

Report of the Technical Consultation

on

***Advances in Clinical Trial Design for
Development of New TB Treatments***

Glion-sur-Montreux, Switzerland

14-16 March 2018



WHO/CDS/TB/2018.17

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Contents

<i>Acknowledgements</i>	<i>v</i>
<i>List of Acronyms</i>	<i>vi</i>
<i>Welcome, Introduction, and Objectives.....</i>	<i>1</i>
<i>Session 1: Pharmacokinetics/pharmacodynamics, microbiology and biomarkers.</i>	<i>5</i>
<i>Session 2: Phase II to Phase III transition</i>	<i>10</i>
<i>Session 3: New trial designs and how they may facilitate regimen development.....</i>	<i>17</i>
❖ Sub-Session 3.1: Novel trial designs	17
❖ Sub-session 3.2: Measuring and maximizing adherence.	26
❖ Sub-session 3.3: Addressing special populations	31
<i>Session 4: The interplay between trials and guidelines: the importance of sound evidence to inform policy guidance and clinical practice.</i>	<i>37</i>
<i>Technical consultation Wrap-up.....</i>	<i>42</i>
<i>Closing statements</i>	<i>42</i>
<i>References.....</i>	<i>43</i>
<i>ANNEX 1 Agenda of WHO Technical consultation.....</i>	<i>45</i>
<i>ANNEX 2 Summary of Presentations</i>	<i>49</i>

*This report is dedicated to
Professor Denis Anthony Mitchison
who participated in the design of the very first randomised controlled
clinical trial for tuberculosis and devoted his whole life to improving
treatment for tuberculosis.*

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List of Acronyms

ART	antiretroviral therapy
BMI	body mass index
CFU	colony-forming units
DOT	directly observed therapy
DS	drug susceptible
EBA	early bactericidal activity
EMA	European medicine agency
FDA	Food and Drug Administration
GLP	Good Laboratory Practices
GRADE	Grades of Recommendation Assessment, Development and Evaluation
GTB	Global Tuberculosis Programme
HFS	hollow fiber system
HIV	human immunodeficiency virus
HRZE	isoniazid-rifampin-pyrazinamide-ethambutol
LAM	Lipoarabinomannan
LTBI	latent tuberculosis infection
MAMS	Multi-Arm Multi-Stage
MBL	Mannose-binding lectin
MDR	multi-drug-resistant
MGIT	Mycobacterial Growth Indicator Tube
MIC	minimum inhibitory concentration
MRC	Medical Research Council
NNT	number needed to treat
OBR	optimized background regimen
PD	Pharmacodynamics
PET/CT	positron emission tomography/computed tomography
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
QTc	corrected QT interval
SMART	Sequential, Multiple Assignment, Randomized Trial
STEP	Selection Trial with Extended Post-Treatment follow up
TB	tuberculosis
TRPs	target regimen profiles
TSCC	time to stable culture conversion
TTP	time to positivity
WHO	World Health Organization
XDR	extensively drug-resistant

The Global TB Programme of the World Health Organization (WHO) convened a technical consultation on “Advances in Clinical Trial Design for Development of New TB Treatments” in Glion-sur-Montreux, Switzerland, from 14 to 16 March 2018.

The consultation brought together researchers, academics, technical partners, TB drugs and regimens developers, trialists, regulators, guideline developers, programme managers, patient’s representative and nongovernmental organizations.

Welcome, Introduction, and Objectives

Chair Dr. Payam Nahid (UCSF) and Dr. Christian Lienhardt (WHO, GTB/RTE)

In his opening statements, Dr Nahid recognized that the tuberculosis (TB) therapeutics field has reached a key time point wherein broad reflection on the contemporary TB trials of the last 15 years is warranted: what have we done correctly?, what were our mistakes?, and how can we improve? With the anticipated emergence of new drugs for TB, now more than ever, there is a need to revisit our approaches and define best practices for TB clinical trial design for the development of new regimens. Dr. Nahid noted that this is the first ever meeting to gather such a diverse group of stakeholders, including trialists, academia, research institutions, TB drug and regimen developers, contract organizations, regulators, guideline developers, non-governmental organizations and civil society to address these questions, and he thanked the Global Tuberculosis Programme (GTB) of the World Health Organization (WHO) for organizing and sponsoring this unprecedented consultation.

Dr. Lienhardt described the background and objectives of the consultation. The *Task Force on Introduction of New TB Drugs and Treatment Regimens*, established by the WHO/Global TB Programme (GTB), developed in 2016 a series of Target Regimen Profiles (TRPs) for new TB treatment through broad consultation with experts and stakeholders worldwide. The TRPs are intended to guide the development process towards anti-TB treatment regimen characteristics of critical importance to patients and programmes. To assist in the implementation of these TRPs, there is a need to guide the research community on optimal clinical trial designs and features for new anti-TB drugs and regimens, in consultation with relevant stakeholders in the field. The major challenges in the development of new TB treatments include the long developmental pathway to identify best regimens, the lack of direct readout of response and use of surrogate endpoints, and the lack of predictive quantitative relationships between Phase II and Phase III readouts. Clear and rationally justified approaches for the choice of drug combinations, trial design, selection of endpoints and analysis, are critically important, taking

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