is considered acceptable by regulatory authorities. He answered that the implications for sample size are considerable. For example, in a setting where specifying the margin on the risk ratio scale...
rather than on the risk difference scale gave a 100% increase in sample size, using the power-stabilizing frontier still gave a 40% increase in sample size compared with using a margin on the risk difference scale (67), which he did not feel was acceptable. So currently efforts are under way to design HIV trials using a different form of noninferiority frontier (i.e. not the power-stabilizing frontier) that fixes the margin as a risk difference unless the control risk is substantially different from that expected: this avoids most of the power loss. This practice has not yet been presented to regulators because it is still in an early stage of implementation in practice.

It was proposed that the key question for researchers and policymakers is: which is more relevant, absolute or relative risk? Given the heterogeneity of the populations to which an intervention might be applied, relative risk is often the more relevant measure. A risk ratio might in some settings extrapolate better to other outcomes, for example, long-term outcomes (67). However, from discussions with clinical investigators, risk differences are considered most relevant when comparing treatments. The AIR would be a good solution for TPT trials so that the impact of an unknown background prevalence could be explored. If the risk-difference frontier is the preferred approach, then power is lost if risk in the control group is higher than expected. A solution to this might be to conduct interim analyses and do a sample size re-estimation to restore lost power. A potential drawback of the power-stabilizing frontier is that it is primarily statistically motivated and does not get at the margin that balances risks and benefits, nor does it account for other improvements that affect a noninferiority margin.

Professor Crook discussed the differences of using AIR for TPT as opposed to for HIV research and mentioned that in addition to the low number of events in TPT trials, there is imprecision around the diagnostics and imprecision of the end points, which are often composite measures. Professor Dunn stated that the great attraction of the AIR is that strong inferences can be made from a small number of events. But the advantage and precision of using the AIR is a function of how effective the regimen is. For example, the AIR is particularly attractive in HIV prevention trials because PrEP is so effective, and one could conceivably observe zero or very close to zero infections. But even if there is a reasonable background incidence, the AIR still provides a meaningful result, which no other measure does.

**Session 4: Trial populations**

**Introduction**

*Chairs: Yohhei Hamada, Institute for Global Health and the MRC Clinical Trials Unit at UCL, United Kingdom, and Christian Lienhardt, French National Research Institute for Sustainable Development, France*

Dr Hamada explained that the first half of Session 4 would focus on strategies and study designs that could be used to determine individual- and population-level efficacy and safety in different risk groups, including those for whom TPT is not systematically recommended. The second half of the session would discuss other considerations for special populations, including people with diabetes, household contacts of people with drug-resistant TB,
Questions for the session

- How can the individual- or population-level efficacy of TPT be safely investigated in different risk groups?
- What are the considerations for conducting trials in specific populations, such as people with diabetes, contacts of people with drug-resistant TB, children and pregnant women?

Part 4A: Strategies for determining individual- and population-level efficacy and safety in different risk groups

Handling multiple risk groups: basket designs and Bayesian approaches

Becky Turner, MRC Clinical Trials Unit at UCL, United Kingdom

Dr Turner explained that estimating treatment effects in certain risk groups may be challenging because it is not feasible to conduct a separate trial for each risk group, such as people with diabetes or pregnant women. One way to approach this is to use a basket trial design. In a basket trial, separate cohorts of patients are recruited to different “baskets”, but the same randomized treatments are delivered across all baskets. Some baskets may be easy to recruit to and may have sufficient power for a stand-alone analysis, while others may be difficult to recruit to and lack power; estimating treatment effects for these latter baskets would rely on borrowing information from other baskets, which is how this design differs from a more traditional RCT powered to look at subgroups.

The aim of the basket trial is to draw conclusions about the efficacy of the treatment within each subgroup in the trial rather than across the trial as a whole. Basket trials have been mainly used in oncology, for which the baskets typically represent cancers that are linked biologically but occur in different parts of the body. In the TPT setting, it is likely that the baskets would represent different risk groups. An important question is how much information should be borrowed from other groups, and the answer depends on how similar the treatment effects are expected to be in the different groups. If the trial includes enough large baskets with well-estimated treatment effects, then it may be possible to determine from the trial data alone how much information should be borrowed. In most basket trials, this is not the case, and typically the degree of borrowing cannot be determined by the trial data alone. It might be possible to use external data to inform the degree of borrowing if there is some relevant evidence available, for example, from a similar basket trial. Otherwise, the degree of borrowing will need subjective input based on clinical opinion about how similar treatment effects are believed to be in different baskets.

Borrowed information can also potentially be used in conventional trial designs to help with estimating treatment effects in separate risk groups. There are several sources from which information could be borrowed, for example, from another subgroup or subgroups in the same trial, from a previous external trial comparing the same treatment in a similar population or from an external meta-analysis comparing the same treatments in similar populations.

One example comes from the ODYSSEY trial in children with HIV infection (68). The trial was
first undertaken in 707 children weighing ≥14 kg and then 12 months later in 85 children weighing 3–14 kg. The choice of weights in the Bayesian analysis was based on how similar the treatment effects for the two population groups were expected to be, and this expectation was informed by the clinical opinion of 13 paediatricians with relevant expertise in HIV treatment. An elicitation process was used to obtain their opinions about expected differences between the treatment effects in the two groups. The Bayesian analysis provided 84% predictive power to exclude a difference beyond the noninferiority margin of 10%, whereas a stand-alone frequency analysis of the 85 children provided only 20% power.

An additional example of borrowing information comes from the VQUIN MDR (27) and TB-CHAMP (26) trials that compared levofloxacin with placebo for the prevention of TB in contacts of people with multidrug-resistant TB (MDR-TB). Both trials are likely to be underpowered for efficacy in stand-alone analyses due to TB event rates being lower than expected. Proposed Bayesian analyses will allow for the borrowing of information from TB-CHAMP to inform estimation in VQUIN MDR, and vice versa, thus improving power and precision relative to stand-alone analyses of the trial data.

In summary, borrowing information can facilitate estimation in small risk groups, providing gains in power and precision. In a basket trial design, information can be borrowed across risk groups. In a conventional trial, information could be borrowed from a larger risk group in the same trial or potentially from an external trial or meta-analysis if sufficiently similar external data are available. The degree of borrowing needs to be informed by expert opinion or external evidence, or both. Eliciting expert opinion is time-consuming but may provide worthwhile information.

Extrapolation and decision analytic modelling

Guy Marks, University of New South Wales Sydney, Australia

Professor Marks stated that decision-making in clinical practice is not difficult if the benefits are great and the risks are low. However, clinical decision-making is difficult when there is uncertainty about the diagnosis due to poor test validity or a complex diagnosis or when there is uncertainty about the evidence on efficacy or harms, or both. The questions to be considered when deciding to treat TB infection are the following.

- Does the person have TB infection?
- Is the person at risk of progressing to TB disease?
- Is the person at risk of death (or disability) due to TB disease?
- If the person is receiving TPT, what are the risks of serious adverse events?
- If serious adverse events develop, what is the risk of death (or disability)?

Professor Marks presented a decision tree and Markov model to estimate the quality-adjusted life-years (69) resulting from alternative courses of action (either providing or not providing TPT) for various risk values of TB and age group. An online calculator to aid clinicians in interpreting TST results was presented as an example of a decision-making tool that organizes complex information to enable decision-making and consideration of benefits and harms; see http://www.tstin3d.com/en/calc.html.
Discussion

The discussion started with questions on how to elicit expert opinion and about how much information can be borrowed for a basket design trial and how this information can be incorporated into the model so that it does not dominate the analysis. Dr Turner explained that expert opinion is generally elicited through one-to-one interviews using a predefined, piloted questionnaire. The degree of borrowing needs to be determined, and this allows adjustments to be made to the prior distribution according to how similar the treatment effects are believed to be. For example, in the ODYSSEY trial, the data from older children were downweighted so that they were not overrepresented in the analysis (as they would be if the relative weights were determined by sample size alone).

Concern was raised that expert opinion might be wrong. This possibility was acknowledged by Dr Turner, but she explained that the current decision-making process already incorporates expert opinion, but this is done qualitatively and less transparently. In contrast, a Bayesian analysis would allow expert opinions to be incorporated more transparently on matters such as where the borrowed data came from and how the analysis was done. The Bayesian analysis can be presented alongside the pooled and stand-alone analyses so that it is easier to appreciate the impact of borrowing information and to aid in understanding the assumptions that were made. It is also important to obtain opinions from a large number of experts and then use pooled (e.g. median) opinions, so that extreme opinions do not have too much influence.

The discussion then focused on how the basket design would deal with people who have multiple risk factors and how basket analysis could be used for groups who are routinely excluded from trials and whose risk might be quite different from others, such as pregnant women. Dr Turner explained that pregnant women might potentially form their own basket in the trial if there is reason to believe that their treatment effect differs from that of other risk groups, while basket design might be less suitable for people with multiple risk factors (since they would fall into multiple baskets).

Using extrapolation and decision analytic modelling for treatment decisions was also discussed, and a participant asked whether there is sufficient information to decide to provide TPT to people with diabetes or other risk groups (e.g. people with chronic kidney disease who are not on dialysis) for which systematic testing and treatment for TB infection is not currently recommended by WHO. These decisions may be challenging in situations such as when a patient has diabetes mellitus and, therefore, has not only an increased risk of developing TB but also a risk of developing adverse reactions to the TPTs. It is important to be explicit about estimating the utility of the various outcomes. From that perspective, it is better to use the model to answer such a question than to make an instinctive decision. A follow-on question was asked about whether modelling would provide evidence sufficient to make recommendations about which risk groups should receive TPT or whether RCTs are needed. The ability to extrapolate to other groups depends mainly on their expected similarity, or analogy. Sometimes decisions need to be taken in the absence of evidence, but then those decisions need to be revisited when more evidence becomes available that fills the knowledge gaps.
Part 4B: Special populations

A randomized double-blind placebo-controlled trial of rifapentine and isoniazid to prevent TB in people with diabetes – the PROTID trial

Reinout van Crevel, Radboud University Medical Center, Netherlands, and Willyhelmina Olomi, National Institute for Medical Research, United Republic of Tanzania

Professor van Crevel indicated that diabetes mellitus is an important risk factor for TB disease and death from TB, as well as for recurrent TB, and it is an emerging issue for many countries (70-73). The main aim of the PROTID trial is to assess the efficacy of 3HP in preventing TB in people with diabetes. Secondary objectives include monitoring treatment completion, adverse events, all-cause mortality, subgroup characteristics (e.g. age, duration of diabetes mellitus, glycated haemoglobin, body mass index), efficacy in restricted analyses, and quality of life and cost–effectiveness. The safety assessment includes older patients with comorbidities and comedication.

Some specific features of diabetes mellitus and its interaction with TB lead to uncertainties with regards to the assessment of trial end points. There are limited data on TB incidence in people with diabetes mellitus, and this has implications for the power of the study. Therefore, the primary end point in PROTID is the diagnosis of TB (definite or probable) in people with diabetes who have a positive test for TB infection. Definite TB disease is defined as being confirmed by culture or a positive result on a molecular rapid diagnostic test; probable TB is based on an assessment of TB symptoms, chest X-ray abnormality, sputum smear results, histology findings and verbal autopsy. Death from TB is confirmed by verbal autopsy and hospital records. For the safety assessment, it should be considered that people with diabetes mellitus are often older and have comorbidities and use other medications, which might lead to drug–drug interactions. It might also be challenging to distinguish TPT toxicity from the effects of diabetes itself (e.g. peripheral neuropathy).

For the primary efficacy analysis, Professor van Crevel intends to look at the ratio of TB incidence in the intervention and control groups. Secondary analyses will be conducted, using the cumulative incidence function, with death from causes other than TB considered as a competing risk; difference in 24-month cumulative incidence; Cox proportional hazards regression analysis, comparing risk of TB by treatment arm, adjusted from baseline factors; and the number of TB events per person by treatment arm. People with diabetes might be a logical group to target for TPT in addition to people living with HIV and contacts of people with TB. Providing TPT for those with diabetes may have a huge impact if proven effective and safe. PROTID is the first trial of TPT in people with diabetes.

TB infection among contacts of patients with MDR-TB

Gregory Fox, The University of Sydney, Australia

Dr Fox started his presentation with some important considerations for conducting trials of TPT among contacts at risk of MDR-TB. First, the drug-susceptibility testing pattern of incident TB in contacts may differ from that of the index patients, for example, as shown in the PHOENIx feasibility study and others in which 10% to 38% of household contacts in Peru had different strains than their index patients (74-76). The implications for trial design are
that the preventive regimens may be ineffective in some contacts and that it may not be appropriate to use a placebo or the standard of care in the control arm. Second, a high proportion of contacts may have coprevalent TB rather than incident TB, which will have implications for the sample size (i.e., an increased sample size is required to detect a difference in incidence). Third, there are concerns regarding acquired drug resistance when using single-agent therapy. The implications for trial design are that it is important to exclude TB disease prior to randomization and to monitor participants closely for early incident TB during TPT. Finally, it is important to choose the appropriate antibiotic, taking into account antibiotic resistance and considering the possible toxicity of the treatment, for example, when fluoroquinolones or second-line medicines are used. The implications for trial design include impacts on the selection of anti-TB medicines and dosing that are based on animal models and clinical trials in other populations. Additionally, pharmacokinetic studies could be integrated within the trial design, as well as an evaluation of biomarkers, to look at disease progression.

Dr Fox also discussed the VQUIN MDR trial, a double-blind placebo-controlled cluster-randomized trial in Viet Nam of 6 months of levofloxacin versus placebo for preventing TB disease among household contacts of patients with MDR-TB who have TB infection (27). Secondary objectives include evaluating tolerability, adherence, cost and effectiveness; determining the rate of acquired fluoroquinolone resistance; and determining differences in biomarker profiles between contacts with TB infection who progress to TB disease and those who do not. The study is estimated to be completed in March 2022.

TPT trials: methodological considerations for trials in children
Anneke Hesseling, Stellenbosch University, South Africa

Professor Hesseling emphasized the importance of conducting trials with children because they make up about 12% of the global burden of TB, and the assumption of similar efficacy of anti-TB medicines in children compared with adults, which would allow data to be extrapolated, may not hold. The risk of disease progression is high in children. A high proportion of children younger than 5 years develop TB within 6 months of exposure (77). Therefore, to increase efficiency in TPT trials of young children with recent exposure, shorter follow up could possibly be done. Because children have different disease pathogenesis, which is often paucibacillary and has a wide disease spectrum, careful consideration of trial end points is required. For children, pharmacokinetic and safety studies are required to inform dosing since they achieve lower serum concentrations of anti-TB medicines and eliminate these medicines faster than adults when treated with the same mg/kg/day dose. It is important that paediatric data are collected early in the development of anti-TB treatments to inform dosing in children. Timely research in children is also needed for the development of child-friendly formulations that are dispersible, scored and palatable. Once these formulations are evaluated in trials, they need to be made available to children outside of the trial context.
Considerations for TPT trials in pregnant women

Jyoti Mathad, Weill Cornell Medicine, USA, and Sylvia M. LaCourse, University of Washington, USA

Dr Mathad showed that women are at highest risk of developing TB disease during and immediately after pregnancy, with an incidence rate ratio of 1.95 compared with any other time in a woman’s life (78, 79). TB disease during pregnancy results in poor maternal and fetal outcomes. Key considerations in pregnancy are that gestational age matters; safety outcomes should be addressed for both a woman and her foetus; and there may not be an established standard of care during pregnancy.

Gaps in existing trials were highlighted, such as the lack of short-course TPT and the inclusion of only efavirenz-based regimens in the IMPAACT P1078 TB APPRISE trial, which was the first RCT assessing the safety of 6 months of daily IPT in a comparison of HIV-positive antepartum women with HIV-positive postpartum women (80). This trial showed no difference in incident TB, but found an increased risk of composite adverse pregnancy outcomes in the antepartum arm.

IMPAACT 2001 was a phase I/II trial of the pharmacokinetics, safety and tolerability of 3HP in pregnant women with and without HIV infection (81). This study found that there was no need to adjust the dose of rifapentine as women went from the second to the third trimester and that 3HP was well tolerated in the 50 maternal–infant pairs enrolled. However, HIV-positive women were on the older efavirenz-based regimens, and the study was not powered to assess safety.

Dr LaCourse presented information about the proposed DOLPHIN Moms study, which is designed to evaluate the safety and tolerability of 1HP and 3HP and the pharmacokinetics of dolutegravir in pregnant women living with HIV. The DOLPHIN Moms trial is designed to inform TPT guidelines by evaluating the potential benefits of using short-course TB prevention regimens during pregnancy (i.e. regimens that can be completed during pregnancy and, thus, avoid the postpartum risk of hepatotoxicity) and to provide data on short-course TPT given simultaneously with antiretroviral regimens (including regimens containing dolutegravir).

The study hypothesis was that 1HP and 3HP are similarly safe in pregnant women, and this was studied in a two-arm, randomized, multicentre, open-label study. The reason for not choosing a noninferiority trial design was the lack of an established safety profile during pregnancy that could be used for the control arm, given the findings of the TB APPRISE trial with isoniazid. A superiority design would have required a larger sample size, which would have reduced its feasibility and the timeliness of the study results.

In conclusion, pregnant women should be considered a key population for TPT trials. There are unique considerations for this population because of their physiology and due to implementation challenges. Innovative, pragmatic study designs can provide the necessary information to extend the benefits of TPT to pregnant women and their infants.
Discussion

Professor van Crevel was asked about participants in the PROTID trial and whether the type of diabetes was considered as well as the type of treatment used by the people with diabetes (e.g. oral medications such as metformin or insulin). Participants with any type of diabetes were included, but in practice, patients will predominantly have type II. Differences in body mass index, smoking status and medication use will be considered in the analysis. Questions about the duration of TPT or the need for repeated TPT for people with diabetes need to be addressed by further research.

Concerns were raised about the decision to evaluate TPT against placebo in the PROTID trial. Professor van Crevel explained that placebo was justified because there are no guidelines for systematically testing people with diabetes for TB infection and giving them TPT to (2). There are few empirical data about administering TPT to people with diabetes, and there is a need for more information on both its efficacy and its possible harm. In diabetes clinics in low-income countries, many people have poorly controlled diabetes, take many different medications, have kidney dysfunction and possibly liver fibrosis, and there is high mortality (caused by other diseases, such as vascular disease), so administering TPT to this population is not straightforward and, thus, it is too early to compare different regimens.

The study team was asked if they had plans to look specifically at trade-offs between benefits and risks in a way similar to that proposed by Dr Kim because the trade-offs seem to be the key questions for the population with diabetes. It was agreed that it makes a lot of sense to look at efficacy and safety by using the risk–benefit analysis that Dr Kim discussed, although it was emphasized that it is not yet known whether the efficacy of TPT is the same in people with and without diabetes.

Dr Fox and Professor Hesseling were also asked about the placebo comparison in the VQUIN MDR trial. Dr Fox explained that at the time the study was designed, neither Viet Nam nor WHO had guidelines that recommended preventive treatment in the context of MDR-TB. Additionally, the risk of harm had to be balanced against the benefit of choosing a comparator, and isoniazid, the obvious comparator of choice, would have had harms attached to it or not be efficacious in people with isoniazid resistance. Finally, in the trial, patients were typically followed very closely, so any emergent adverse events would be mitigated. This degree of surveillance cannot be replicated under normal programmatic conditions. Professor Hesseling explained that the considerations for children were similar, agreeing that there would probably be little benefit to administering isoniazid in the control arm, highlighting the equipoise between offering a placebo or having an active control arm.

Dr Mathad and Dr LaCourse were asked to explain the choice of a randomized clinical trial designed to precisely estimate the safety and tolerability of 1HP and 3HP. Dr Mathad explained that they wanted to focus on the precision around the safety events because demonstrating safety is most important for pregnant women, the population of interest. They were asked if they had considered 4 months of daily rifampicin as a control arm since the safety of rifampicin in pregnant women is well established. Dr LaCourse stated that the resources to add an additional arm for 4 months of rifampicin were not available, but emphasized that safety data on 1HP and 3HP are needed as soon as possible because these regimens are currently being rolled out.
Conclusions

During the meeting a number of innovative methodological and statistical approaches were presented that can be used to evaluate new TPT. Innovations in other diseases areas, such as PrEP for preventing HIV infection and from oncology, may be applicable to trials of TPT. New insights into the spectrum of TB infection and disease, the application of personalized medicine in the field of TB, and developments in diagnosis and biomarkers have the potential to further advance innovation in this area. Collaboration and data sharing remain essential to ensure that progress is made in trials of TPT.
References


59. Campbell JR, Winters N, Menzies D. Absolute risk of tuberculosis among untreated populations with a positive tuberculin skin test or interferon-gamma release assay result: systematic review and meta-analysis. BMJ. 2020;368:m549. doi:10.1136/bmj.m549.


## Annex 1. Agenda

### Wednesday, 15 September 2021

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<td>15:00–15:10</td>
<td>Opening and introduction</td>
<td>Saskia den Boon (WHO GTB)</td>
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<td>15:10–15:15</td>
<td>Welcome</td>
<td>Tereza Kasaeva (director, WHO GTB)</td>
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### Session 1: Models of delivery

Chairs: Thu Anh Nguyen (Woolcock Institute of Medical Research and The University of Sydney) and Susan Swindells (University of Nebraska Medical Center)

#### Questions for the session

- Which types of trials are needed to address the challenges of implementing TPT?
- How can we address patient-important outcomes in trials?
- How can trials address gaps in the delivery of TPT?
- Which implementation challenges are not being addressed in clinical trials?

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<tr>
<td>15:15–15:20</td>
<td>Context and objectives of the session</td>
<td>Chairs</td>
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<tr>
<td>15:20–15:30</td>
<td>Addressing TPT needs with trials</td>
<td>Gavin Churchyard (Aurum Institute for Health Research)</td>
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<td>15:30–15:40</td>
<td>Opt-out studies</td>
<td>Christopher Hoffmann (Johns Hopkins University School of Medicine)</td>
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<td>15:40–15:50</td>
<td>Evaluating models of delivery for TPT: example of the Opt4TPT study</td>
<td>Violet Chihota (Aurum Institute for Health Research)</td>
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<td>15:50–16:00</td>
<td>Reducing the gap between policy and practice: example of the ACT4 study</td>
<td>Thu Anh Nguyen (Woolcock Institute of Medical Research and The University of Sydney)</td>
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<td>16:00–16:10</td>
<td>Offering a choice: example of the 3HP Options implementation trial</td>
<td>Adithya Cattamanchi (University of California, San Francisco) and Fred Semitala (Makerere University)</td>
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<td>16:10–16:30</td>
<td>Discussion</td>
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### Session 2: Estimating the benefits and harms of TPT

Chairs: Richard Chaisson (Johns Hopkins University School of Medicine and Bloomberg School of Public Health) and Lele Rangaka (Institute for Global Health and the MRC Clinical Trials Unit at UCL)
Questions for the session

- Is TB incidence the best primary outcome? Can we incorporate patient-important outcomes and, if so, how?
- How can we better evaluate the balance between benefits and harms within trials?
- What are the key ethical considerations for TPT trials?

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<tr>
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<td>Context and objectives of this session</td>
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<tr>
<td>16:50–17:05</td>
<td>Benefits and harms for individuals versus communities</td>
<td>Guy Marks (University of New South Wales Sydney)</td>
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<td>17:05–17:20</td>
<td>Applying a risk–benefit analysis to outcomes in TB clinical trials</td>
<td>Soyeon Kim (Frontier Science Foundation)</td>
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<td>17:20–17:35</td>
<td>Ethics of preventive treatment trials</td>
<td>Rieke van der Graaf (University of Utrecht)</td>
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<td>17:35–18:00</td>
<td>Discussion</td>
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Thursday, 16 September 2021

Session 3: Trial design and analytical approaches

- Chairs: Angela Crook (MRC Clinical Trials Unit at UCL) and Dick Menzies (McGill University)

Questions for the session

- Is there a role for surrogate markers and end points for preventive efficacy in TB prevention trials?
- Are there promising biomarkers in the pipeline, and what are their characteristics?
  - Are there biomarkers for end points?
  - Are there biomarkers for selecting populations who are likely to benefit most from TPT?
- How can we evaluate these markers in TB prevention trials?
- How can patients be selected for trials, considering the limitations of current tests used to identify those at highest risk for developing TB disease?
- Can novel designs or statistical measures help new TB prevention trials so they are conducted more efficiently and reliably?

3A. Biomarkers and the spectrum of TB

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</table>
15:05–15:15 Promising biomarkers and their utility in TPT trials
Morten Ruhwald (FIND)

15:15–15:25 Evaluating biomarkers in TB prevention trials: example of the CORTIS trial
Thomas Scriba (South African Tuberculosis Vaccine Initiative [SATVI], University of Cape Town)

15:25–15:35 Immunogenetic predictors of active and incipient TB
Timothy Sterling (Vanderbilt Institute for Global Health)

15:35–15:45 Stratified medicine trial designs and the spectrum of TB
Payam Nahid (University of California, San Francisco)

15:45–16:15 Discussion
All

16:15–16:30 Break

3B. Eligibility criteria and selection of trial populations

16:30–16:45 Eligibility and inclusion criteria: challenges
Jason Stout (Duke University Medical Center)

16:45–17:00 Eligibility & inclusion criteria: example of the BRIEF TB trial
Amita Gupta (Johns Hopkins Bloomberg School of Public Health)

3C. Dealing with few TB events

17:00–17:15 Averted infections ratio: an example of pre-exposure prophylaxis (PrEP) for HIV
David Dunn (MRC Clinical Trials Unit at UCL)

17:15–17:30 Noninferiority trials of TPT
Ian White (MRC Clinical Trials Unit at UCL)

17:30–18:00 Discussion
All

Friday, 17 September 2021

Session 4: Trial populations

Questions for the session
- How can the individual- or population-level efficacy of TPT be safely investigated in different risk groups?
- What are the considerations for conducting trials in specific populations, such as people with diabetes, contacts of people with drug-resistant TB, children and pregnant women?
### 4A. Strategies for determining individual- and population-level efficacy and safety in different risk groups

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15:00–15:05</td>
<td>Context and objectives of this session</td>
<td>Chairs</td>
</tr>
<tr>
<td>15:05–15:20</td>
<td>Handling multiple risk groups: basket designs and Bayesian approaches</td>
<td>Becky Turner (MRC Clinical Trials Unit at UCL)</td>
</tr>
<tr>
<td>15:20–15:35</td>
<td>Extrapolation and decision analytic modelling</td>
<td>Guy Marks (University of New South Wales Sydney)</td>
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<tr>
<td>15:35–16:00</td>
<td>Discussion</td>
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#### 4B. Special populations

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<tr>
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<th>Speaker(s)</th>
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<tbody>
<tr>
<td>16:15–16:30</td>
<td>Prevention of TB among people with diabetes: examples from the PROTID trial</td>
<td>Reinout van Crevel (Radboud University Medical Center) and Willyhelmina Olomi (National Institute for Medical Research, United Republic of Tanzania)</td>
</tr>
<tr>
<td>16:30–16:45</td>
<td>Contacts of patients with MDR-TB: examples from the VQUIN MDR trial</td>
<td>Gregory Fox (The University of Sydney)</td>
</tr>
<tr>
<td>16:45–17:00</td>
<td>TPT trials: methodological considerations for trials in children</td>
<td>Anneke Hesseling (Stellenbosch University)</td>
</tr>
<tr>
<td>17:00–17:15</td>
<td>Considerations for TPT trials in pregnant women</td>
<td>Jyoti Mathad (Weill Cornell Medicine) and Sylvia LaCourse (University of Washington)</td>
</tr>
<tr>
<td>17:15–17:45</td>
<td>Discussion</td>
<td>All</td>
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</table>

#### CLOSING

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<tr>
<th>Time</th>
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<th>Speaker(s)</th>
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<tbody>
<tr>
<td>17:45–18:00</td>
<td>Closing statements</td>
<td>Matteo Zignol &amp; Saskia den Boon (WHO GTB)</td>
</tr>
</tbody>
</table>
Annex 2. List of participants

<table>
<thead>
<tr>
<th>Participants</th>
<th>Affiliation</th>
<th>City and country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jay Achar</td>
<td>Karolinska Institutet</td>
<td>Stockholm, Sweden</td>
</tr>
<tr>
<td>Menonli Adjobimey</td>
<td>National TB Programme</td>
<td>Porto-Novo, Benin</td>
</tr>
<tr>
<td>Sevim Ahmedov</td>
<td>US Agency for International Development</td>
<td>Washington, United States of America (USA)</td>
</tr>
<tr>
<td>Teeb Al-Samarrai</td>
<td>Office of the Global AIDS Coordinator</td>
<td>Washington, USA</td>
</tr>
<tr>
<td>Draurio Barreira Cravo Neto</td>
<td>Unitaid</td>
<td>Geneva, Switzerland</td>
</tr>
<tr>
<td>Radu Botgres</td>
<td>European Medicines Agency</td>
<td>Amsterdam, Netherlands</td>
</tr>
<tr>
<td>Rosanna Boyd</td>
<td>Centers for Disease Control and Prevention</td>
<td>Atlanta, USA</td>
</tr>
<tr>
<td>Grania Brigden</td>
<td>The Union</td>
<td>Paris, France</td>
</tr>
<tr>
<td>Jonathon Campbell</td>
<td>McGill University</td>
<td>Montreal, Canada</td>
</tr>
<tr>
<td>Martina Casenghi</td>
<td>Elizabeth Glaser Pediatric AIDS Foundation</td>
<td>Geneva, Switzerland</td>
</tr>
<tr>
<td>Adithya Cattamanchi</td>
<td>University of California, San Francisco</td>
<td>San Francisco, USA</td>
</tr>
<tr>
<td>Richard Chaisson</td>
<td>Johns Hopkins University School of Medicine and Bloomberg School of Public Health</td>
<td>Baltimore, USA</td>
</tr>
<tr>
<td>Macarthur Charles</td>
<td>Centers for Disease Control and Prevention</td>
<td>Atlanta, USA</td>
</tr>
<tr>
<td>Violet Chihota</td>
<td>Aurum Institute for Health Research</td>
<td>Johannesburg, South Africa</td>
</tr>
<tr>
<td>Churchyard, Gavin</td>
<td>Aurum Institute for Health Research</td>
<td>Johannesburg, South Africa</td>
</tr>
<tr>
<td>Daniela Cirillo</td>
<td>Supranational TB reference Laboratory</td>
<td>Milan, Italy</td>
</tr>
<tr>
<td>Angela Crook</td>
<td>Medical Research Council Clinical Trials Unit at University College London</td>
<td>London, United Kingdom of Great Britain and Northern Ireland</td>
</tr>
<tr>
<td>David Dunn</td>
<td>Medical Research Council Clinical Trials Unit at University College London</td>
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</tr>
<tr>
<td>Trinh Duong</td>
<td>Medical Research Council Clinical Trials Unit at University College London</td>
<td>London, United Kingdom</td>
</tr>
<tr>
<td>Greg (Gregory) Fox</td>
<td>The University of Sydney</td>
<td>Sydney, Australia</td>
</tr>
<tr>
<td>Mike Frick</td>
<td>Treatment Action Group</td>
<td>New York, USA</td>
</tr>
<tr>
<td>Diana Gibb</td>
<td>Medical Research Council Clinical Trials Unit at University College London</td>
<td>London, United Kingdom</td>
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<tr>
<td>Unyeong Go</td>
<td>Green Cross Laboratories</td>
<td>Yongin, Republic of Korea</td>
</tr>
<tr>
<td>Jonathan Golub</td>
<td>Johns Hopkins Bloomberg School of Public Health</td>
<td>Baltimore, USA</td>
</tr>
<tr>
<td>Celeste Gracia Edwards</td>
<td>The Global Fund to Fight AIDS, Tuberculosis</td>
<td>Geneva, Switzerland</td>
</tr>
<tr>
<td>Participants</td>
<td>Affiliation</td>
<td>City and country</td>
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<tr>
<td>Amita Gupta</td>
<td>Johns Hopkins Bloomberg School of Public Health</td>
<td>Baltimore, USA</td>
</tr>
<tr>
<td>Yohhei Hamada</td>
<td>Institute for Global Health and the Medical Research Council Clinical Trials Unit at University College London</td>
<td>London, United Kingdom</td>
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<tr>
<td>Anneke Hesseling</td>
<td>Stellenbosch University</td>
<td>Cape Town, South Africa</td>
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<tr>
<td>Chris Hoffmann</td>
<td>Johns Hopkins University School of Medicine</td>
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<tr>
<td>Soyeon Kim</td>
<td>Frontier Science Foundation</td>
<td>Amherst, USA</td>
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<tr>
<td>Sylvia M. LaCourse</td>
<td>University of Washington</td>
<td>Washington, USA</td>
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<tr>
<td>Christian Lienhardt</td>
<td>French National Research Institute for Sustainable Development</td>
<td>Montpellier, France</td>
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<tr>
<td>Guy Marks</td>
<td>University of New South Wales</td>
<td>Sydney, Australia</td>
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<tr>
<td>Jyoti Mathad</td>
<td>Cornell University</td>
<td>New York, USA</td>
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<tr>
<td>Alberto Matteelli</td>
<td>University of Brescia</td>
<td>Brescia, Italy</td>
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<tr>
<td>Dick Menzies</td>
<td>McGill University</td>
<td>Montreal, Canada</td>
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<tr>
<td>Christiaan Mulder</td>
<td>KNCV Tuberculosis Foundation</td>
<td>The Hague, Netherlands</td>
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<tr>
<td>Kissa Mwamwitwa</td>
<td>Tanzania Regulatory Authority</td>
<td>Dodoma City, United Republic of Tanzania</td>
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<tr>
<td>Payam Nahid</td>
<td>University of California, San Francisco</td>
<td>San Francisco, USA</td>
</tr>
<tr>
<td>Thu Anh Nguyen</td>
<td>Woolcock Institute and The University of Sydney</td>
<td>Ha Noi, Viet Nam</td>
</tr>
<tr>
<td>Andrew Nunn</td>
<td>Medical Research Council Clinical Trials Unit at University College London</td>
<td>London, United Kingdom</td>
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<tr>
<td>Willyhelmina Olomi</td>
<td>National Institute for Medical Research</td>
<td>Dar es Salaam, United Republic of Tanzania</td>
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<tr>
<td>Elena Pallari</td>
<td>Medical Research Council Clinical Trials Unit at University College London</td>
<td>London, United Kingdom</td>
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<tr>
<td>Patrick Phillips</td>
<td>University of California, San Francisco</td>
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<tr>
<td>Molebogeng (Lele) Rangaka</td>
<td>Institute for Global Health and the Medical Research Council Clinical Trials Unit at University College London</td>
<td>London, United Kingdom</td>
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<tr>
<td>Morten Ruhwald</td>
<td>FIND</td>
<td>Geneva, Switzerland</td>
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<tr>
<td>Nicole Salazar-Austin</td>
<td>Johns Hopkins School of Medicine</td>
<td>Baltimore, USA</td>
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<tr>
<td>Kevin Schwartzman</td>
<td>McGill University</td>
<td>Montreal, Canada</td>
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<tr>
<td>Thomas Scriba</td>
<td>University of Cape Town</td>
<td>Cape Town, South Africa</td>
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<thead>
<tr>
<th>Participants</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Fred Semitala</td>
<td>Makerere University</td>
<td>Kampala, Uganda</td>
</tr>
<tr>
<td>Timothy Sterling</td>
<td>Vanderbilt Institute for Global Health</td>
<td>Nashville, USA</td>
</tr>
<tr>
<td>Jason Stout</td>
<td>Duke University Medical Center</td>
<td>Durham, USA</td>
</tr>
<tr>
<td>Susan Swindells</td>
<td>University of Nebraska Medical Center</td>
<td>Lincoln, USA</td>
</tr>
<tr>
<td>Ezio Távora dos Santos Filho</td>
<td>WHO Civil Society Task Force</td>
<td>Rio de Janeiro, Brazil</td>
</tr>
<tr>
<td>Anete Trajman</td>
<td>Rio de Janeiro Federal University</td>
<td>Rio de Janeiro, Brazil</td>
</tr>
<tr>
<td>Becky Turner</td>
<td>Medical Research Council Clinical Trials Unit at University College London</td>
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<td>Reinout van Crevel</td>
<td>Radboud University Medical Center</td>
<td>Nijmegen, Netherlands</td>
</tr>
<tr>
<td>Rieke van der Graaf</td>
<td>University of Utrecht</td>
<td>Utrecht, Netherlands</td>
</tr>
<tr>
<td>Andrew Vernon</td>
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</tr>
<tr>
<td>Brenda Waning</td>
<td>Global Drug Facility</td>
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<tr>
<td>Genevieve Wills</td>
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<tr>
<td>Ian White</td>
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**Participants from the World Health Organization**

<table>
<thead>
<tr>
<th>Participants</th>
<th>Department</th>
<th>Country</th>
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<tbody>
<tr>
<td>Saskia den Boon</td>
<td>Global TB Programme</td>
<td>Geneva, Switzerland</td>
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<tr>
<td>Dennis Falzon</td>
<td>Global TB Programme</td>
<td>Geneva, Switzerland</td>
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<tr>
<td>Avinash Kanchar</td>
<td>Global TB Programme</td>
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<td>Tereza Kasaeva</td>
<td>Global TB Programme</td>
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<td>Samuel Schumacher</td>
<td>Global TB Programme</td>
<td>Geneva, Switzerland</td>
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<tr>
<td>Matteo Zignol</td>
<td>Global TB Programme</td>
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<tr>
<td>Fabrizia Del Greco</td>
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<tr>
<td>Martina Penazzato</td>
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<tr>
<td>Corinne Merle</td>
<td>Special Programme for Research and Training in Tropical Diseases</td>
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<tr>
<td>Vineet Bhatia</td>
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<td>New Delhi, India</td>
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<tr>
<td>Partha Mandal</td>
<td>Regional Office for South-East Asia</td>
<td>New Delhi, India</td>
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<td>Kenza Bennani</td>
<td>Regional Office for the Eastern Mediterranean</td>
<td>Cairo, Egypt</td>
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<tr>
<td>Martin van den Boom</td>
<td>Regional Office for the Eastern Mediterranean</td>
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<tr>
<td>Fukushi Morishita</td>
<td>Regional Office for the Western Pacific</td>
<td>Manila, Philippines</td>
</tr>
<tr>
<td>Kyung Oh</td>
<td>Regional Office for the Western Pacific</td>
<td>Manila, Philippines</td>
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Annex 3. Declarations of interest

No conflicts of interest


Interests declared

Grania Brigden declared that, as part of her work with The Union, she led the development of an open access online course about TB infection. The development of this course was paid for by Sanofi. The content of the course was developed completely independent of Sanofi.

Martina Casenghi declared that her position is supported through a Unitaid grant awarded to the Elizabeth Glaser Pediatric AIDS Foundation. Unitaid is funding projects aimed at improving the availability of TPT regimens. She also declared receiving study budgets from Unitaid to support the research studies that are being carried out under the paediatric TB project awarded to the Foundation. The CONTACT study is assessing community-based initiation of a 3-month regimen of rifampicin and isoniazid in child contacts.

Adithya Cattamanchi declared receiving a research grant (US$ 2.5 million) from the US National Institutes of Health awarded to the University of California, San Francisco, to evaluate different delivery strategies for 3HP in the context of routine HIV/AIDS care.

Richard Chaisson declared consulting work, including serving as a technical or other adviser for Sanofi for chairing a session on TB infection at The Union meeting in 2019 that included speakers from WHO and the Stop TB Partnership (US$ 6000).

Violet Chihota declared receiving nonmonetary support valued at more than US$ 1000 overall for donations of rifapentine and isoniazid from Sanofi–Aventis, awarded to the Aurum Institute for the WHIP3TB trial, the DOLPHIN trial and the DOLPHIN TOO trial.

Gavin Churchyard declared consulting, including serving as a technical or other adviser. He also declared receiving research support, including grants, collaborations, sponsorships and other funding, from the Bill & Melinda Gates Foundation to the Aurum Institute to evaluate TB host-directed therapy (approximately US$ 10 million), from the European Commission under the Horizon 2020 funding programme to the Aurum Institute to evaluate a TB host-directed therapy trial, and a grant from the US Agency for International Development via KNCV/Challenge TB for the WHIP3TB trial (US$ 14.2 million). He also declared that Sanofi donated rifapentine and isoniazid to the Aurum Institute for the WHIP3TB trial (<US$ 350 000). Furthermore, he declared that he participated in a Sanofi advisory board on rifapentine for TPT but did not receive any travel support or payment for attending.
Angela Crook declared receiving research support, including grants, from Unitaid for the TB CHAMP trial (GB£ 500 000) and from the National Institute for Health Research for the RID-TB trial (GB£ 2 million).

Gregory Fox declared receiving in-kind support from Sanofi pharmaceuticals towards provision of rifapentine for a clinical trial between 2018 and 2022 (approximately US$ 30 000).

Diana Gibb declared receiving academic funding for conducting TB trials in children. Funding was received from the Medical Research Council, Wellcome Trust and Department for International Development for the SHINE trial (approximately GB£ 3 000 000); from the Department for International Development, Wellcome Trust, Medical Research Council and National Institute for Health Research for the SURE trial (approximately GB£ 3 500 000); and from the Medical Research Council, Wellcome Trust, and Department for International Development’s Joint Global Trials programme and Unitaid for the TB CHAMP trial (approximately GB£ 450 000). All funding is situated with the MRC’s Clinical Trials Unit at UCL.

Unyeong Go declared being an employee of Green Cross Laboratories, which is a nonprofit organization under the GC Holdings group and one of the Republic of Korea’s largest clinical laboratories in the private sector that provides clinical and anatomical pathology reference testing. None of the sister companies is related to the meeting subject.

Jonathan Golub declared receiving research support, including grants, collaborations, sponsorships and other funding, from the US National Institutes of Health (US$ 2.4 million).

Amita Gupta declared receiving research support, including grants to her university, from the US National Institutes of Health and Centers for Disease Control and Prevention, Unitaid, the Gilead Foundation and the Wyncote Foundation.

Anneke Hesseling declared receiving research support from Stellenbosch University (US$ 2 million per annum) for several investigator-initiated research studies, and from the US National Institute of Health’s IMPAACT network, the Tuberculosis Trials Consortium, Biomedical Research Computing at the Wellcome Centre for Human Genetics/Wellcome Trust and Unitaid, for clinical research on prevention, diagnosis and treatment of children with TB.

Soyeon Kim declared receiving salary support through grants from the US National Institutes of Health. She works on studies in the areas of TB prevention, treatment and diagnostics. The studies that she works on could benefit from better trial designs.

Guy Marks declared receiving research support, including grants, from the National Health and Medical Research Council of Australia and also declared holding an office with The Union where he represented interests or defended a position related to the subject of the meeting.

Jyoti Mathad declared receiving research grants to study the prevention of TB in pregnant women. She was protocol chair of a study looking at the safety, pharmacokinetics and tolerability of 3HP in pregnant women with and without HIV.
Dick Menzies declared receiving research support, including grants, collaborations, sponsorships and other funding, from the Canadian Institutes of Health Research (Can$ 1.1 million annually for 2015–2023).

Thu Anh Nguyen declared receiving research grants from the National Health and Medical Research Council of Australia to her research unit at the Woolcock Institute of Medical Research to conduct studies on TB infection (Aus$ 10 000 000 from 2016).

Andrew Nunn declared receiving research support, including grants, collaborations, sponsorships, and other funding, from Janssen Pharmaceuticals and the US Agency for International Development for the STREAM trial, which partly covers his salary.

Elena Pallari declared possible research support, including grants, collaborations, sponsorships, and other funding, awarded to her institution, the MRC Clinical Trials Unit at UCL, that was not directly related to her work.

Patrick Phillips declared receiving research support, including grants, collaborations, sponsorships, and other funding, from the US Centers for Disease Control and Prevention and the National Institutes of Health, and the Bill & Melinda Gates Foundation, awarded to his institution for support for research activities.

Molebogeng (Lele) Rangaka declared being an infectious diseases clinician with active research and intellectual interest in the space of TB prevention.

Morten Ruhwald declared previous employment with the Statens Serum Institut in Denmark and a patent (WO2017084671A1), as well as explaining that employees and former employees of the Institute can be paid up to US$ 40 000 in taxable income if a license agreement involving patents with an employee as an inventor generates an extraordinarily high income for the Institute.

Jason Stout declared receiving research funding from the United States Centers for Disease Control and Prevention, awarded to his institution (approximately US$ 200 000 per year).

Susan Swindells declared receiving research support from the US National Institutes of Health as protocol chair of the BRIEF TB clinical trial (approximately US$ 40 000 in salary support and US$ 4000 in travel support). She also declared travel support to serve as a member of the US National Institute of Health’s guidelines panel on the TB section of antiretroviral guidelines for adults and adolescents (approximately US$ 2000).

Ezio Távora Dos Santos Filho provided expert opinion or testimony related to the subject of the meeting and holds a position where he represents interests or defends a position related to the subject of the meeting, by virtue of being a member of the WHO Civil Society Task Force, The Brazilian Research Network and the Brazilian National TB Community Advisory Board. As such, he advocates for the introduction and incorporation into health systems of improved technologies for TPT and he often remarks on the need to speed up related studies and adopt improved guidelines. He also declared that the outcome of the meeting would benefit the interests of others with whom he has a substantial common professional interest— that is, by knowing the communities affected by TB.
Rieke van der Graaf declared being a member of the independent Bioethics Advisory Committee to Sanofi. The topic of this meeting is not discussed in any of the independent advice that is given to Sanofi.

Andrew Vernon declared receiving nonmonetary support valued at more than US$ 1000 overall, including contributions (e.g. medications, costs of pharmacokinetic testing) from Sanofi to his employer, the US Centers for Disease Control and Prevention, to conduct a multinational phase III trial in collaboration with the US National Institutes of Health and Sanofi on daily rifapentine treatment. Previously, Sanofi contributed to the Centers for Disease Control Foundation to support research on rifapentine (approximately US$ 3 million over 10 years). These funds were applied to study supplies and materials, pharmacokinetic testing, and two to three contract staff who worked to support these trials. He also declared providing expert opinion or testimony related to the subject of the meeting and holding a position where he represented interests or defended a position related to the subject of the meeting by virtue of working for the Division of TB Elimination at the Centers for Disease Control and Prevention, where he directs a branch that conducts clinical trials in TB treatment and prevention.

Ian White declared receiving research support, including grants, collaborations, sponsorships, and other funding, awarded to the MRC Clinical Trials Unit at UCL, for a research programme in infections, including TB.

Genevieve Wills declared research support from the TB Alliance to the MRC Clinical Trials Unit at UCL to support TB trials (approximately GB£ 500 000).