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

END TB

World Health Organization

WHO/CDS/TB/2018.17

Suggested citation. 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. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.17). Licence: CC BY-NC-SA 3.0 IGO).

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

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Contents

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.

Acknowledgements

Overall organization of the technical consultation

Christian Lienhardt & Payam Nahid

Chairman and Facilitators

Chairman: Payam Nahid. *Facilitators*: Lori Dodd, Michael Hoelscher, John Johnson, Carole Mitnick, Sumati Nambiar, Jim Neaton, Michael Rich, Rada Savic, Monique Surette, Andrew Vernon.

WHO Task Force on Introduction of New TB Drugs and Treatment Regimens

Payam Nahid (Chairman), Draurio Barreira, Grania Brigden, Geraint Davies, Kelly Dooley, Michael Hoelscher, Michael Kimerling, Alberto Matteelli, Norbert Ndjeka, Nguyen Viet Nhung, Michael Rich, Alena Skrahina, Andrew Vernon.

Technical consultation Participants

Abdel Babiker (United Kingdom), Draurio Barreira (Switzerland), Nilesh Bhatt (Mozambique), Martin Boeree (Netherlands), Grania Brigden (France), Marco Cavaleri (United Kingdom), Tsira Chakhaia (Geaorgia), Edward Cox (USA), Geraint Davies (United Kingdom), Rodney Dawson (South Africa), Anne-Marie Demers (South Africa), Lori Dodd (USA), Kelly Dooley (USA), Kathy Eisenach (USA), Katherine Fielding (United Kingdom) , Mengqiu Gao (China), Jan Gheuens (USA) , Amita Gupta* (USA), Debra Hanna (USA), David Hermann (USA), Anneke Hesseling* (South Africa), Michael Hoelscher (Germany), Michael Hughes (USA), Amina Jindani (United Kingdom), John Johnson (USA), Soyeon Kim (USA), Michael Kimerling (Netherlands), Barbara Laughon (USA), Regine Lehnert (Germany), Vidya Mave (India), Alberto Matteelli (Italy), Carl Mendel (USA), Carole Mitnick (USA), Sachiko Miyahara (USA), Stella Mpagama (Tanzania), Sumati Nambiar (USA) , Norbert Ndjeka* (South Africa), Jim Neaton (USA), Nguyen Viet Nhung* (Vietnam), Andrew Nunn (United Kingdom), Bern-Thomas Nyang'wa (United Kingdom), Patrick Phillips (USA), Michael Rich (USA), Rada Savic (USA), Alena Skrahina* (Belarus), Jason Stout (USA), Monique Surette (Netherlands), Cherise Scott (Switzerland), Elin Svensson (Netherlands), Anete Trajman (Brazil), Andrew Vernon (USA) , Robert Wallis (South Africa). (*: remote participation)

WHO/HQ Secretariat

Christian Lienhardt (GTB/RTE), Dennis Falzon (GTB/LDR), Lorenzo Moja (EMP), Nicola Cocco (GTB/RTE), Piero Luigi Olliaro (TDR), Matteo Zignol (GTB/TME), Tereza Kasaeva (GTB).

Administrative and secretarial support

Lou Maureen Comia, Michael Tabiszewski

Meeting Report written by

Marjorie Imperial & Christian Lienhardt, with input from Payam Nahid and review by all participants

Financial support:

This consultation was financially supported by the Bill and Melinda Gates Foundation, grant Number: OPP1126615

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