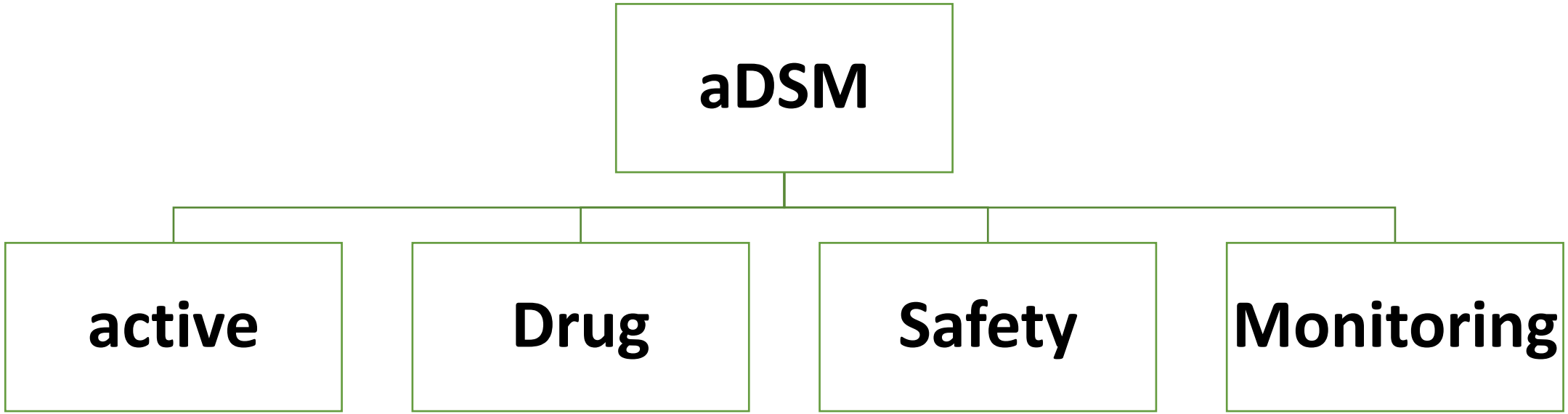
Good practice in aDSM within mSTR operational research.

7th webinar of the Virtual Medical Consilium (VMC) within framework of the Regional operational research on introduction of modified fully-oral shorter treatment regimens for DR-TB (mSTR)

June 4, 2021

Liga Kuksa


aDSM
active
Drug
Safety
Monitoring

aDSM components

1. Clinical monitoring
   - active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs
2. Management of AEs in a timely manner
3. Systematic and standardized recording and reporting of AEs
   - Data collection to include safety data
   - At least all SAEs reported and assessed for causality
   - Close coordination between national TB and PV structures

aDSM Level of drug safety reporting

"Intermediate Package«

- that includes recording and reporting of
  - **all Serious Adverse Events (SAEs),** and
  - **Adverse Events of Special Interest (AEIs)**

A **Serious Adverse Event (SAE)** is

- any untoward occurrence in a patient given a pharmaceutical product and that at any dose:
  - Results in death,
  - Is immediately life-threatening,
  - Requires inpatient hospitalisation or prolongation of hospitalisation.
  - Results in persistent or significant disability/incapacity
  - Is a congenital anomaly/birth defect
  - Is considered otherwise medically significant and requires intervention

AEs of interest (AEI) within mSTR OR

Peripheral neuropathy

Myelosuppression

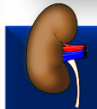
(anemia, thrombocytopenia, neutropenia)

Optic nerve disorder

Hepatitis

Prolonged QTcF interval

Hypokalaemia



Acute kidney injury

Severity Grading Scale

- It is based on the standardized and commonly used toxicity table of NIAIDS the Division of Microbiology and Infectious Diseases (DMID) grading system, complemented with a selection of terms from the NCI's Common Terminology Criteria for Adverse Events (CTCAE) scale.
- Severity of an Adverse Event is the evaluation of its intensity based on the scale detailing signs and symptoms and/or lab values matching with what is generally admitted as being a mild, moderate, severe or life-threatening intensity for the condition.

GUIDELINES FOR COMPLETION OF THE ADVERSE EVENT OF INTEREST (AEI) AND SERIOUS ADVERSE EVENT (SAE) REPORT FORM

For parameters not included in the table, the following general definitions apply:

Grade 1 - MILD	Grade 2 - MODERATE	Grade 3 - SEVERE	Grade 4 - LIFE-THREATENING
Transient or mild discomfort (<48 hours); no medical intervention/therapy required	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Example #1

- Patient started treatment on 26.10.2020 with QTcF was 415 msec after 4 month of treatment(25.02.21) QTcF is 502 msec

Grade 3

Example #2

- Patient, 17 years old, with primary pulmonary TB, smear and culture positive; MDR (HR) FQ sensitivity. There are no concomitant diseases. Treatment started on 04/05/2021 with regimen # 1: Bdq Lfx Lzd Cfz Cs in standard doses.
- The patient is compliant to treatment, but over the past 10 days, she cries a lot, does not come into contact, sits in a corner and cries.

Grade 1 ?

Grade 2 ?

Grade 3?

Grade 4?

Which adverse event?

For parameters not included in the table, the following general definitions apply:

Grade 1 - MILD	Grade 2 - MODERATE	Grade 3 - SEVERE	Grade 4 - LIFE-THREATENING
Transient or mild discomfort (<48 hours); no medical intervention/therapy required	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Example #3

- A 46-year-old female with new pulmonary MDR-TB, resistant to R, H but sensitive to FQ
- 29.12.20 started treatment with Lfx 1000 mg, Bdq 400/200mg, Lzd 600mg, Cfz 100 mg, Cs 750 mg. –
- 18.01.2021 registered severe pain in joints and muscles what started to impact daily activities. NSAID was prescribed as well

Adverse Event of Interest (AEI) and Serious Adverse Event (SAE) Report Form (part I)

Country 0 **Study site** 0 **Participant ID** 0 0 0 0

A Visit Information

nr. of month

B AEI/SAE information

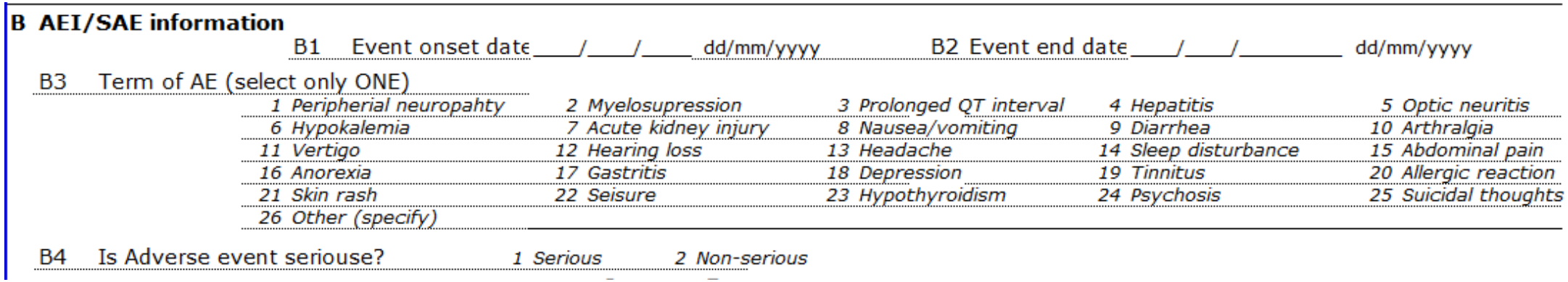
B1	Event onset date	dd/mm/yyyy	
B2	Event end date	dd/mm/yyyy	
B3	Term of AE (select only ONE	*If other, specify*	
B4	Is Adverse event seriouse?		
B4.1	If YES, seriousness criteria:		
B5	Severity Grade		
B6	Event outcome		

C Relevant laboratory tests

Relevant laboratory tests	Date (dd/mm/yyyy)	Result (unit)	Reference range

SAE/AEI form

- The AEI/SAE Report Form is designed to allow for a proper case assessment and appropriate reporting in accordance with the applicable international standards (ICH E2B). The available fields must be completed as much as possible with the relevant information available at the time of reporting.
- In case of the any serious adverse event or **grade 3 and grade 4 adverse** event of interest (7 AEIs), the SAE/AEI form should be completed
- The form contains the essential information that is required to conduct proper causality assessment and is user friendly (most fields are just checkboxes)



B AEI/SAE information

B1 Event onset date ____/____/_____ dd/mm/yyyy B2 Event end date ____/____/_____ dd/mm/yyyy

B3 Term of AE (select only ONE)

1 Peripherial neuropahty	2 Myelosupression	3 Prolonged QT interval	4 Hepatitis	5 Optic neuritis
6 Hypokalemia	7 Acute kidney injury	8 Nausea/vomiting	9 Diarrhea	10 Arthralgia
11 Vertigo	12 Hearing loss	13 Headache	14 Sleep disturbance	15 Abdominal pain
16 Anorexia	17 Gastritis	18 Depression	19 Tinnitus	20 Allergic reaction
21 Skin rash	22 Seisure	23 Hypothyroidism	24 Psychosis	25 Suicidal thoughts
26 Other (specify)				

B4 Is Adverse event seriouse? 1 Serious 2 Non-serious

SAE/AEI form

- If all signs and symptoms experienced by a patient can be grouped under a single diagnosis, diagnosis should be reported by selecting one of the Adverse Event Terms under section “B”.
  - In the situations, where diagnosis is not feasible at time of reporting, and/or event other than listed has occurred, the other term or the signs and symptoms should be listed under “other” in section B.
- Please note that only one AE term should be selected or listed.
- In case of more than one adverse event another AEI/SAE reporting form should be completed separately.

Adverse Event of Interest (AEI) and Serious Adverse Event (SAE) Report Form (part II)

Country	0	Study site	0	Participant ID	0	0	0	0

AEI/SAE information Adverse event (from part I) 0 If other specify

D			1-Levofloxacin	2-Bedaquiline	3-Linezolid	4-Clofazimine	5-Cycloserine	6-Delamanid
D1	Suspected drug							
		Daily dose (g)						
		Batch number						
		Treatment start date dd/mm/yyyy						
		Treatment stop date dd/mm/yyyy						
D2	Action taken in response to A							
	If dose reduced, New daily dose (g)							
		On dd/mm/yyyy						
	If drug interrupted							
		From dd/mm/yyyy						
		To dd/mm/yyyy						
	If drug permanently withdrawn							
		On dd/mm/yyyy						
D3	Event diminished after drug stopped/dose reduced?							
D4	Event reappeared after drug/dose reintroduction?							
D5	Causality assessment: Is AE related to drug?							

if other drug, specify:

Other causal factors or Interacting Drugs

E Concomitant medications (Including the drugs taken within 2 week prior to the event and drugs with the long half file)

Drug name (INN)	Daily dose (g) and route	Indication	Treatment start date	Treatment stop date	Continued

Form Completion Name of person completing form Date Form completed dd/mm/yyyy

Код участника

4

I исследуемое нежелательное явление (ИНЯ) или серьезное нежелательное явление (СНЯ)

B1. Дата начала НЯ: 12/15/2020

B2. Дата окончания явления: M/D/YYYY

B3. Наименование НЯ: 2 - Миелосупрессия

B3.1. Если другое, указать:

B4. Является ли НЯ серьезное?: 2- Несерьезное

B.4.1. Если " ДА", критерия серьезности:

B5. Степень тяжести: 2 - Степень II

B6. Исход явления: 2 - Улучшение

Клиническое

Месяц лечения	Д с
0	9
1	1
2	1
3	1
4	1
5	2

Подозреваемое лекарство (укажите все препараты схемы лечения)

D1. Подозреваемое лекарство	D2. Меры, принимаемые в ответ	D3. НЯ ослабло после отмены/снижения дозы?	D4. НЯ снова возникло после повторного назначения преп/ дозы	D5. Оценка причинно-следственной связи: Связано с препаратом?
1 - Lfx	1 - Доза оставлена без и...	9 - н/п	9 - н/п	9 - н/п
2 - Bdq	1 - Доза оставлена без и...	9 - н/п	9 - н/п	9 - н/п
3 - Lzd	2 - Доза снижена	1- ДА	1- ДА	1- ДА
4 - Cfz	1 - Доза оставлена без и...	9 - н/п	9 - н/п	9 - н/п
5 - Cs	1 - Доза оставлена без и...	9 - н/п	9 - н/п	9 - н/п

Condition term	Grade 1	Grade 2	Grade 3	Grade 4
Anaemia	10.5 - 9.5 g/dL [105 - 95 g/L]	9.4 - 8.0 g/dL [94 - 80 g/L]	7.9 - 6.5 g/dL [79 - 65 g/L]	< 6.5 g/dL [< 65 g/L]

Comments

The transformation is pretty bad, but the worst part is filling out the paperwork for the adverse events.