First annual meeting of the national study teams: regional operational research on the introduction of fully oral modified shorter treatment regimens (mSTR) for multidrug/ rifampicin-resistant tuberculosis

Report

Virtual meeting hosted from Copenhagen, Denmark
25–26 August 2022
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Abstract

The First annual meeting of the national study teams was held on 25–26 August 2022. Due to the COVID-19 pandemic, the meeting was held virtually, allowing all participants to join remotely. The objectives of the meeting were to review the progress of implementation of operational research on modified shorter treatment regimens (mSTR) for multidrug/rifampicin-resistant tuberculosis in the 13 WHO European Region countries involved; present the preliminary findings from the regional mSTR cohort; discuss the data quality for the regional mSTR cohort and plan steps for its improvement; introduce the results of the mid-project evaluation; and agree on the next steps for the initiative for 2022–2023. It was established that mSTR operational research had shown visible progress, with 13 countries enrolling 2805 patients into the regional research cohort as of June 2022. Although promising preliminary results are outlined, the research is in progress and final conclusions are yet to be drawn. The new action plan 2023–2030 will be endorsed in September 2022 and, aligning with the pillars of the new plan, countries are called upon to strengthen and establish research units within national tuberculosis control programmes and to further work on the quality of mSTR data in order to prepare datasets for further analysis and delivering recommendations from the results in 2023–2024.

Keywords: TUBERCULOSIS; PREVENTION AND CARE; OPERATIONAL RESEARCH; EPIDEMIOLOGY; EUROPEAN REGION

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## Abbreviations

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<th>Definition</th>
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<tbody>
<tr>
<td>aDSM</td>
<td>active TB drug-safety monitoring and management</td>
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<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AEI</td>
<td>adverse event of interest</td>
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<tr>
<td>BPaL</td>
<td>bedaquiline, pretomanid and linezolid</td>
</tr>
<tr>
<td>BPaLM</td>
<td>bedaquiline, pretomanid and linezolid with moxifloxacin</td>
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<tr>
<td>DR-TB</td>
<td>drug-resistant tuberculosis</td>
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<tr>
<td>DST</td>
<td>drug-susceptibility testing</td>
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<tr>
<td>GDF</td>
<td>Global Drug Facility</td>
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<tr>
<td>Global Fund</td>
<td>Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
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<tr>
<td>MDR/RR-TB</td>
<td>multidrug- and rifampicin-resistant tuberculosis</td>
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<tr>
<td>MSF</td>
<td>Médecins sans Frontières</td>
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<tr>
<td>mSTR</td>
<td>modified shorter treatment regimens</td>
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<tr>
<td>MTB</td>
<td>mycobacterium tuberculosis</td>
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<tr>
<td>NTP</td>
<td>national tuberculosis control programme</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<tr>
<td>SAE</td>
<td>serious adverse event</td>
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<tr>
<td>sSTR</td>
<td>standard short-treatment regimen</td>
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<tr>
<td>VMC</td>
<td>Virtual Medical Consilium</td>
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<tr>
<td>VOT</td>
<td>video-observed treatment</td>
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<tr>
<td>VST</td>
<td>video-supported treatment</td>
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<tr>
<td>XDR-TB</td>
<td>extensively drug-resistant tuberculosis</td>
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</table>
Acknowledgments

WHO Regional Office for Europe is grateful to the participants who attended the First annual meeting of the national study teams of the regional operational research on the introduction of fully oral modified shorter treatment regimens (mSTR) for multidrug/rifampicin-resistant tuberculosis on 25–26 August 2022.

Report by Ms Myroslava GERMANOVYCH and Mr Oleksandr KOROTYCH, WHO Regional Office for Europe.
Introduction

As a part of the transition to the latest WHO policy guidance on drug-resistant tuberculosis (DR-TB), the WHO Regional Office for Europe, via the European Tuberculosis Research Initiative which has been promoting tuberculosis (TB) research in Member States since 2016, launched the regional operational research on the introduction of the fully oral modified shorter treatment regimens (mSTR) for multidrug/rifampicin-resistant TB (MDR/RR-TB). The objectives of the project are:

- to improve treatment success rates for MDR/RR-TB;
- to facilitate the introduction of all-oral mSTR for patients with MDR/RR-TB under operational research conditions;
- to foster good clinical care for patients with MDR/RR-TB through operational research;
- to build and strengthen the research capacity in countries; and
- to contribute to the global knowledge on the effectiveness and safety of all-oral mSTR for MDR/RR-TB and to provide a basis for future recommendations by WHO.

In September 2019 the WHO Regional Office for Europe established a task force with the following aims: to develop a package for regional operational research to include a standard set of materials and tools; to facilitate the implementation of research at the country level; to harmonize and analyse data; and to generate quality evidence for further submission to the next round of the WHO Guideline Development Group. Subsequently, the Regional Office has been providing technical support to Member States that joined the regional mSTR operational research initiative through the mSTR task force, including guidance on the country-specific adaptation of the study package, training for country study teams, support for ethical approvals and guidance on the use of the data collection tool and monitoring the progress of the implementation.

The master protocol of the regional operational research on the introduction of mSTR for MDR/RR-TB was approved by the WHO Ethics Review Committee at the beginning of July 2020. The first patients were enrolled into the study in August 2020 in Armenia and by June 2022 there were more than 2800 patients in the regional cohort. A total of 13 WHO European Region countries (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, Tajikistan, Turkmenistan, Ukraine and Uzbekistan) have joined the initiative and initiated patient enrollment by June 2021.

In September 2020 the WHO Regional Office for Europe, in collaboration with the Center for Health Policies and Studies (Republic of Moldova), launched the mSTR Virtual Medical Consilium (VMC) within the TB REP 2.0 Project (a Regional eastern European and central Asian TB Project). The objectives of the VMC are to support countries to enrol patients to mSTR operational research, provide expert advice and discussions on complicated clinical cases, provide guidance on treatment adjustment/discontinuation
according to the study protocol, contribute to the further strengthening of clinical and programmatic capacity and to foster good clinical care in the Region.

To summarize the regional experiences and share the latest initiative updates and developments, on 25–26 August 2022 the WHO Regional Office for Europe hosted the first annual meeting of the mSTR national study teams from the 13 of the WHO European Region countries involved. Objectives of the meeting were:

- to review the progress of mSTR implementation in the 13 WHO European Region countries involved;
- to present the preliminary findings from the regional mSTR cohort;
- to discuss the data quality for the regional mSTR cohort and plan steps for its improvement;
- to introduce the results of mid-project evaluation; and
- to agree on the next steps for the initiative for 2022–2023.

Day 1: meeting overview
Session 1. TB regional action plan 2023–2030: pillar I and pillar III

Dr Askar Yedilbayev, Team Lead, TB, Joint Infectious Diseases Unit, Division of Country Health Programmes, WHO Regional Office for Europe, Annual Meeting Chair and Mr Oleksandr Korotych, Joint Infectious Diseases Unit, Division of Country Health Programmes, WHO Regional Office for Europe, welcomed annual meeting speakers and participants. Dr Yedilbayev shared mission scope and agenda.

In the opening presentation Dr Yedilbayev informed participants that the burden of DR-TB poses a public health security threat to the many countries from eastern Europe and central Asia, with nine countries within the Region accounting for more than 97% of the estimated number of incident MDR/RR-TB cases, each registering more than 1000 cases per year. Although certain successes have been achieved, overall treatment success for MDR/RR-TB remains suboptimal. The treatment success rate for extensively drug-resistant TB (XDR-TB) in 2018 was 51%, higher than previously, which indicates that patients have benefited from these new TB medications. Subsequently, Dr Yedilbayev presented the data for the 12 countries that make up the regional operational research initiative (data from Latvia are missing) and pointed out that in 2018, a year before the regional operational research started, treatment outcome for MDR/RR-TB was 64%, which was higher than the regional average, although still suboptimal. It is expected that the cohort of 2019 will show greater treatment success, as access to the new TB treatment has scaled up and the cohort of 2020 will contribute to further increases in treatment outcomes through the introduction of mSTR under operational research conditions. WHO has developed a new action plan 2023–2030 for TB that will be endorsed in September 2022, addressing challenges such as the COVID-19 pandemic (caused by severe
acute respiratory syndrome coronavirus 2 (SARS-CoV-2)), the humanitarian crisis triggered by the war in Ukraine, the high burden of DR-TB and the high prevalence of HIV coinfection among patients with TB. The plan has strategic and operational aspects which will help to get progress outcomes back on track. Intensified research and innovations as a part of the plan will also facilitate better outcomes for Member States. The original Tuberculosis action plan for the WHO European Region 2016–2020 (1) follows the structure of the global End TB strategy, with three pillars: integrating people-centred care and prevention, shaping policies and supportive systems, and intensifying research and innovation. The vision of the new regional action plan is a Region free of TB burden by 2030, with the goal of preventing the spread of drug-susceptible TB and DR-TB by achieving universal access to diagnosis and treatment in all Member States. Dr Yedilbayev described the aims of TB deaths by 25% and TB incidence by 35% by 2020, and the goal of improvement of treatment success (2). He further presented examples of the action points from the regional action plan, stressing that that all actions in combination are meant to lead to achieving targets of 2030 on reducing the burden of TB. Finally, Dr Yedilbayev outlined how pillar III is intended to create an enabling environment for TB research and innovation, promote and improve approaches, increase investments and targets for funding contributions and promote equitable access to the benefits of research and innovation. The WHO Regional Office for Europe, together with partners, will support Member States with operationalization of the objectives set up in the Global Strategy for TB Research and Innovation. The mSTR operational research will also provide contribution to achieving these aims.

Session 2. Progress of research implementation

Mr Korotych updated participants on the background of the mSTR operational research, which was initiated based on the WHO consolidated guidelines on drug-resistant tuberculosis (released in 2019 and updated in 2020) (3,4). In the guidelines, introduction of modification to the standard short-treatment regimen (sSTR) for MDR/RR-TB using group A and group B drugs from the WHO priority list was allowed under operational research conditions. The WHO Regional Office for Europe, aiming to support Member States with the operationalization of this recommendation and its regimens, established the mSTR task force in September 2019, with the primary goal of shaping and supporting the new initiative. The objectives of the initiative were to facilitate and speed up implementation of regimens, contribute to the provision of proper clinical care, establish and strengthen research capacity in the Region and deepen global knowledge on mSTR to inform future rounds of DR-TB guidelines development. Further, Mr Korotych reminded participants about three treatment regimens included in the initiative, with two regimens intended for adult
patients\textsuperscript{1,2} and one for children under 6 years of age.\textsuperscript{3} It was also noted that according to the most recent WHO recommendations on dosages for bedaquiline and delamanid (5), the two adult regimens can also be used for children. In December 2019 countries were introduced to the regional operational research package developed by the mSTR task force including protocol, management guidelines for adverse events (AEs), data collection forms, databases and other research materials. As of June 2022, 2805 patients had been enrolled into the regional mSTR cohort in 13 countries. Following completion of enrollment in the regional cohort, countries initiated national cohorts, with additional 1419 patients enrolled as of 2022. Advantages of the treatment offered within this initiative are the reduced pill burden (dropped by six compared with 2019), no painful injections and the overall duration of treatment shortened by half. The Secretariat recommends countries to continue enrollment into the mSTR national cohorts until the programmatic implementation of bedaquiline, pretomanid, linezolid (BPaL) or BPaL with moxifloxacin (BPaLM) regimens begin, and to further consider the implementation of mSTR operational research for children under the age of 15 years as the BPaL or BPaLM regimens are not recommended for children and adolescents. Mr Korotych gave an overview of research timelines and milestones, starting with a regional meeting in Kyiv in December 2019, where all participating countries were presented with the operational research initiative package, and ending with the latest interventions undertaken in 2022, such as the mid-project evaluation of the mSTR project to assess the regional experience and the establishment of a subgroup of the mSTR task force to support countries with preparations for programmatic scale up of BPaL or BPaLM. The plans for 2020–2024 were outlined: for WHO to visit countries to provide on-site monitoring and detect possible issues and any help needed; to launch mSTR data backup and a cohort monitoring platform; to virtually train data managers on mSTR data cleaning and analysis; to deliver a final report on the mid-project evaluation; to launch a VMC online platform; to hold a second annual meeting of national mSTR study teams in February 2023; to provide training for primary investigators and the managers of national TB control programmes (NTPs) on the use of data in programmatic practice and strategies; to conduct an advanced course on data analysis in June 2023; to finalize the regional dataset; to prepare and to disseminate the research report; and to publish the findings of the regional cohort in a peer-reviewed journal. Mr Korotych reminded participants that there is still the possibility of educating patients as to the benefits of mSTR by scaling up national cohorts beyond pilot regions (for those countries that did not implement mSTR operational research countrywide). It was also noted that it is desirable to include children in the research; only 40 children were enrolled into the regional cohort, but not all countries allowed enrollment of children in their operational research protocols. By the end of the presentation, it was

\textsuperscript{1} Regimen 1 consists of levofloxacin, bedaquiline, clofazimine and cycloserine.
\textsuperscript{2} Regimen 2 consists of levofloxacin, bedaquiline, clofazimine, cycloserine and delamanid.
\textsuperscript{3} Regimen 3 consists of: levofloxacin, delamanid, linezolid, and clofazimine.
established that the important next step for mSTR research was to recommend countries to offer screening for hepatitis C virus (HCV), which would allow an estimation of the burden of HCV among patients with MDR/RR-TB. The prevalence of HCV in the cohort of patients was found to approach 11%, which led to the development of a new initiative. In May 2022 this new initiative on concomitant treatment of HCV and MDR/RR-TB was introduced, and participating countries are encouraged to join this initiative.

Session 3. The VMC and its role in the introduction of mSTR

Dr Elmira Gurbanova, mSTR Task Force Member, Coordinator of the VMC and Consultant, WHO Regional Office for Europe, updated participants as to the main goals of the VMC: provision of technical assistance to participating countries; counselling on management of complicated clinical cases; and development of clinical capacity through monthly webinars. Dr Gurbanova confirmed that VMC experts are ready to advise countries on the management of patients on BPaL or BPaLM regimens, in addition to consulting on mSTR and on the co-management of MDR/RR-TB and HCV. A well-developed schedule ensures that three experts are always on duty and alternative experts are available for the cases of emergencies. In practice, it was clear that countries submit cases to the VMC after they have already been discussed at their national medical councils. After an application is received, a VMC coordinator forwards the request to the experts on duty, and countries receive the consensus reply from three international experts within two days via email. On average the VMC provides a response within 39 hours. During the course of the study, exponential growth in the cumulative number of consultations was observed. At the beginning of the practice, the VMC received single requests, but as the VMC became better known during the course of the research, the number of consultations increased. As of June 2022 as many as 200 consultations had been provided. Depending on the request or in severe cases, the VMC tries to provide its response immediately. Dr Gurbanova described the sociodemographical profile of the average case submitted to the VMC as a 40 year-old male, but also mentioned that the youngest age of a patient consulted was 3 months, and the oldest patient consulted was 82 years old. The majority of questions addressed to VMC were related to the treatment of RR-TB in patients who were susceptible or resistant to fluoroquinolone. Subsequently more questions arose about the management of patients with resistance to fluoroquinolones, including patients on BPaL treatment regimens. Dr Gurbanova stressed that despite comprehensive WHO policy guidance and training, physicians required additional assistance regarding the interpretation of the guidelines. A lot of new recommendations and approaches to TB management have been introduced, and the amount of information is increasing quickly. Physicians do not always have time to keep up with such updates and introduce them into their practice. Hence, the VMC offers webinars where experts try to present critically important changes in recommendations that can potentially improve TB management in the countries, in a timely manner. Records of those seminars are available online. At the end of her presentation, Dr
Gurbanova stated that her next webinar will be dedicated to the regional action plan for tuberculosis 2023–2030, and that all interested parties are welcome to join.

**Session 4. Preliminary findings**

**Dr Gurbanova** initially presented information based on the country logbooks for the regional cohort, where the number of enrolled patients and the reasons for non-enrollment were registered by country teams. Almost 6500 patients were screened for enrollment into the study; almost half were patients from Ukraine, and 43% of patients screened started treatment with mSTR. The key reason for non-enrollment was resistance to fluoroquinolones, accounting for 30% of all non-enrolled cases, while 16% of patients were not enrolled because of reasons not foreseen in the protocol as exclusion criteria. These were exposure to the component drugs of mSTR regimens for more than one month; severe clinical conditions; decline of the patient; no drug-susceptibility testing (DST) for fluoroquinolones; or occurrence of miliary TB, TB osteomyelitis or TB meningitis. In addition, 5% of patients had other exclusion criteria that were defined after enrollment into mSTR operational research; for example, electrocardiography abnormality (QTc more than 500 ms) or allergic reaction to the components drug of mSTR. Among non-enrollment reasons not set out in the protocol were clinically confirmed RR-TB, decisions made by the VMC without the indication of the cause, cases of extrapulmonary TB (Armenia, Georgia) and patients under 18 years of age – even though the generic protocol allowed for the enrollment of children and adolescents. Some patients were not enrolled because they were currently enrolled in other clinical trials. Several reasons were socially related, such as the lack of a permanent place of residence or multiple occasions of discipline violations. At this point, participants were reminded that social reasons might be tackled through collaboration with civil society organizations and nongovernmental organizations to enhance social support. Inmates and military officers were often deprived of an opportunity to be treated within mSTR research. The percentage of fluoroquinolone-resistant cases registered in 2020 based on surveillance and the percentage based on enrollment screening in countries conducting mSTR operational research were either similar or the fluoroquinolone resistance rate was lower among the screened population than in the mSTR cohort. This might be explained by the fact that some countries enrolled patients only in pilot regions and not countrywide. The average percentage of patients with a history of use of mSTR drugs for more than one month was 12% of the entire cohort. Therefore, they were ineligible for mSTR treatment. About 6% of all screened patients had severe clinical critical conditions, and this percentage varied from zero in Latvia and Lithuania, to 9–10% in the Republic of Moldova and Ukraine. Refusal rate on average was 7%, but varied from 0–3% in Azerbaijan, Belarus, Tajikistan and Ukraine, to 20% in Turkmenistan and 40% in Kyrgyzstan. There were also some potential patients with no DST for fluoroquinolones but this was mainly an issue at the start of operational research. Supervision within research acted to strengthen country capacity and
helped to improve the quality of care and quality of TB services, because by the end of enrollment period there were almost no patients screened who had not had DST.

**Mr Korotych** introduced participants to the preliminary outcomes of the mSTR operational research (regional cohort) based on the analysis of country datasets, stressing that all data are preliminary, and that findings are based on a research project that is still in progress. A slight gender imbalance was observed in the regional cohort, with one quarter being female patients and the rest males. This, nevertheless, follows the regional gender pattern of RR-TB. The age groups within the studied cohort were outlined, alongside the fact that 3% of patients had no data on TB history, which signifies the issue of incompleteness of data collection. The concomitant diseases observed within the cohorts were HIV (10.4%), HCV (10.8%), diabetes mellitus (8.5%) and hepatitis B virus (2.5%). Mr Korotych stressed that the database revealed that testing for hepatitis B virus and HCV did not occur for about 1% of patients. Potential risk factors for unfavourable outcome were malnourishment (22.0%), alcohol abuse (15.6%), injected drug use (3.6%) and homelessness (2.7%). In future, additional statistical analysis will be performed in order to assess how the risk factors affected the treatment outcomes and how they affected the incidence of AEs, particularly serious adverse events (SAE). The majority (83%) of patients had unilateral or bilateral lesions detected via radiography. At least one abnormality of assessed related factors was registered at baseline in 60% of patients (1683). The most common disturbances were myelosuppression (22%), elevated liver enzyme/enzymes (20.8%), electrolyte disturbance (13.9%) or reduced visual acuity (17.8%). Fewer patients had signs of peripheral neuropathy, elevated creatinine or QT prolongation on electrocardiography. Culture conversion rate among eligible patients was over 85%, but this is a preliminary outcome, as some data are still missing and the rate is likely to increase. Among eligible patients who achieved conversion, median time to culture conversion was 34 days. Successful end-of-treatment outcomes were registered in 86% of patients (among those started treatment before September 2021 with available data). It was stressed that not all patients' data were analysed, as 15.9% of information about treatment outcome was missing. The analysis will be repeated after countries enter all their data into databases. In the operational research protocol, a great deal of attention was paid to the safety and the monitoring and reporting of AEs. Seven conditions were selected as adverse events of interest (AEIs): peripheral neuropathy, myelosuppression, prolonged corrected QTcF interval on electrocardiography (corrected QT interval to avoid influence of extreme heart rates), optic nerve disorder, hepatitis, hyperkalaemia and acute kidney injury by the mSTR task force.

In total, 495 SAEs were registered, and of these, 489 occurred during treatment. Most of the SAEs occurred in the early months of treatment; the occurrence of SAEs in the later stages of treatment was significantly lower. About half of the AEs were in those that were monitored in the study protocol as AEI. The majority of patients tolerated the treatment well, with 86.5% of patients not experiencing any SAE. It was observed that 115 SAEs were of severity grade 1 or 2 (mild/moderate), which likely reflects the fact that in some
countries the management of AEs, even if they are of grade 1 or 2, should be organized in inpatient settings because the drugs needed for their management are not available free of charge for outpatients. As for the actions taken in response to SAEs: 8% of cases required temporary or permanent cessation of one or more drugs or of the full regimen; in 11% of cases dosage was reduced for one or more drugs; in 23% no dosage changes were required; and in 29.3% one or more drugs had to be interrupted. The majority of SAEs (62.6%) were successfully resolved or improved. An AEI of grade 3 or higher was not experienced by 90% of patients; 289 AEIs of grade 3 or 4 were identified, of which 288 occurred during treatment. As in the case of SAEs, most AEI were reported at the beginning of treatment, and decreased significantly in incidence later on during the course of treatment. The management of 50% of AEI did not require temporary or permanent withdrawal of one or more drugs, and the vast majority of AEI were successfully resolved or improved; however, 38 instances (13.1%) of AEI remained unresolved and nine (3.1%) AEI resulted in death. Mr Korotych noted that, based on the data in the majority of cases, AEI can be successfully managed and patients’ conditions improve over time.

Questions and answers

Dr Yedilbayev announced time for the questions and invited participants to discuss the presented information. The first question came from a Kazakh team member, concerning the possibility to apply to a VMC with questions that go beyond mSTR operational research.

Dr Gurbanova replied that the VMC evolves; it was initially organized as a tool to serve the benefit of mSTR operational research, and now countries can ask questions about BPaL regimens, treatment of drug-susceptible TB and treatment of DR-TB under individual regimens. Country teams can apply to the VMC for all cases related to the treatment of TB; but the VMC has limitations regarding diagnosis as the form currently used for case presentation is designed for provision of advice regarding treatment and not diagnosis. Diagnosis includes reviewing a large number of examinations, including computed tomography results, in order for VMC experts to offer advice regarding diagnosis. Despite these barriers, countries can apply with such questions and VMC experts will switch to the format of video consultations when they can join the country team online and, together with the treating physicians, discuss the case, preferably with the opportunity of seeing examination results on-screen.

Dr Gunta Dravniece, VMC expert, mSTR Task Force Member, WHO Regional Office for Europe, asked if a benchmark analysis of culture conversion with the breakdown by countries has already been performed.
Mr Korotych answered that the analysis of culture conversion by country had not yet been performed as not all the necessary data are available and the quality of country databases vary; even databases of the regional cohort are still lacking data. Once the databases are cleaned and missing information obtained, the analysis of culture conversion will be repeated and reported by country in the final project report. Mr Korotych also reminded all participants that in September 2022 a workshop on analysis of mSTR data will be conducted, and that countries are encouraged to provide their nominees.

Mr Abdylat Kadyrov, NTP Manager, Kyrgyzstan, asked when the Russian translation of the regional action plan for TB 2023–2030 presented by Dr Yedilbayev will be available. His second question concerned ways for Kyrgyzstan to join the ongoing operational research on concomitant management of MDR/RR-TB and HCV.

Dr Yedilbayev stated that the proposed regional action plan for TB 2023–2030 will be discussed at the WHO Regional Committee for Europe session in September 2022 (6). Operationalization and implementation of the plan at country level will be discussed at a regional meeting in November 2022 in Istanbul. Translation of the document is in progress and it will soon be available on the WHO website. As for the operational research of concomitant management of MDR/RR-TB and HCV, expressions of interest can be sent to the Secretariat and the WHO Regional Office for Europe will provide support accordingly.

Dr Myahri Durdyyeva, Principal Investigator, Turkmenistan, asked if the correlation of AE and risk factors have been analysed already.

Mr Korotych confirmed that multivariate analysis will be performed once the database is finalized. This analysis will become a part of a final report that will be available at the end of 2023.

Session 5. Best country practices

Dr Yedilbayev opened Session 5; the floor was given to the countries' principal investigators to share their experiences.

Dr Alena Skrahina, Principal Investigator, Belarus first presented the factors that facilitated the implementation of the operational research in Belarus: previous experience in operational research
implementation, readiness to perform first- and second-line DST, video-observed treatment (VOT) enabling
drug administration seven days a week, extensive experience in active TB drug-safety monitoring and
management (aDSM) and experience in collecting and storing strains since 2015. WHO's budgeting tool was
very useful in resource estimation. Dr Skrahina outlined the context of operational research implementation
in Belarus, where a similar project to the mSTR project was conducted in 2018–2019. She highlighted the
differences between country and regional operational research projects and noted that regional approaches
have allowed harmonization of data between countries. Enabling high-quality monitoring within the
operational research was a key tool for aDSM and the involvement of the national MDR/RR-TB Concilium.
The national MDR/RR-TB Concilium has the approval of the Ministry of Health and is entitled to prescribe
regimens, even if clinical guidelines have not been approved at country level yet. During operational
research, several challenges were faced by Belarus: lack of funding at the initial stage; problems with
reagents (potassium); lack of experience with assessing peripheral neuropathy, visual acuity and colour
perception; and the absence of a legislative framework for administrating drugs for seven days a week.
Belarus allocated funds for monitoring visits twice a year to all research regions for quality assessments and
making timely corrections. Within the research, 300 patients were enrolled in the prospective cohort and
250 into a retrospective cohort (those treated in 2018–2019); therefore, the total number of patients was
550, with men representing 80%. Out of the 550 patients, 166 (30%) had been previously treated for TB,
usually with first-line drugs. Almost one third of enrolled patients suffered from harmful alcohol use.
Initially, Belarus used version 5 of the Common Terminology Criteria for Adverse Events, which differs from
the previous version used in the regional mSTR operational research. This resulted in an increase in the
numbers of AEs related to QT prolongation. Later, the Belarus research adjusted the findings on safety in
line with the severity grading scale used in the mSTR operational research. Dr Skrahina reported that 86% of
patients had a successful treatment outcome, and that the country feels proud and excited about the
research results.

Dr Fируза Saidova, mSTR Country Coordinator, Tajikistan stated that their country protocol was approved by
the Research Ethics Committee on 9 October 2020 but research could not start until 4 December 2020. Prior
to the research start, study sites were identified; a protocol for the treatment of MDR/RR-TB was approved
for pilot districts; health-care providers in the pilot districts were trained, including training on the Epi Info
database; and stocks of drug supplies were analysed. During the first stage of the operational research,
three districts were engaged, with a population of 1 743 300 people (18.5%); and by the end of March 2021,
a territory with a population of 3 454 000 people was covered, which constituted 36.7% of the population of
Tajikistan. During the pilot implementation period, a territory with a total of 5 871 300 people was covered
(62.4% of the population). The regions for the pilot were chosen because of their geographical proximity to
the centre of the country where there is good infrastructure and a laboratory network. During patient
enrollment, there were challenges related to limited knowledge of the management of operational
research, and a misunderstanding of the eligibility criteria. Mentoring, retraining of on-site staff, and a
checklist developed for the study by mSTR task force members supported Tajikistan in resolving these issues. A new practice of administrating drugs seven days a week was initiated. The study enrolled 107 patients, with 159 being excluded for the following reasons: detected fluoroquinolone resistance; no DST results available: negative second-line culture results (line probe assay and/or mycobacterium growth indicator tube); prolonged (more than one month) exposure to bedaquiline in a previous episode of treatment; exposure to other mSTR component drugs for more than one month in the previous episode of treatment; contact with patients with XDR-TB (with resistance to fluoroquinolone), osteoarticular TB, miliary TB or TB meningitis; very severe conditions, psychiatric disorders, advanced visual impairment or history of low adherence to treatment.

The next step is to expand this research as it will increase capacity of health-care workers and provide experience of research implementation. However, currently such enrollment is only possible in the pilot regions. The speaker concluded by outlining Tajikistan’s country cohort implementation status.

Dr Valentina Vilc, Principal Investigator, Republic of the Republic of Moldova, introduced the research team and the Kirill Draganyuk Research Institute of Phthisiopulmonology that implements mSTR operational research. Dr Vilc stressed that members of the national DR-TB Management Committee are all members of the mSTR task force team, which ensures careful monitoring at every stage of research. As the research cohort expanded, the number of experts involved in the research doubled. The national team made an effort to employ young physicians in order to build a research capacity in terms of human resources. The Republic of Moldova enrolled 111 patients to the regional cohort. Further, considering the experience with the regional cohort, particularly in terms of the influence of the COVID-19 pandemic, the estimated size of the national cohort was set at 100 patients. For the mSTR research, the Republic of Moldova updated the material base at both central and local levels, equipping regions with new computers, printers and web cameras and revising the national clinical protocol. A series of training sessions were carried out for research personnel and a refresher course on protocol materials was made available on the online platform of the National Monitoring System. The “Patient screening and enrollment log” file was made available online to allow automatic synchronization of the work of mSTR research team members, who could log on and independently enter participant data and extract the necessary patient information. Even in the setting of the COVID-19 pandemic, the national team made efforts to ensure patient-centred care: engaging local authorities and psychologists and providing assistance for dealing with patients' social problems. VOT was also used extensively. Problems due to lack of funding were experienced, but this was resolved and the experience gained within the research is now being scaled up to the programmatic level.
Dr Iana Terleieva, Principal Investigator, Ukraine stated that the national team opted for country-wide coverage within the implementation of mSTR operational research. In order to supervise and assist study sites, it was decided to develop the team’s capacities. In order to have a standardized assessment of the situation in the regions, a checklist for clinical monitoring was developed. Experts with significant clinical experience performed monitoring visits to the study regions to see how well regional sites complied with the research protocol. Overall, 84 monitoring visits were conducted. As a result of research implementation Ukraine enrolled the highest number of patients and half of the regional cohort is represented by the patients from Ukraine. During in-country monitoring visits, the country team came across some clinical issues or issues related to the enrollment criteria and aDSM, but those issues were resolved. The screening logbooks included 95% of patients with MDR/RR-TB (2817 patients) and 42% of the screened patients (1189) were enrolled into the regional mSTR cohort of the operational research. While introducing the operational research, the country team updated the national TB standards and improved national routine practice. Screening for HCV among patients with MDR/RR-TB was scaled up programmatically after successful experience with mSTR operational research. With the help of WHO experts, it was realised that receiving DST results takes more than 30 days and so limits the ability to enrol patients into the operational research in a timely manner. The situation was analysed and it was established that the existing system created a barrier for timely access to DST. Four line probe assays were available in December 2020 across the country and so interregional transportation of specimens was established. In parallel, the negotiation with partners and donors started and in February 2021 Xpert MTB/XDR assay cartridges were introduced, and the country reduced the number of days for fluoroquinolone-susceptibility testing from 35 to four days. It is hoped to reduce the time even more by optimizing specimen transportation time from rural areas to regional sites. Currently, Ukraine is facing additional challenges created by the ongoing war: shortages of medical staff and additional workload within the medical system; patients migrating to safer countries; interregional migration from the regions affected by the war to the west of Ukraine; and TB facilities that have been damaged (in eight regions) or completely destroyed (in two regions). Due to the war, operational research had to be stopped in a few regions, but later it was re-established in all regions apart from three. Issues related to monitoring and logistics were also experienced. The country is grateful to WHO for developing the operational research package and mentorship, which enabled the achievement of results that the country can be proud of.

Dr Hakob Ashtemyan, Clinician, Armenia presented the experience of Armenia in screening, diagnosis and treatment of patients with TB–HCV coinfection. It was established that parallel administration of HCV treatment to patients with MDR/RR-TB is crucial since HCV is a risk factor for drug-induced liver injury during MDR/RR-TB treatment. HCV has been a treatable disease since 2014, allowing concomitant treatment of the two diseases; therefore, systematic and active screening of patients with MDR/RR-TB for
chronic active HCV in Armenia took place from January 2016 to December 2018. The screening activity was adopted as best practice and is planned to be conducted long-termly. Of 322 patients that started MDR-TB treatment, 266 (82.6%) were screened using a rapid antibody test, with 78 patients (29.3%) being HCV antibody positive. Polymerase chain reaction quantitative tests were carried out for 70 of these 78 patients (89.4%) and 50 were confirmed to have HCV infection. Thirty patients (60.0%) started treatment and 20 patients were not eligible to receive direct-acting antiviral agents. The article devoted to the study was published in the Open Forum Infectious Diseases Journal. Completed successful treatment was achieved in 80% of the study population as defined by a negative polymerase chain reaction and sustained virological response 12 weeks after the end of treatment. It was also stressed that a well-established system of pharmacovigilance was developed during the study. The speaker stated that the study had significant value for the structuring of health care in Armenia. Patients with MDR/RR-TB and HCV coinfection were treated with at higher rates of sustained virological response. The combination of direct-acting antiviral agents with anti-TB drugs did not cause any safety concerns and concomitant HCV and MDR/RR-TB care seems to be feasible. HCV treatment for patients with TB was implemented in close cooperation with Médecins Sans Frontières (MSF) France and was then transferred to the Ministry of Health and continued after the closure of the MSF mission in Armenia. Further useful information was presented in regards to sustainability and expansion of the programme. The future plan in Armenia was stated as a close cooperation and integration of activities with the State HCV response project.

Session 6. Subgroup of mSTR task force to support scale up of novel six-month treatment regimens

Mr Korotych introduced participants to the next set of presentations dedicated to the rapid communication on upcoming changes to the guidelines for treatment of DR-TB (7). Listeners were reminded that in 2020 recommendations to introduce the BPaL regimen with a linezolid dose of 1200 mg within operational research was issued and the many countries in the Region followed the recommendation. The pilot operational research cohorts were established at national level to test the regimen and gather more data on its safety and effectiveness. Belarus, Kyrgyzstan, Tajikistan, Ukraine and Uzbekistan are among the countries that launched BPaL operational research projects with the support of the Royal Netherland Tuberculosis Foundation, MSF and WHO. In Lithuania, operational research has been approved but there are no patients yet to enrol with a suitable pattern of drug resistance. In Georgia, the NTP decided to implement the regimen with linezolid dosage of 1200 mg under programmatic conditions for patients with fluoroquinolone resistance.

The new rapid communication from May 2022 on the upcoming changes in DR-TB (7) stated, in particular, that BPaL or BPaLM regimens will soon be recommended for programmatic implementation. Dose of
linezolid will be reduced to 600 mg. This regimen will be recommended over sSTR and individualized long-treatment regimens for patients with susceptibility to fluoroquinolones who are over 15 years of age. The regimen could be used without moxifloxacin in patients with fluoroquinolone resistance. In the rapid communication, WHO also mentioned that DST for fluoroquinolones is highly recommended but should not delay the start of treatment. Additionally, WHO stated that it will soon be possible to replace ethionamide with linezolid in sSTR. The recommendations stated that, when selecting a treatment regimen, the DST pattern, medical history and the risk of AEs as well as their severity and the site of disease should be taken into account. It is also necessary to ensure proper support, observation, clinical practice and aDSM when providing treatment. The overall regular monitoring of the patient's condition is essential in order to detect and manage AEs. These issues were discussed by the Secretariat of the WHO Regional Office for Europe and it was decided that, in order to support countries during programmatic implementation of BPaL and BPaLM, it would be pertinent to establish a subgroup of the mSTR task force with the primary goal of supporting scale up of the use of novel six-month regimens with the specific objectives of developing a checklist for country preparedness and planning for introduction of novel six-month treatment regimens; advising countries on planning with regard to BPaL or BPaLM regimens; supporting countries in resource quantification and, if necessary, in capacity assessment and identifying the areas of improvement in order to introduce and scale up novel six-month treatment regimens; and providing technical assistance to countries implementing BPaL and BPaLM operational research initiatives. Participants were informed that Turkmenistan and Ukraine with subgroup support are currently planning BPaL operational research projects. The requests from six countries were received to monitor the rollout of novel six-month regimens (Armenia, Kyrgyzstan, Lithuania, Tajikistan, Turkmenistan and Ukraine), but the subgroup is open to support any of the 18 high-priority countries for TB upon their request. The subgroup consists of mSTR task force members, members of the VMC and the Green Light Committee and country experts. Participants were informed that in November 2022 a meeting will take place in Istanbul where the operationalization and implementation of the proposed regional action plan for TB 2023–2030 will be discussed; in the meeting country representatives will be invited to discuss scenarios for programmatic implementation of the novel six-month treatment regimens. An update of the WHO consolidated guidelines on drug-resistant tuberculosis is expected to be published by the end of 2022; therefore, countries should not postpone the preparation and planning process and be ready to start implementing new regimens next year. For this reason, the subgroup has developed a preliminary triage algorithm so that countries can plan procurement of medicines accordingly. For patients older than 15 years of age, BPaL or BPaLM can be a primary regimen of choice, while for children and adolescents under 15 years of age these regimens have not yet been recommended. Therefore, mSTR is the most feasible choice for patients under 15 years of age in the region. Since mSTR is not yet recommended in WHO guidelines for programmatic implementation, operational research remains a valid tool to offer mSTR for children or other categories of patients. The algorithms for patients under and over 15 years old are shared with countries in two languages. The VMC is also available
to support countries in questions related to BPaL and BPaLM regimens and countries are encouraged to seek expert advice, when in doubt.

Dr Nino Lomtadze, mSTR Task Force Member, Consultant, WHO Regional Office for Europe, informed that to ensure smooth transition to the novel six-month treatment regimens it is important to have a clear understanding of the different baseline programmatic landscapes related to regimen implementation from country to country. For the purposes of assessing these programmatic situations and learning about different potential implementations scenarios, the subgroup of the mSTR task force has developed a questionnaire, to be self-administered by NTPs. Knowledge of different scenarios will allow WHO, other international partners and funding agencies such as StopTB Partnership, Global Drug Facility (GDF) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) to better plan, tailor technical or financial assistance with due consideration of country specifics, to forecast revenue for drugs and consumables at the global level and to better support future rollout. The sections of the questionnaire that will be considered by countries are: treatment guidelines and policy context; information about the treatment policy and service delivery systems; drug supply and management; VOT coverage, as an opportunity to ensure observed drug administration seven days a week; laboratory diagnostics and monitoring, programme management; the need for technical assistance; training of staff and the development of training programmes and training materials; revision of national monitoring and assessment planning and reporting; availability of clinical consultants; a functional clinical consilium for ensuring the use of clinical guidelines and for ensuring good mentoring during the process of implementation; and ability of the national recording and reporting system to register information on novel six-month treatment regimens.

Dr Kai Blondal, mSTR Task Force Member, Consultant, WHO Regional Office for Europe, presented the checklist that countries can use in order to evaluate readiness and prepare for introduction of BPaL programmatically. It is important to describe background information, TB epidemiology, drug resistance in all regions and the extent of drug resistance: resistance to fluoroquinolones, bedaquiline, linezolid or delamanid. Countries are to evaluate the ability to administer drugs seven days a week, legislative aspects, number of centres across the country, human capacity and resources, as well as any need for capacity-building. They must also decide on pretomanid procurement, registration and delivery to the country; review the list of required tests; check the availability of an expert committee at the treatment facility; estimate the number of patients to be enrolled on the novel six-month treatment regimens; review the suitability of pharmacovigilance and aDSM systems; and ensure access to oral vitamin B₆ and drugs for management of AEs.
**Discussion**

**Dr Yedilbayev** encouraged countries to take part in the discussion and discuss the benefits of participation in the operational research for the programmatic practice and the extent to with operational research helped the NTPs in improving programmatic delivery.

**Dr Nana Kiria**, Principal Investigator, Georgia stated that Georgia has been using mSTR short regimens under programmatic conditions before it joined the regional operational research. Country representatives consulted with local and external experts and the decision was made to implement short regimens, which resulted in further improvements in treatment adherence for patients. Georgia experienced the following difficulties after joining the research: collection of information on the retrospective cohort was problematic; and lack of training for clinicians and patients resulted in a low yield of patients attending six- and 12-month follow-ups after treatment completion. In contrast, the opportunity to be treated with shorter regimens and the very few AEs experienced by patients was inspiring both for patients and doctors. Dr Kiria also mentioned that Georgia implements BPaL programmatically with a 1200 mg linezolid dosage. She stressed, that despite the fact that this dosage can cause myelosuppression, patients tolerated the regimen well. Singular cases of myelosuppression were observed and SAE were very rare.

**Dr Liga Kuksa**, Principal Investigator, Latvia, pointed out five significant factors for research implementation in the country. First, mSTR research was registered in the country as an observational research, which allowed it to continue work within the country cohort without resubmission of a research protocol. Latvia informs the drug regulatory agency on continuation and submits results regularly. Even for countries with low burden of DR-TB, a clear roadmap should be developed explaining for physicians what should be done at the beginning, during and after the treatment. The cost of drugs varies based on the country in the WHO European Region and it is important to take into account that the shorter treatment regimens are justified because they will be at least half less expensive. AEs are less frequent when a systematic approach of aDSM is used. If the systematic monitoring of AEs takes place, that results in timely management measures and resources are not wasted. Social support and social follow-up do not become obsolete and should not be neglected because of the shortening of the treatment regimens.

**Dr Yedilbayev** added that there is a set of other issues such as challenges associated with the COVID-19 pandemic and ethical clearance at the national level arising when countries switch from a regional to national cohort.
Dr Durdyyeva stressed that operational research allowed data to be generated that will inform future recommendations. A lot of evidence is generated jointly by the 13 countries in a harmonized manner. Joining this research was a first and important experience for Turkmenistan and 108 patients were enrolled during the first year. Initially, there were certain reservations when selecting and enrolling patients in Turkmenistan, which resulted in some patients not being enrolled despite fulfilling inclusion criteria. Most patients have completed treatment and computer tomography was performed to check the dynamics. Some patients were switched to an extended regimen according to the national recommendations. Currently the cohort is under follow-up and treatment and success rates will be evaluated further. Dr Durdyyeva stressed that the role of mentoring and training is valuable, particularly when clinicians are facing either patients with concomitant diseases such as HCV or diabetes mellitus, or pregnant women. The desire was expressed to maintain the practice of virtual mentoring, intercountry consultations, training and webinars.

Professor Natalia Litvinenko, Clinician, Ukraine, commented that results in Ukraine are optimistic, with high treatment cure rates observed, and stressed her belief that there should be a choice of short regimens for both patients and physicians because one regimen (such as BPaLM) might not be suitable for all patients, and there may be a need to switch to another regimen. The COVID-19 pandemic was acknowledged to be a major challenge, particularly at the beginning when everyone was unprepared, but Ukraine’s Ministry of Health managed to find the funds to tackle issues that arose. Also, the Global Fund allocated a grant targeting COVID-19 treatment. VOT is well established and well practiced in Ukraine and played a significant role during the height of the pandemic. Therefore challenges were present, but also properly managed.

Dr Yedilbayev added that duration of treatment regimens, not needing to use injectable agents and introduction of video-supported treatment (VST) turned out to be particularly important during the COVID-19 pandemic.

Dr Yerkebulan Algozhin, Partners in Health, Kazakhstan, reported that operational research in Kazakhstan started in the midst of the COVID-19 pandemic. TB infrastructure was redirected to the fight against COVID-19. Therefore, many physicians were engaged in COVID-19 treatment in almost all regions. The pandemic affected treatment outcomes in the regional cohort, as one death case was related to COVID-19-associated pneumonia. Initially Kazakhstan engaged two regions in implementation of the regional cohort but by the time of the annual meeting 14 regions were covered. Overall, four regions are not included in the operational research so far as proper training for the regional teams is still needed. The funds for training were provided by the Global Fund. It was also stressed that, at the beginning, some clinicians were not
certain that major TB changes could be treated within such a short time period (nine months). To address these concerns, the research team had patients' radiography results presented during training courses to illustrate cure progress with shorter treatment periods, with the examples of patients who had begun treatment with extensive TB processes in the lungs and had good treatment outcomes after nine months of treatment. Other challenges related to patients being afraid to visit health-care facilities or leave their homes during the height of the pandemic. This resulted in some underdetection of TB, which has now increased the TB notification rate in the country.

**Day 1: summary**

**Dr Yedilbayev** adjourned Day 1 of the annual meeting and asked **Dr Andrei Dadu**, Medical Officer, Joint Infectious Diseases Unit, Country Health Programmes, WHO Regional Office for Europe to summarize the discussion. Dr Dadu stressed that the study has evolved significantly and has managed to improve treatment outcomes for patients most in need. Hope was expressed that in future the initiative's results will have an impact on amending and adjusting the global guidelines. Dr Dadu thanked all the speakers and participants for their presence and engagement.

**Day 2: meeting overview**

**Session 1. Introduction to Day 2**

**Dr Yedilbayev** opened Day 2 of the annual meeting by outlining the scope and purpose of the day before initiating the first presentation.

**Session 2. Update on data quality**

**Dr Arax Hovhannesyan**, mSTR Task Force Member, WHO Regional Office for Europe, stressed the importance of high-quality data as it facilitates accurate and informed decisions. The factors that cause poor data quality were presented: lack of data completeness; bias; deviation from protocol; lack of consistency; and errors in data processing. To tackle these factors, monitoring missions are conducted within the operational research. The standard checklist and the Excel tool are the instruments used to identify consistency and completeness of data during monitoring missions. Monitoring missions prove themselves an effective measure and improvement in data quality is observed over time. Another procedure is an ad hoc assessment, within which databases are checked for duplicates, completeness, accuracy, consistency and logical errors. Dr Hovhannesyan drew attention to the fact that there are also mistakes that affect or
compromise the outcomes that must not be allowed, including duplicated records when patients are reported in a database several times and absence of information about treatment outcome and completeness of culture test results; only 38% of patients who receive treatment over nine months had at least nine culture test results as expected by the protocol. Other issues of accuracy are treatment outcome date earlier than treatment start date; patients with successful treatment outcome having more then 270 days of treatment duration; and patients having over 300 days of treatment duration. Dr Hovhannesyan presented questions that need to be answered when checking data consistency for treatment outcomes of AEI/SAE and the concept of bias, with different types of bias accruing within the research. There are a number of pertinent examples. Selection bias is the tendency for a sample to differ from the general population as a result of systematic exclusion of some section of the population. Another example is when patients who died or developed an AE at the early stage of the treatment were not included in the study or if patients in severe condition are not included, resulting in only "healthy" patients with MDR/RR-TB being assessed. Measuring bias is a bias that occurs when the results of the experiment are influenced by researcher’s expectations. For example, underreporting of AEs because of fear of giving faulty treatment or overreporting favourable treatment outcome if there are incentives for high achievement of a cure rate. Dr Hovhannesyan stressed that national teams should be careful and avoid biased approaches. At the end of the presentation she reminded about the upcoming Workshop on Data Analysis and that participants need to ensure completeness of the logbooks, making sure that there are no duplicates in the databases and that treatment outcomes are entered correctly in order to prepare databases for the Workshop.

Session 3. Update on recording of SAE/AEI

Dr Lomtadze moved into presenting AE-related secondary objectives of the protocol targeted towards evaluating the frequency of occurrence of SAE and AEI of grade 3 or greater severity; AE resulting in discontinuation (temporarily or permanently) of any study drugs; outcomes of all recorded AEs whether or not resolved and any consequences; and any AEs that resulted in death. Participants were reminded about the aDSM framework that should be used during treatment of MDR/RR-TB and the fact that the overall objective of aDSM is to reduce risks from drug-related harms in patients on second-line treatment for DR-TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines. It was stressed that patients targeted for aDSM should undergo active and systematic clinical and laboratory assessment during the course of treatment. All AEs detected should be managed in a timely manner in order to deliver the best possible patient care. Another important aDSM aspect is that standardized data should be systematically collected and reported for any detected SAEs. In research, three different levels of aDSM can be used. The core package obliges research to report all SAEs. The medium package foresees additional reporting of AEI, which should be monitored and reported. The most advanced package covers all
AEs. The study uses the medium package, meaning reporting of all SAEs, AEI of grade 3 and higher and AEs of clinical significance which result in discontinuation of the study drugs. Dr Lomtadze reminded participants that the definition of an SAE is an unfavourable or unintended sign/symptom/disease (including laboratory abnormality) that at any dose is fatal; immediately life threatening; leads to hospitalization or prolongation of hospitalization; leads to significant disability, incapacity, birth defect or congenital anomaly; or is otherwise medically important (for example necessitating an intervention to prevent one of the above listed outcomes). In mSTR operational research the following AEI of grades 3 and 4 are closely monitored: peripheral neuropathy, optic nerve disorder, myelosuppression, hepatitis, acute kidney injury, prolonged QTcF interval on electrocardiography (corrected QT interval to avoid influence of extreme heart rates) and hypokalaemia. However, while the operational research focuses on SAE and AEI of severity grades 3 and 4, it is important to remember that AEI of grade 1 and 2 and non-serious AEs of grade 1 and 2 can also lead to treatment discontinuation or change in drug dosage. Therefore, within mSTR operational research it is expected that attention will be given to any SAE, the seven chosen AEI, grade 3 and 4 AEs and other events resulting in discontinuation of the study drugs. Dr Lomtadze further discussed questions asked during monitoring missions regarding reporting of AEs and noted that considering most AEs as serious can lead to bias because the number of SAE will be overestimated. AEs that should not be reported within the operational research are those that are not serious, are below severity grade 3 and do not lead to TB treatment discontinuation, excluding dose reduction. It should be remembered that death for any reason during the course of treatment and in the 12-month follow-up period requires registration of the outcome of death and also requires an SAE form to be filled out regardless of the causality assessment. If the cause of death is known, then the form should be completed using that cause. At the end of the presentation Dr Lomtadze reminded participants that it is important to remember that each field in the form is essential for the purposes of evaluation and should be completed in full, and assessment of the severity grade should be accomplished based on the severity grading scale used in mSTR operational research to ensure a standardized approach and validity across all sites.

Session 4. Online platform for storage and overview of data

Dr Jay Achar, mSTR Task Force Member, WHO Regional Office for Europe, described the online platform as having two applications. The first is a country application that will allow country study teams to review country cohorts, perform a simple descriptive analysis of the cohorts and simplify study data reporting. This application will be available in English and Russian. It can be used together with the Excel data-quality tool to check and improve data quality and securely backup the data to the WHO Regional Office for Europe server. If the dataset has errors that require fixing, the data will be prevented from being uploaded into the study dataset. The second application is an administration application, designed for WHO staff. It allows the
review of summary (regional) and individual country statistics, as well as to monitoring backup processes. These applications will help to simplify study reporting and allow easier analysis of regional and country level datasets for reporting purposes. The service is run, owned and managed by the WHO Regional Office for Europe. All connections are encrypted and all study data are stored on a dedicated database managed by the Secretariat. Access to the two applications will be managed by WHO. In addition to country/local backup, there will be a regular backup process within WHO, in order that no important information is lost.

Dr Achar demonstrated the platform, commenting that it is accessible through the Internet using a login and two-factor authentication method. When demonstrating the work of the country application, Dr Achar stressed that the system only backs up fresh data: that is, when a new record is added or when data are updated in the records. The interface and assistance buttons were also demonstrated, with information on how to upload the database and how to check different sites, etc. The administrational application is similar to the country version; however, instead of requiring the user to upload data, this application pulls data directly from the database. This will be useful as a management tool for mSTR task force members when monitoring multiple countries. The challenge presented by the platform relates to the fact that data files can be large, so the process of uploading data can be time-consuming. This may be sensitive in countries with big datasets or slow Internet connections. The platform will not replace the Excel-based data quality monitoring tool, which can be used by data managers on local computers.

Session 5. Mid-project evaluation to document regional and country experience

Ms Myroslava Germanovych, Member of the mid-project Review Evaluation Team, WHO Regional Office for Europe, started her presentation with an explanation of mid-term methodology and its basic components. The timeline of evaluation development was presented and the fact that the final report will be available by the end of Autumn 2022. The main goals for evaluation were defined as describing bottlenecks and enablers of operational research implementation at regional, country and district level; assessing impact of the initiative on programmatic practice in participating countries; and providing recommendations and informing further implementation of operational research projects in the area of MDR/RR-TB. The evaluation design was presented and considered perspectives of all participating countries, partners, the WHO Regional Office and WHO country offices; three methods for data generation (documentary review, secondary data analysis, qualitative study) were used, and three approaches to data analysis (evaluation team-led analysis, external review and triangulation meetings) were applied. In total, 60 interviews were conducted during the evaluation, with participants from all countries implementing operational research. The bottlenecks identified were limitations in national legislation; difficulties with access to the treatment with short regimens for people in prison and patients living in the areas remote
from research centres; lack of previous experience in conducting research within a country; low motivation to take part in the research for clinicians in the certain study sites; difficulties with keeping patients under follow-up after the completion of treatment; and the start of the operational research coinciding with the spread of SARS-CoV-2 and the COVID-19 pandemic. The most common deviations from the treatment monitoring schedule were associated with performing blood biochemistry, screening for hepatitis B virus, HCV, SARS-CoV-2 and peripheral neuropathy. The enablers of operational research were defined as short duration of treatment regimens, mentoring, funding for research components and missing tests and VST. The impact on programmatic practices was also documented as advanced training for clinicians in baseline evaluation, AE detection and management; update of national MDR/RR-TB treatment standards; systematic freezing of cultures taken at the beginning of treatment institutionalized in the diagnostic protocols; and increased awareness of the necessity to accelerate DST turnaround time. One country also reported presentation of patients to the Country Committee on DR-TB Management following the model of VMC. In some countries operational research facilitated transition to rapid TB laboratory measurements with the Xpert MTB/XDR assay cartridges; procurement of tuning forks, visual acuity and colour perception evaluation tables; and procurement of analysers for biochemical blood tests and reagents. In terms of research capacity, operational research provided research experience to previously inexperienced national teams. For some NTPs, the research was the first experience of obtaining ethical approval. It also led to initiation of national mSTR, BPaL cohorts, and research on concomitant treatment of MDR/RR-TB and HCV.

**Breakout sessions**

Dr Yedilbayev invited participants to work in groups and join group sessions of choice in one of three breakout rooms.

**Breakout room 1. Programmatic experience of introducing mSTR**

**Participants:** NTP managers, programmatic specialists, laboratory specialists, partners, donors

**Facilitators:** Dr Naira Khachatriyan, Dr Terleieva

**Rapporteur:** Dr Dravniece

**Question 1.** What were the key programmatic challenges for the introduction of mSTR?

Representatives from the Republic of Moldova reported that all patients from the regional cohort are at the follow-up stage. The challenge in the Republic of Moldova is external migration. Internal migrants
communicate with doctors, but connection with external migrants is lost. In Ukraine the situation is very
difficult because of the war. In Kyrgyzstan, 40 patients have completed treatment and the final group of
patients will complete treatment in November 2022. External and internal migration was also an issue here.
Interlinking clinicians within cities was also a problem in the Republic of Moldova, as the central level is
unable to follow up on all clinicians. The country has a TB registry that operates at all levels. There is also a
laboratory medical information system. There are cost savings from the closure of TB hospitals and the
expansion of outpatient treatment. Funds still remain in the programme, including funds for the motivation
of primary care workers (US$ 300 for a patient who is cured of DR-TB in addition to salary). Turkmenistan
has had difficulties with examinations at outpatient stage because of the mobility restrictions caused by the
COVID-19 pandemic. There is a national monitoring system that includes checklists, but Turkmenistan needs
to develop checklists fine-tuned for monitoring within mSTR operational research. Turkmenistan also
experienced difficulties in the delivery of reagents, and, as a result, interruptions occurred in access to
diagnosis and treatment. A large number of potential patients were not included into the operational
research due to the very careful selection criteria. Mr Korotych added that it would be optimal to do a
smear and culture, but if this was impossible, then a telephone consultation with patients should be
performed with a verbal assessment of symptoms.

**Question 2.** What were the challenges with budgeting and funding for the operational research?

Kazakhstan was the first to share the experience that initially clinicians were hesitant about enrolling
patients with advanced TB and that new patients were apprehensive. The solution was training and
explanation for clinicians, including training regarding special situations (for example pregnancy or
concomitant diseases). As a result, all patients with DR-TB were considered for inclusion in mSTR. There
were almost no refusals in the regional cohort, but there were some in the country cohort, particularly in
some regions where physicians were unable or unwilling to explain the research, resulting in patients
becoming afraid of the research itself. A particular example concerned a group of patients who believed
that they were to be experimented upon. However, when the concept was explained to them the issue was
neutralized. In the Republic of Moldova limitations are similar to those described in Kazakhstan. All patients
are presented to the central Concilium at the beginning of their treatment. Doctors in the Republic of
Moldova prefer to start treatment on an inpatient level and there are patients who do not want to start
treatment as inpatients. In addition, between 5 and 10% of patients abandon treatment after starting the
course. The problem at the beginning of treatment is distrust, which was exacerbated by the COVID-19
epidemic. To tackle this, the research team in the Republic of Moldova used word of mouth – they
disseminated information to patients, who then passed the "privileged" information to others. Currently,
there is no problem with recruitment, although it still sometimes remains an issue among elderly people,
sociopaths and individuals who had previously been in prison.
Question 3. Describe the factors that facilitated the introduction of mSTR in your country?

Representatives from Kyrgyzstan commented that before mSTR research, one of the causes for inefficient treatment was its duration. After the introduction of nine-month regimens, the situation improved and efficiency of treatment increased from 50% to 70%. After rapid communication, Kyrgyzstan is now also implementing the six-month schemes.

In Ukraine, treatment of HCV was started with DR-TB treatment once it was realized that there was a significant burden of HCV coinfection among patients enrolled in mSTR. Additionally, as the results of mSTR have become available, the country has modified approaches to clinical management, management of AEs and comorbidities.

In the Republic of Moldova, a team was created to work in operational research. National protocols were revised and the national cohort was extended to include penitentiary patients, the Administrative-Territorial Units of the Left Bank of the Dniester, pregnant women and children.

Breakout room 2. Clinical and aDSM components of mSTR operational research

Participants: key clinicians, heads of consilium

Facilitators: Dr Gurbanova, Dr Vilc

Rapporteur: Dr Lomtadze

Question 1. What were the key concerns of clinicians for the introduction of mSTR?

Country teams had considerably high baseline vigilance and were treating the entire process of patient screening and selection with greater caution during the introductory phase than afterwards during the implementation process. In some countries unavailability of one overarching clinical centre or of one central clinical concilium was expected to cause some challenges but these could be dealt with during implementation. With expansion from pilot to countrywide enrollment within country cohorts there are more challenges related to the amount of work and proper management of bigger cohorts of patients under operational research conditions. Countries were concerned that they would not be able to enrol the expected number of patients, particularly with hospital beds being repurposed for COVID-19, but the solution was start treatment directly at outpatient level. There were also concerns regarding registering and completing logbooks and case response forms; these seemed to be very demanding, but the actuality was
encouraging. There were also anxieties related to the shortness of treatment itself, because these same drugs were already used by countries as part of longer 18–20 month fully oral regimens. The shortness of treatment was, however, motivating for both patients and clinicians who were managing patients with the longer 18–20 month regimens. mSTR should stay at the same level in the regimen selection triage scheme. SAE/AEI registration seemed quite challenging but participants were happy with the presentation on aDSM during the annual meeting. The availability of the VMC was of great help addressing all of these concerns.

**Question 2.** How did the introduction differ in practice from your expectations?

Visual acuity testing and colour vision testing was performed by TB doctors and some countries even performed fundoscopy before sending patients to an ophthalmologist. Peripheral neuropathy screening became part of routine practice, which was beneficial. The training materials and practical training developed and conducted by specialists (neurologists, ophthalmologists, haematologists, etc.) proved to be extremely effective for the TB doctors. The ancillary drug lists were updated, became more comprehensive and were funded by the donors. AE recording and reporting has greatly improved.

**Question 3.** What changes were made in treatment administration and monitoring to comply with the study requirements?

Colour vision tests, evaluation of vibration perception for peripheral neuropathy and blood potassium measurements were added for all patients, not just for mSTR operational research; previously, only those who had problems were eligible for these tests. The mSTR operational research helped to involve clinicians in public health centres more actively. To ensure treatment effectiveness and safety monitoring of patients during the COVID-19 related restrictions, home visits were performed to obtain materials (samples) and evaluate patients.

**Question 4.** What were the main challenges in the introduction of mSTR and adhering to the treatment monitoring schedule?

Many countries started the screening process during the emergence of the COVID-19 pandemic, and there were concerns regarding the potential adherence of patients to the assigned schedules for treatment and safety-monitoring visits, directly observed treatment and so on.

**Question 5.** Which processes have been improved as a result of the operational research?
It has opened possibilities for training TB doctors in the aspects of the psychosocial management of patients with TB and in proper techniques for communication with patients.

**Question 6.** What elements of this operational research have already been, or can be, introduced into the routine programme management of TB and MDR/RR-TB in your country?

Some countries have even adopted the VMC case presentation form to be used as part of the national consilium case presentations as it was found to be very comprehensive and useful. There is a growing willingness from countries to use the same format for patients in TB care programmes beyond the operational research.

**Question 7.** Do you consider the support from the VMC beneficial to the implementation of the operational research? What could be improved?

The VMC was considered to have had great impact on overall performance and care quality within mSTR operational research, including the didactic VMC workshops, which were instrumental in enhancing performance. While everyone gains experience through working, this process requires time. Through the VMC this "time to experience" was greatly shortened and the VMC was seen as a "magic stick" in many instances. It allowed qualified solutions to be obtained rapidly from experienced specialists.

**Breakout room 3. Data collection and quality in mSTR operational research**

**Participants:** database managers, form completion specialists, data quality monitors

**Facilitators:** Dr Kuksa, Dr Mahmud Rashidov, Clinician, Partners in Health

**Rapporteur:** Dr Ana Ciobanu, mSTR Task Force Member, Consultant, WHO Regional Office for Europe

**Question 1.** What were the key challenges for form completion and data entry in the mSTR operational research?

Challenges cited included human factors (lack of personnel, lack of skill), poor Internet connections, information duplication (entering information from main documentation to information system plus entering information from documentation to the information system of the operational research) and collection of additional information.
Question 2. Which factors influence data quality for this project in your country?

Factors cited were duplicate cases within Epi Info; the transfer of information in several stages: from doctor to operator to coordinator, and so on; human factors (when data are included in the system); cross-validation (between responses) in the database not always being possible; the size of the cohort; clinical tests that are left undone; and low Internet quality.

Question 3. What is the system for mSTR operational research data quality monitoring in your country?

The Republic of Moldova used an online subject screening log with monitoring dates added. Other systems were the monitoring and evaluating Excel tool; verification of data at all stages (collection, inclusion in the system, transfer of information); monitoring and evaluating visits (validation with primary sources carried out by the country team); remote data validation by telephone and mail carried out by the country team; and quarterly remote monitoring and evaluating visits from WHO consultants.

Question 4. Please describe the most successful interventions that helped you to improve data quality?

The following were cited: education/training and availability of manuals, individual training (Tajikistan); timely data entry, monthly monitoring of the data collection procedure (Republic of Moldova); monitoring and evaluating visits that enable discussion and problem-solving during the visits (in-country as well as external); and financial incentives for personnel entering data into the database;

Question 5. What could have been done differently to ensure better data quality?

Suggestions given included simplified data collection when data is entered directly into the operational research system; a fixed number of patients per data administrator in the region so that data administrators are not overloaded with work and quality does not fall; financial incentives; regular re-training and individual training for personnel who require it; use of Excel data quality tools on all levels; and improvement of the electronic validation system (automatic validation of more fields).

Plenary session

Dr Yedilbayev announced that further discussion would be on issues related to transition to the novel six-month treatment regimens recommended for programmatic use, full genome sequencing and the treatment of MDR/RR-TB in children and adolescents. Dr Fuad Mirzayev, Medical Officer, WHO, and Dr
Dravniece, mSTR Task Force Member, WHO Regional Office for Europe, were invited to moderate the discussion.

In his introduction Dr Mirzayev mentioned that he was impressed by the scope of work that had been implemented and by the presented findings. The impression of the potential use of mSTR in the WHO European Region is positive and the fact that 13 countries were able to introduce new treatment regimens in the framework of operational research gives hope that other countries will be able to do the same thing successfully. Major changes will take place in the guidelines that will be issued at the end of 2022. The chapter dedicated to BPaL and BPaLM and to nine-month treatment regimens will lead to major changes in programmatic practice. Dr Mirzayev felt that the mSTR initiative helped WHO headquarters to prepare countries for implementation of novel six-month regimens. Implementation of operational research projects is important while the transition to the new regimens is taking place, because different patients with varying characteristics and different patterns of drug resistance need to have access to a variety of treatment regimens. The future of MDR/RR-TB treatment is to offer several effective regimens from which a clinician will be able to select the proper treatment regimen based on the profile of the patient. This is a positive change as it gives an opportunity to have a stratified approach to dealing with challenges that clinicians encounter while treating patients with drug-susceptible TB and DR-TB. When more data on mSTR are available, the WHO Consolidated Guidelines Development Group will review the evidence and it is hoped that this will help to find at least one additional treatment regimen that will benefit at least a certain group of patients.

Dr Dravniece added that when the introduction of new DR-TB treatment regimens first started in 2012, clinicians, hospital administrations and managers quickly adopted these novel treatments and realized that patients tolerated the new drugs well. When the WHO rapid communication document was released, many did not know how to interpret it, but now many countries are preparing for implementation of these recommendations. The majority of the countries realize the need to be well-prepared, to do diligent planning and estimate their needs, including quantification of drugs, and this also pushes the WHO team to be more flexible and to look for better innovations.

Dr Kadyrov queried whether WHO has a plan to recommend sequencing of the mycobacterial genome and what is the timeline for the process. In 2017 Kyrgyzstan introduced full genome sequencing. The country performed more than 1000 tests and during the past three years the country started performing targeted sequencing and performed more than 200 further tests. The method can provide information about the range of drug resistance, and with the results of these tests physicians have an opportunity to design
individualized treatment regimens that can help in breaking the chain of infection and improving the TB situation in the country. The country was able to save some funds and would like to use them for sequencing, but the sequencing is not yet recommended by WHO and so Kyrgyzstan is not allowed to use those funds for reagents.

Dr Mirzayev replied that sequencing is an important technology that should be applied in practice with the new treatment regimens and new drugs. It was also noted that manufacturers develop DSTs quickly with the use of available platforms. It is known that platforms for sequencing are more flexible and if the targets for mutations are known, it is possible to quickly introduce the test for detection of the drugs to which mycobacteria are resistant. A new generation of sequencing can help, but it is also associated with certain challenges. Well-trained staff and equipment are needed. With time equipment will become more affordable and the areas of its application will expand. The Global TB Programme shared the call for collection of data on the use of next-generation sequencing and Kyrgyzstan will share their information with WHO. Dr Dravniece added that the meeting will take place on 18 September 2022 and that countries need to provide WHO with their data in order for the WHO Consolidated Guidelines Development Group to review it and formulate recommendations. Dr Dravniece noted that approaches to testing change; some tests disappear from practice and there may be a time when the programmes will have to bear expenses to procure new reagents and tools for their laboratories. Next-generation sequencing will give answers that can impact current practice, and in this way there will be the possibility to tailor approaches to individual patients based on good knowledge of their resistance patterns. These new tests are currently expensive, with the possible price being over €100 and, in addition, highly-trained laboratory technicians are needed, but this might change in the future and cheaper tests will become available. Dr Dravniece again stressed that if countries want to receive recommendations from WHO they need to remember that WHO needs to receive data from them.

Dr Yedilbayev added that if countries need technical assistance on the issue, they can communicate their needs to WHO. There is a European Laboratory Initiative hosted by the WHO Regional Office for Europe and collaboration within this initiative can continue in order to expand the use of the sequencing.

Dr Terleieva stated that XDR-TB diagnostics now can compete with high-end tests. Manufacturers offer necessary products, but unfortunately, it takes time to diagnose patients with those tools, and countries want to speed up the process of diagnosis. Dr Terleieva suggested having a high-level meeting with test manufacturers in order to outline these needs. Alongside Kyrgyzstan, Ukraine is interested in the introduction of sequencing, but among the barriers identified by Ukraine is that all the offered equipment is
complex. A need was identified to have easy-to-operate tools that do not compromise on quality. Another issue raised by Dr Terleieva is the lack of domestic funding for the implementation of operational research projects. At certain stages, countries still depend on donor funding and it would be beneficial if they were supported by internal resource allocation. Governments remain to be unwilling to allocate targeted money for research. Therefore, there is a need to address ministries of health and work towards sustainability; 5–10% of a country's budget should be allocated to specific initiatives, not only pertaining to the treatment of DR-TB, but also for preventive measures.

**Dr Yedilbayev** added that countries are asked to strengthen and establish research units within their NTPs, which would help in advancement of operational research and innovation.

**Dr Kuksa** asked for countries to share data on mutations so that WHO can collect fuller data libraries and define which mutations are clinically significant and which are related to resistance. Dr Kuksa explained that in case of new drugs within new regimens the library of mutation is probably incomplete as there are cases when sequencing does not confirm existing resistance.

**Dr Mavlyuda Makhmudova**, Regional Technical Advisor, GDF Team, StopTB Partnership mentioned that countries are on the verge of moving to new regimens and within the transition period, it is important to ensure coordination of activities of all agencies, technical donor organizations and other counterparts engaged in planning delivering procurement of these drugs to the countries. The GDF has all the drugs required for the treatment of DR-TB and for DST available in its catalogue. This does a lot to reduce the prices of new drugs, but the process of placing orders with manufacturers is slow and time consuming. As many countries depend on donor funding, it is important to start planning when the implementation of new regimens will start and when countries are going to place orders for new drugs. The GDF tries to model various scenarios to evaluate the risk of shelf-life expiration of drugs already available or currently used by the NTPs. Through these modelling scenarios, GDF will be able to assess volumes; particularly regarding pretomanid, in order to be able to approach manufacturers and for manufacturers to be able to meet the needs of all the countries and to reduce the price. Just such a significant reduction in the price of bedaquiline occurred through GDF's active negotiations, as GDF calculated the required global need and the manufacturer agreed to reduce the price. The belief was expressed that mSTR operational research has simplified the process of implementation of new regimens and that the subgroup established within mSTR will help countries in the future to implement BPaL and BPaLM.
Dr Yedilbayev queried whether manufacturers can provide pretomanid in sufficient quantities.

Dr Makhmudova replied that the GDF had received a request from the Global Fund to develop scenarios of both rapid and slow implementation of BPaL and BPaLM in high-burden countries. After the scenarios are discussed with the Global Fund, it will be further decided whether the manufacturers are capable of meeting the needs. The countries that are planning to start implementing BPaLM have already placed their orders. The GDF will liaise with those countries and discuss their targets for the years 2023–2024. So far, the GDF is able to fulfil orders entirely. Some countries will finish their Global Fund projects in 2023 and they need to have clear plans on targets for each of the treatment regimens for 2023 as soon as possible. Countries whose projects end in 2024 can place their orders at any time. The countries that will start implementing regimens in January 2023 have already placed orders and the GDF is in touch with them to discuss the mentioned issues with each country separately.

Dr Mirzayev added that WHO expects countries to share their data. As the data need to be gathered somewhere an individual patient data platform has been established and the new round of data collection will start soon. Countries will have an opportunity to provide systematized data from country cohorts on the platform, including which patients receive treatment under the country’s NTP and which under operational research conditions. This kind of data was beneficial in informing guidelines and recommendations, both in the past and more recently. As countries move towards new drugs and new regimens, it will be important to increase the volumes of information as the number of patients enrolled into operations research and the country research projects is not sufficiently large at present; therefore, many recommendations are conditional, which impedes their implementation. Dr Mirzayev announced that BPaL and BPaLM regimens might be a challenge for countries to implement. Challenges might be expected with the availability of drugs, the treatment of patients and with the regimens themselves. Therefore, closer to the end of the year, there will be announced a new initiative that will gather together key technical partners and countries. This will be a monthly virtual group to discuss issues and to allow countries to ask questions directly to the representatives of the manufacturer or the GDF. This will help to deal with issues during the implementation of these regimens. The group will be most active throughout the next year to help countries to cope with the first months of implementation of BPaL or BPaLM regimens. Additional information on this will be provided closer to the end of the year.

Dr Yedilbayev announced the last question which concerned the treatment of DR-TB in children and adolescents. WHO has recently published a module of WHO Consolidate Guidelines for TB that formulates a set of recommendations on the treatment of DR-TB in this category of patients. The rapid communication
published in December 2021 helped many countries to adopt the protocol of the operational research and increased access to mSTR for a wider cohort of children. The module has been translated into Russian and quite soon it will be published officially, which will help countries in their routine practice. Dr Yedilbayev asked Dr Makhmudova to comment on the availability of paediatric formulations of anti-TB drugs which are now recommended for the age group.

Dr Dravniece thanked those countries that started enrolling paediatric patients into mSTR operational research from the very beginning. Dr Dravniece reminded attendees that there are good paediatric specialists available in Latvia and in Belarus, and that if needed they can be invited as satellite experts whenever there are questions on paediatric TB.

Mr Korotych reminded participants that a triage algorithm for adults, adolescents and children under the age of 15 years has been developed within the subgroup on the BPaL or BPaLM regimens, given that in the upcoming recommendations these regimens are not yet recommended for children. The algorithm suggests mSTR under operational research conditions for this group of patients. The algorithm is available for consideration and in case of questions the subgroup is ready to support countries.

Dr Veriko Mirtschulava, Senior Epidemiologist, Royal Netherland Tuberculosis Foundation, asked about the availability of substances for phenotypic DST in the GDF catalogue and about paediatric formulations.

Dr Makhmudov stated that the GDF has a catalogue of products for children. Eight paediatric formulations for the treatment of DR-TB are available in the updated catalogue of August 2022. GDF added linezolid 150 mg and the rest of the drugs were added earlier (bedaquiline, linezolid, clofazimine, cycloserine, ethionamide, levofloxacin and moxifloxacin). For about five years eastern European countries have received grants for paediatric drugs. In 2021 only one country was eligible for the grants to procure those drugs and the rest of the countries procured paediatric drugs themselves. The dynamic of countries placing those drugs in their orders is good. Due to the COVID-19 pandemic, the GDF and the regional Green Light Committee hosted by the WHO Regional Office for Europe identified certain challenges. Despite countries having access to the drugs, there were insufficient cases detected and the drugs were not requested from the central level; therefore, some of the drugs were not used. Dr Makhmudova stressed that it is important to forecast cases properly. It is also important to forecast reliable data on the number of patients whose weight is below 25 kg and all factors should be taken into consideration when countries start placing orders. Despite the fact that overall volume for the global production of the paediatric formulation is not large,
manufacturers agreed to reduce prices to about 30–40%. It is not very beneficial for them to make these drugs, but countries are asked to continue ordering child-friendly formulations because these are available, pre-qualified by the WHO and have stringent regulatory authority status. As for the substances themselves, the situation has not changed yet. It is possible to procure substances through the GDF except for delamanid and bedaquiline, which can be procured through the special programmes.

**Plans and next steps**

**Dr Dravniece** summarized that in regard to sequencing, the goals and objectives related to mSTR operational research should be outlined and a generic protocol that countries will be able to use in their practice should be developed. It is important to know what sequencing equipment countries already possess, so that these countries can start preparation for the expanded use of sequencing in their clinics.

**Dr Mirzayev** added that in comparison with other regions of the world, the WHO European Region has good capacity for laboratory diagnosis and for the introduction of sequencing. It gives the Region advantages, but also responsibilities, as the Region should use the knowledge and experience in DST for the new drugs. As for the introduction of the new treatment regimens, the transitional phase is now taking place and will last for over a year. Funds will be invested into studies that can result in the development of the drugs and treatment regimens of the future. Therefore, the current initiative provides an opportunity to prepare for the introduction of the new tools and new drugs which in future will result in major improvements of the health-care system.

**Closing remarks**

In summary **Dr Yedilbayev**, Annual Meeting Chair, announced that the TB action plan 2023–2030 will be endorsed at the 72nd session of the WHO Regional Committee for Europe in September 2022 (6). In November 2022, the meeting on operationalization of the action plan will be organized, where issues related to expanded access to the new drugs and shorter treatment regimens not only in the framework of the operational research but also in programmatic conditions, will also be discussed. **Dr Yedilbayev** thanked the moderators, all participants and the WHO team members and closed the second annual meeting.
References


Annex 1. Provisional programme: Day 1

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<td>09:00–09:20</td>
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<td>Dr Askar Yedilbayev&lt;br&gt;Team Lead, TB, Joint Infectious Diseases Unit, Division of Country Health Programmes, WHO Regional Office for Europe</td>
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<td>The TB regional action plan 2023–2030: pillar I and pillar III</td>
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<td>Session 2: Progress of research implementation</td>
<td>Mr Oleksandr Korotych&lt;br&gt;Technical Officer (TB Operational Research Initiatives), Joint Infectious Diseases Unit, Division of Country Health Programmes, WHO Regional Office for Europe</td>
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<td>09:40–10:00</td>
<td>Session 3: The VMC and its role in the introduction of mSTR</td>
<td>Dr Elmira Gurbanova&lt;br&gt;mSTR Task Force member, Coordinator of Virtual Medical Concilium, Consultant, WHO Regional Office for Europe</td>
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<td>10:00–10:45</td>
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<td>Dr Elmira Gurbanova&lt;br&gt;Mr Oleksandr Korotych</td>
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<td>• Analysis of the reasons for non-enrollment</td>
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<td>10:45–11:00</td>
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<td>Session 5: Best country practices</td>
<td>Dr Alena Skrahina&lt;br&gt;Principal Investigator</td>
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<td>12:45–13:15</td>
<td><strong>Session 6: Sub-group of mSTR task force to support scale up of novel six-month treatment regimens</strong></td>
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<td>WHO Rapid Communication on the upcoming changes in DR-TB treatment</td>
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- From pilot project to gradual scale up: Tajikistan
- Improving clinical monitoring: Republic of Moldova
- Internal study monitoring system, optimization of DST timelines: Ukraine
- Experience of HCV screening and treatment: Armenia

**Dr Sadulo Saidaliev**
Principal Investigator

**Dr Valentina Vilc**
Principal Investigator

**Dr Iana Terleieva**
Principal Investigator

**Dr Hakob Ashtemyan**
Clinician

**Mr Oleksandr Korotych**
mSTR Task Force member, Consultant, WHO Regional Office for Europe

**Dr Nino Lomtadze**
mSTR Task Force member, Consultant, WHO Regional Office for Europe

**Dr Kai Blondal**
mSTR Task Force member, Consultant, WHO Regional Office for Europe

**Discussion moderators:**

**Dr Askar Yedilbayev**
mSTR Task Force member, Consultant, WHO Regional Office for Europe

**Dr Michael Rich**
mSTR Task Force member, Consultant, WHO Regional Office for Europe

**Dr Andrei Dadu**
Medical Officer, Joint Infectious Diseases Unit, Division of Country
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# Annex 2. Provisional programme: Day 2

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<td>Dr Askar Yedilbayev Mr Oleksandr Korotych</td>
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<td>Dr Arax Hovhannesyan mSTR Task Force member, Consultant, WHO Regional Office for Europe</td>
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<td>Session 2: Update on data quality</td>
<td>Dr Nino Lomtadze</td>
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<td>Session 3: Update on recording of SAE/AEI</td>
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<td>10:00–10:20</td>
<td>Session 4: Online platform for storage and overview of data</td>
<td>Dr Jay Achar mSTR Task Force member, Consultant, WHO Regional Office for Europe</td>
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| 10:20–10:50  | Session 5: Mid-project evaluation to document regional and country experience  
• Rationale  
• Methodology  
• Findings | Ms Myroslava Germanovych Consultant, WHO Regional Office for Europe                                                                   |
| 10:50–11:00  | Questions and answers                                                |                                                                                                                                       |
| 11:00–11:15  | Break. Participants are assigned into breakout groups by switching meeting links |                                                                                                                                       |
| 11:15–12:10  | Breakout room 1: Programmatic experience of introducing mSTR         | Participants: NTP managers, programmatic specialists, laboratory specialists, partners, donors  
Facilitators: Dr Naira Khachatryan mSTR Task Force member, Consultant, WHO Regional Office for Europe |
- Describe the factors that facilitated the introduction of mSTR in your country?
- What were the challenges with the diagnostic and enrollment algorithm? How did you overcome them?
- What are the challenges and successes of 12-month follow-up of patients?
- Which programmatic practices have been changed as a result of mSTR implementation?
- What achievement are you most proud of?
- What would you do differently if you were to start the project now?
- What lessons from mSTR will you take into account when scaling up novel six-month regimens for DR-TB?

**Breakout room 2: Clinical and aDSM components of mSTR operational research**

*Questions for discussion:*

- What were the key concerns of clinicians for the introduction of mSTR?
- How was the introduction different in practice to your expectations?
- What changes were made in treatment administration and monitoring to comply with the study requirements?
- What were the main challenges in the introduction of mSTR and adhering to the treatment monitoring schedule?
- Which processes have been improved as a result of the operational research?
- What elements of this operational research have already been, or can be, introduced

**Participants:** key clinicians, heads of consilium

**Facilitators:**
- Dr Elmira Gurbanova
- Dr Valentina Vilc

**Rapporteur:**
- Dr Nino Lomtadze
into the routine programmatic management of TB and MDR/RR-TB in your country?

- Do you consider the support from the VMC beneficial to the implementation of the operational research? What could be improved?

| 11:15–12:10 | Breakout room 3:  
Data collection and quality in mSTR operational research

Questions for discussion:

- What were the key challenges for form completion and data entry in the mSTR operational research?
- Which factors influence data quality for this project in your country?
- What is the system for mSTR operational research data quality monitoring in your country?
- Would you please describe the most successful interventions that helped you to improve data quality?
- What could have been done differently to ensure better data quality?

Participants: database managers, form completion specialists, data quality monitors

Facilitators:
- Dr Liga Kuksa
- Dr Mahmud Rashidov
  Doctor, Partners in Health

Rapporteur:
- Dr Ana Ciobanu
  mSTR Task Force member, Consultant, WHO Regional Office for Europe

| 12:10–12:15 | Participants return to the main session using the link received in the email after the initial registration for Day 1

| 12:15–13:00 | Plenary session
Rapporteurs summarize discussions in the groups (15 minutes per group)

Participants: Dr Gunta Dravniece  
Dr Nino Lomtadze  
Dr Ana Ciobanu

| 13:00–13:40 | Plans and next steps:
- Novel six-month treatment regimens

Participants: Dr Askar Yedilbayev
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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<tbody>
<tr>
<td></td>
<td>• WHO consolidated guidelines development process</td>
<td>Dr Fuad Mirzayev</td>
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<td></td>
<td>• Whole genome sequencing (plans, capacity, challenges)</td>
<td>Dr Gunta Dravniece</td>
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<td>• Treatment of children with DR-TB</td>
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<td>13:40–14:00</td>
<td>Closing remarks</td>
<td>Dr Askar Yedilbayev</td>
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<td>Group picture</td>
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