Update on Regional operational research on introduction of fully-oral modified shorter treatment regimens for RR/MDR-TB

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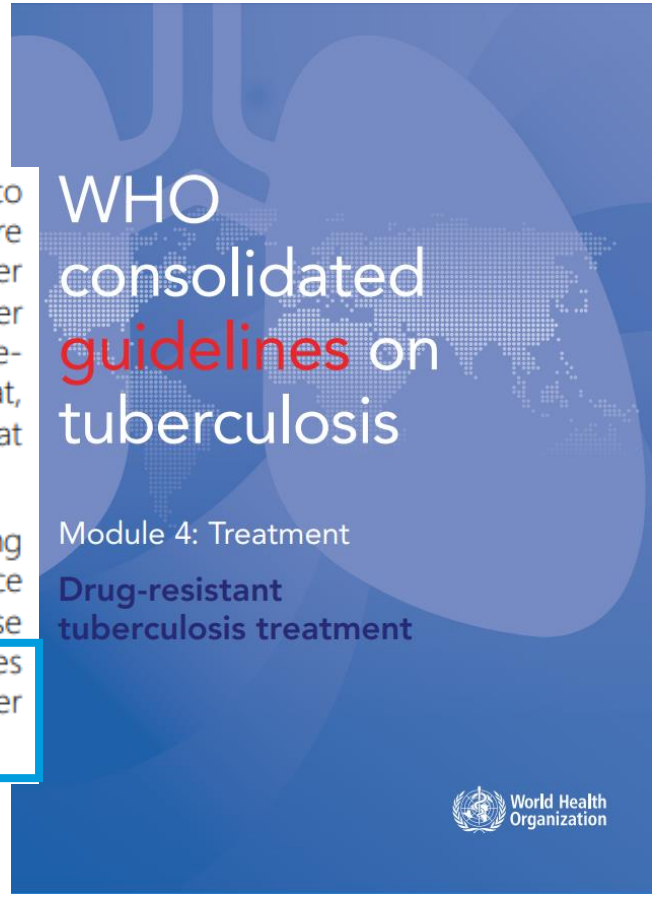
WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment – Drug-Resistant Tuberculosis Treatment

Secondary analyses determined that a bedaquiline-containing shorter regimen was comparable to an all-oral longer regimen containing both bedaquiline and linezolid, in terms of death and failure outcomes; however, the shorter regimen seemed to have significantly less loss to follow-up. Further sensitivity analyses (albeit in the longer regimens containing bedaquiline–linezolid versus longer regimens containing bedaquiline only) determined that the addition of linezolid to bedaquiline-containing regimens would, overall, improve outcomes. Nevertheless, the GDG concurred that, because of the lack of direct data for shorter regimens, no general conclusions could be drawn at the time.

Until new evidence is forthcoming and available to WHO, the shorter all-oral bedaquiline-containing regimen advised to be used does not include linezolid. In settings with a high probability of resistance to, or confirmed resistance to, ethionamide, ethambutol, pyrazinamide, clofazimine and high-dose isoniazid, further modifications of the regimen using priority grouping of second-line oral medicines may be implemented; however, the efficacy, safety and tolerability of additionally modified shorter regimens are unknown and should be evaluated under operational research conditions.



Introduction of fully-oral shorter regimens for MDR/RR-TB under operational research conditions (ERI-TB initiative)

Currently 13 countries joined the initiative:

ARM, AZE, BLR, GEO, KAZ, KGZ, LVA, *LTA*, *MDA, TJK, TKM, UKR, UZB*

Official invitation sent to: *ROM*

Objectives:

- To facilitate introduction of all-oral mSTR for MDR-TB under OR;
- To foster good clinical care for MDR-TB through OR;
- To build and strengthen the research capacity in countries;
- To contribute to global knowledge for generation of new policy guidance for DR-TB.

WHO accompaniment

mSTR Task Force and Secretariat ensure:

- Development of Regional operational research package and data collection instrument;
- Support on adaptation of country-specific OR protocols, guidance for national study teams on essentials of implementation, including form completion and data collection;
- Submission of country OR protocols to WHO ERC;
- Methodological support throughout research implementation, data management and analysis, as well as quarterly external monitoring.

List of TF members:

Jay Achar
Ana Ciobanu
Gunta Dravniece
Elmira Gurbanova
Arax Hovhannesyan
Naira Khachatryan
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Nino Lomtadze
Michael Rich
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Secretariat:

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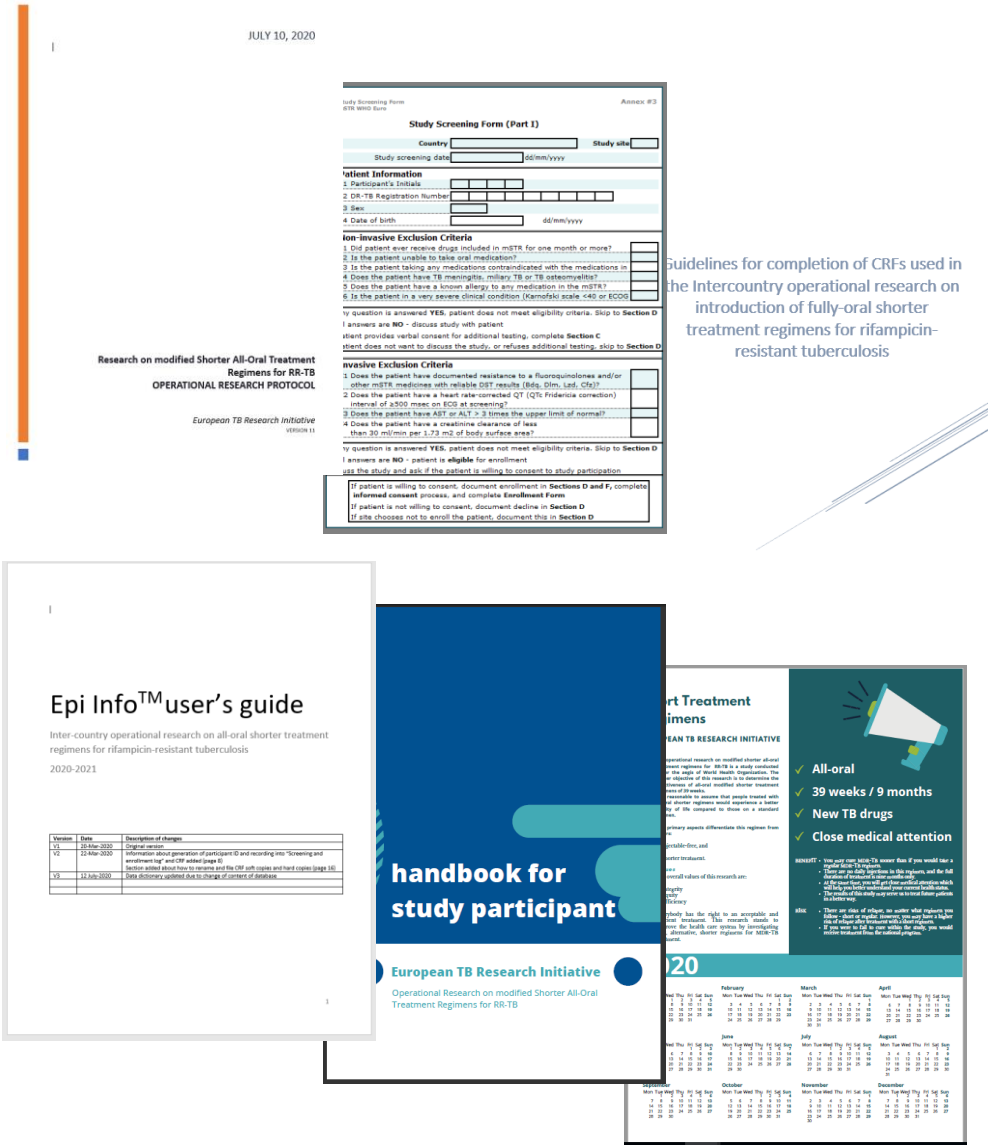

Treatment regimens under investigation

In this study, three all-oral shorter RR-TB treatment regimens are proposed, based on knowledge of their safety and efficacy as of 2020.

For adult patients:

Regimen 1: 39 weeks Lfx + Bdq + Lzd + Cfz + Cs

Regimen 2: 39 weeks Lfx + Bdq + Lzd + Cfz + Dlm

Treatment regimen 1 is preferred in adults as it includes all Group A and Group B anti-TB drugs. In patients with suspected resistance or intolerance of Cs, regimen 2 should be considered as primary choice of therapy.

For children:

Regimen 3: 39 weeks Lfx + Dlm + Lzd + Cfz

Fully-oral STRs: initial step to making treatment less painful

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Standard treatment regimen for DR-TB (before 2018)

24 months

14 600 pills

280 daily injections

x3 times lower pill burden

Fully-oral standard treatment regimen for DR-TB (2020)

18-20 months

4 500 pills

0 injections

mSTRs: six times less pill burden for patients

Fully-oral modified shorter treatment regimen for DR-TB

9 months

2 300 pills

0 injections

More than 6 times less burden for patients compared with standard treatment regimen (before 2018)

mSTR project timelines

September - December 2019

First draft of regional OR package is prepared by mSTR task force, which includes:
- OR protocol
- Case report and informed consent forms
- Patient education materials
- Clinical guide on mSTRs
- aDSM system
- Standardized data collection instrument
- Form completion and data entry guidelines

December 2019
Package is presented to 11 EECA countries

January – February 2020

Regional OR package is adapted based on the feedback from the countries

End of February 2020:
1) Regional OR package submitted to countries to begin adaptation

March – June 2020

- mSTR task force assists countries with adaptation of regional OR set to country specific conditions
- Implementation of initial country missions to:
  - Discuss project implementation plans
  - Support development of country protocols
  - Train national study teams on practical aspects of study implementation, such as aDSM, form completion and data entry

11 July 2020:
Protocol of the 1st country is approved by scientific reviewers and WHO ERC (now regarded as Master Protocol)

July – September 2020

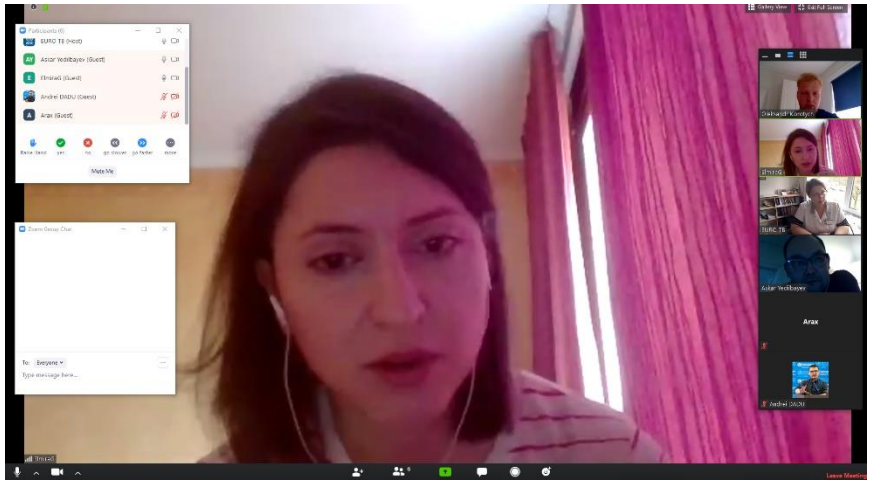
- mSTR task force members assist countries in **aligning their protocols with WHO ERC approved Master Protocol** (with changes based on scientific and ERC reviews)
- Country protocols are submitted for review of national IRBs and, subsequently, for WHO ERC for fast-track review
- Preparation of regional virtual medical consilium launch
- Invitation to join the initiative is extended to Latvia, Lithuania and Romania

September 2020:
1) Virtual medical consilium (VMC) is launched
2) First patients are enrolled in Armenia and Republic of Moldova

October 2020 - and for 33 months

- All countries have their protocols submitted to WHO ERC by October 2020
- Local research team members are being trained to begin enrollment of patients
- Implementation starts in the rest of the countries (start date varies across countries) and last for 33 months
- **First webinar of the VMC is planned for 7 October 2020**

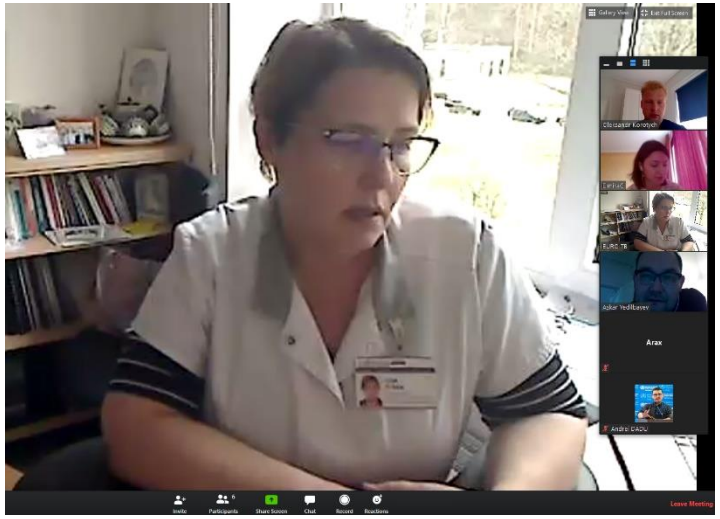
Virtual country missions



Эффект Ноцебо

«Принцип информированного согласия обязывает врачей объяснять возможные побочные эффекты при назначении лекарств. Это раскрытие может само по себе вызывать неблагоприятные воздействия посредством механизмов ожидания, **известных как эффекты** Ноцебо, противоречащих принципу неэффективности. Серьезные исследования показывают, что предоставление пациентам подробного перечня всех возможных побочных эффектов может фактически усилить побочные эффекты»

Говорить правду, всю правда, может навредить пациентам: проблема эффекта Ноцебо для информированного согласия. R.E. Wells; Am J Bioeth. Март 2012 года; 12 (3): 22–29.



Individual country progress

Country	National IRB approval	WHO ERC approval	Expected cohort size	Enrollment start date	Current status
Armenia	Approved	Approved	35 patients	28 August 2020	**Enrollment started**
Republic of Moldova	Approved	Approved	200 patients	15 September 2020	
Ukraine	Approved	Approved	From 2230 to 3470 patients	October 2020	Launch of the study is being prepared
Azerbaijan	Approved	Approved	180 patients		
Belarus	Approved	Approved	500 patients		
Uzbekistan	Approved	Approved	600 patients		
Georgia	Approved	Being reviewed	110 patients + ‘100 retrospective		Approval of National IRB is granted. OR package is submitted to WHO ERC. Awaiting decision
Tajikistan	Approved	Being reviewed	150 patients		
Kazakhstan	Approved	Being reviewed	200 patients		
Latvia	Approved	Submission in progress	40 patients		Approval of National IRB is granted. Submission to WHO ERC is in progress
Turkmenistan	Submission planned	Submission planned	100 patients	November 2020	OR package is under finalization; to be submitted to National IRB
Lithuania	Submission planned	Submission planned	*Tentatively 40 patients*		
Kyrgyzstan	Submission planned	Submission planned	100 patients	January 2021	

Planned cohort size

Country	Cohort size	Regions
Armenia	**35 patients**	All country
Azerbaijan	**180 patients**	Baku, Sumgait, Absheron and Ministry of Justice
Belarus	**500 patients**	All country
Georgia	**110 patients + '100 retrospective**	All country
Kazakhstan	**200 patients**	▪ In 2020: Turkestan and Karaganda Oblast ▪ Additionally from May 2021: Akmola, Atyrau, Zhambyl Oblast with a possibility of expanding to other regions
Kyrgyzstan	**100 patients**	Bishkek city and Chui oblast
Latvia	**40 patients**	All country
Lithuania	***Tentatively 40 patients***	Klaipeda hospital
Republic of Moldova	**200 patients:** 160 on Bdq&Cs; 40 on Bdq+Dlm	Public Medical Sanitary Phthisiopneumology Institute (IMSP) "Chiril Draganiuc" (covering the left bank of the country), Penitentiary sector
Tajikistan	**150 patients**	▪ In 2020: Dushanbe city and rayons: Hisor, Tursunzoda, Shahrinaw, Vahdat, Rudaki, Faizobod, Roghun, Nurobod, Rasht, Tojikobod, Laksh, Sangvor, A. Jami, Temumalik, Dangara. ▪ Additionally from January 2021: Kulab, Vase, Muminabad, Khovaling, Baldjuan, Shurabad, Khamadoni, Parkhar, Khojent, J.Rasulov, B. Gafurov, Isfara, Mastchoh, Panjakent.
Turkmenistan	**100 patients**	National Center for the Prevention and Treatment of Infectious Diseases (Ashgabat)
Uzbekistan	**600 patients** 540 on Bdq&Cs; 60 on Bdq+Dlm	▪ In 2020: Republic of Karakalpakstan, Tashkent city, Bukhara, Fergana ▪ Additionally from January 2021: Andijan, Jizzakh, Surhandarya, Sirdarya, Tashkent region
Ukraine	**From 2230 to 3470 patients**	▪ In 2020: 15 regions and National Institute of Phthisiology and Pulmonology ▪ From January 2021: the study will be rolled out to all regions

Thank you!

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