Active TB drug-safety management & monitoring

Global TB Programme, WHO, Switzerland

6 August 2015
Pharmacovigilance: definition of

“science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.”

WHO
3 Methods

- Spontaneous reporting
- Targeted reporting
- Active monitoring
Active drug-safety monitoring (1)

• Pro-active efforts made to elicit adverse events
• Events detected by asking patients directly, screening patient records, laboratory & clinical tests
• It is best done prospectively
• Follow-up continues after treatment has ended
• Adverse event (AE) reporting not just focused on known reactions for a drug or which are plausible based on pharmacology
Active drug-safety monitoring (2)

• Cohort approaches are the most comprehensive; they fit the framework which national TB programmes are familiar with when monitoring TB cases for response to treatment and assigning outcomes.

• In addition to monitoring, drug-safety concerns detected should lead to action for the benefit of the individual patient, and, possibly, on national and international policy in the use of the drug.
WHO advice to countries (since 2012):

1. Approval of the project by a national ethics review committee, ahead of patient enrolment;
2. Delivery of treatment under operational research conditions following international standards (including Good Clinical Practice and safety monitoring), with the objective of assessing the effectiveness and safety of these regimens (active pharmacovigilance);
3. Monitoring of the MDR-TB component of the TB programme, and its corresponding research project, by an independent monitoring board set up by and reporting to WHO.
The evaluation of effectiveness and safety of a shorter standardized treatment regimen for multidrug-resistant tuberculosis

A publication of the Global Drug-resistant TB Initiative (GDI)
A Working group of the Stop TB Partnership

May 2015
Shorter regimens for MDR-TB (3)

UNION multi-centre project

As shown in Table 3, follow-up will be continued up to 12 and 24 months after the patient is declared ‘cured’ in order to detect any relapse.

Table 3. Follow-up of MDR patients during and after their treatment (M = Month)

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* If initial ECG shows QT interval > 500 ms, the patient will not receive moxifloxacin (excluded from study). ECG will be done at the first of treatment and again if any heart problem - especially rhythm problem - is suspected during treatment.

MSF centres (Uzbekistan, Swaziland)

FORM 6

SIDE EFFECTS FORM

The Form 6 is completed each time a patient is reviewed for/presents with side effects. A patient’s TB doctor or attending doctor in a TB inpatient facility completes this form (or pilot nurse in case of the Short Course project), depending on treatment location at the time of the side effect episode. The form is sent to MSF-Epi, after the entry into the database - the form is kept in patient’s medical chart.

Patient’s name (surname, name):

Date form completed:

Month of treatment:

1. Symptoms (check all that apply) for details refer to the protocol:

<table>
<thead>
<tr>
<th>General:</th>
<th>Gastrointestinal</th>
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<td>Systemic allergic reaction</td>
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<td>Arthralgia</td>
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<td>Rash</td>
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<td>Pruritis</td>
<td>Abdominal pain</td>
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<td>Mental health:</td>
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<td>Depression</td>
<td>Constipation</td>
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<td>Psychosis</td>
<td>Dysphagia</td>
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<td>Anxiety</td>
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Other, specify

Neurological:

<table>
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<tr>
<th>Headache</th>
<th>Decreased hearing</th>
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<tr>
<td>Ringing in the ears</td>
<td>Decreased vision</td>
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<tr>
<td>Seizures</td>
<td>Insomnia</td>
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<td>Neuroromotor weakness</td>
<td>Neuroromotor weakness</td>
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<td>Neuromotor alteration</td>
<td>Vertigo</td>
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<td>Grade</td>
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</table>

APID: |

Grade: |

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ANNEX 4.1

‘How-to’ guide on the use of bedaquiline for MDR-TB treatment

ANNEX 4.2

‘How-to’ guide on the use of delamanid for MDR-TB treatment

A4.2.1 Background on delamanid

Introduction

Delamanid is a nitro-dihydro-imidazo-oxazole derivative, inhibiting a novel target in *Mycobacterium tuberculosis* cell wall mycolic acid synthesis (1). The drug received marketing authorization from the Committee for Medicinal Products for Human Use for the treatment of MDR-TB patients in the European Union (2). Delamanid has demonstrated potent preclinical in vitro and in vivo activity against both drug-susceptible and drug-resistant strains of *M. tuberculosis* (1). The evidence for efficacy and safety has been gathered primarily in a two-month Phase II, multicentre, randomized, double-blind, stratified (by extent of pulmonary disease), placebo-controlled clinical trial in three parallel groups of male and female patients (18–64 years old) with pulmonary, sputum culture positive MDR-TB (3). That study was followed by a six-month, open-label, multicentre clinical trial in which subjects who successfully completed the initial two-month study were eligible to enrol (4).
Companion handbook
to the WHO guidelines for the
programmatic management of
drug-resistant tuberculosis

CHAPTER 11
Management of adverse effects
and pharmacovigilance

ANNEX 11.1
Treatment initiation form –
CEM for TB drugs

Interview date: dd/mmm/yyy

PATIENT DETAILS

Patient Name: ____________________________ 
Patient ID: ______________________________
Date of birth: dd/mmm/yyy 
Age: __________________ Sex at birth: □ male □ female

TREATMENT PROVIDER

District: __________________________ 
Health Facility & address: __________________________
Clinician/Team: __________________________ 
Patient File number: __________________________
Interview site: □ Health Centre □ Hospital Clinic □ Phone interview □ Home visit □ Other

MEDICAL DETAILS

Weight (kg): __________________________ 
Height (cm): __________________________
Indication for treatment: □ Pulmonary TB □ Extra-pulmonary TB □ TB site/s: __________________________ 
□ MDR-TB □ Prophylaxis
Prior exposure to anti-TB medicines: □ No □ Yes □ Unknown

Pregnant: □ Yes □ No □ Unknown
Date of LMP: dd/mmm/yyy __________________________ 
Estimated current gestation (weeks): __________________________
Other online resources:

www.who.int/tb/challenges/pharmacovigilance/en/

Inter-regional workshop on pharmacovigilance for new drugs and novel regimens for the treatment of drug-resistant tuberculosis
Hanoi, Viet Nam 12 – 14 November 2014

The “Inter-regional workshop on pharmacovigilance for new drugs and novel regimens for the treatment of drug-resistant tuberculosis” was organised jointly by WHO Headquarters (the Global TB Programme (GTB) and Essential Medicines and Pharmaceutical Policies (EMP)), the WHO Regional Office for the Western Pacific (WPRO), and the WHO Representative Office in Viet Nam with the support of USAID and UNITAID. The meeting objectives fit within the framework of assistance being provided to national TB programmes (NTPs) and national regulatory authorities to strengthen their pharmacovigilance systems in accordance with WHO policies and ensure that patient safety is effectively monitored during treatment of MDR-TB with new drugs and novel regimens.

Meeting report
pdf, 979kb

Sample data collection forms for cohort event monitoring for anti-TB drugs
pdf, 234kb
Meeting of technical agencies on active TB drug-safety management and monitoring

Geneva, 28-29 July 2015

• Task force composed of technical and financial partners
• Principles and practices underpinning active TB patient drug-safety management and monitoring (“aDMM”), focused on the specifics of TB programmes
• Revise definitions and methods for aDMM
• Update WHO policy and implementation guidance (incl. FAQs)
• Creation of a global database for active TB drug-safety monitoring data
• Develop plan to improve competence in aDMM methods, including signal detection & causality assessment
Active TB drug-safety management and monitoring: features

Prospective surveillance of adverse events associated with one or more medicines in a cohort of TB patients and rapid action upon detected harms
Active TB drug-safety monitoring framework (1)

- Serial testing / screening for AEs

- Drug start
- Drug exposure
- F/u after treatment

- Serious event
- Other event

- Death
- Success
- Loss to f/u
- Change of treatment
- Serious event
- Other event

- Drug start
- Drug exposure
- F/u after treatment
Define the cohort, start recruitment

Size of cohort: not necessarily 10,000
10,000 observations -> 95% chance of observing a specific rare event that has a frequency of 1/3,000.

Planning, resource mobilization, coordination of treatment sites, supervision, monitoring, data management, analysis and communication of results
ANNEX 11.1

Treatment initiation form – CEM for TB drugs

Interview date: dd/mmm/yyyy

PATIENT DETAILS

Patient Name: ___________________________ Patient ID: _______________________

Date of birth: dd/mmm/yyyy Age: ______ Sex at birth: ☐ male ☐ female

TREATMENT PROVIDER

District: ___________________________ Health Facility & address: ___________________________

Clinician/Team: ___________________________ Patient File number: ___________________________

Interview site: ☐ Health Centre ☐ Hospital Clinic ☐ Phone interview ☐ Home visit ☐ Other

MEDICAL DETAILS

Weight (kg): ___________________________ Height (cm): ___________________________

Indication for treatment: ☐ Pulmonary TB ☐ Extra-pulmonary TB ☐ TB site(s): ___________________________ ☐ MDR-TB ☐ Prophylaxis

Prior exposure to anti-TB medicines: ☐ No ☐ Yes ☐ Unknown

Pregnant: ☐ Yes Date of LMP: dd/mmm/yyyy or estimated current gestation (weeks): ___________________________

Uncertain: ☐ If PREGNANT record patient details in PREGNANCY REGISTER for follow-up ☐ No

Breastfeeding an infant: ☐ No ☐ Yes

Injecting Drug Use Within Past Year: ☐ No ☐ Yes ☐ Unknown Excessive alcohol use in the past year: ☐ No ☐ Yes ☐ Unknown

Tobacco use within the past year: ☐ No ☐ Yes ☐ Unknown Documented HIV infection: ☐ No ☐ Yes ☐ Unknown

CURRENT AND PAST MEDICAL CONDITIONS & EVENTS (List)

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<th>Date of recovery</th>
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LABORATORY & OTHER TESTS.

Include laboratory tests taken at any time during the PAST 30 DAYS

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<th>Result (units)</th>
<th>Test</th>
<th>Date</th>
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MEDICINES

Medicines & traditional medicines taken at any time in PAST 30 DAYS

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<th>Dosage</th>
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<th>Route</th>
<th>Start date</th>
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* DST to the following drugs may be useful to record on this form or elsewhere in an accessible electronic medical record: Isoniazid, rifampicin, kanamycin (and/or amikacin), ciprofloxacin, ofloxacin (or ciprofloxacin), levofloxacin and moxifloxin

All NEW anti-TB medicines prescribed at this interview

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<th>Anticipated Stop date</th>
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All other NEW medicines prescribed at this interview

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<th>Dosage</th>
<th>Frequency</th>
<th>Route</th>
<th>Start date</th>
<th>Anticipated Stop date</th>
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</tbody>
</table>

* More updated versions of this form may be published in future at: www.who.int/ib/challenges/pharmaceutical/vigilance/
Active TB drug-safety monitoring framework (4)

Treatment review form – CEM for TB drugs

Interview date: dd/mmm/yyyy

**PATIENT DETAILS**

Patient Name: ____________________________ Patient ID: ____________________________

Date of birth: dd/mmm/yyyy Age: ________ Sex at birth: [ ] male [ ] female

**TREATMENT PROVIDER**

District: ____________________________ Health Facility & address: ____________________________

Clinician/Team: ____________________________ Patient file number: ____________________________

Interview site: [ ] Health Centre [ ] Hospital Clinic [ ] Phone interview [ ] Home visit [ ] Other

**MEDICAL DETAILS**

Weight (kg): ____________________________ Height (cm): ____________________________

Indication for treatment: [ ] Pulmonary TB [ ] Extra-pulmonary TB [ ] TB site/s: ____________________________ [ ] MDR-TB [ ] Prophylaxis

Prior exposure to anti-TB medicines: [ ] no [ ] yes [ ] unknown

Pregnant: [ ] yes Date of LMP: dd/mmm/yyyy or estimated current gestation (weeks): ____________________________

Uncertain if pregnant? Record patient details in pregnancy register for follow-up

[ ] no

Breastfeeding an infant: [ ] no [ ] yes

---

<table>
<thead>
<tr>
<th>Events</th>
<th>AE MedDRA/WHO-ART code*</th>
<th>Record all NEW EVENTS or CHANGES in pre-existing conditions since last interview</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date onset</td>
<td>Date resolved</td>
</tr>
</tbody>
</table>

* To be completed by PEP link after data collection (see also Instructions for completion)

** OUTCOME**

R1 Recovered/ resolved 1 N Not serious
R2 Recovering/resolving 2 M Moderate
S Recovered with sequelae 3 Severe
N Not recovered/not resolved 4 Life threatening
D Died 5 Death
U Unknown 6 Unknown

---

**MAXIMAL SEVERITY†**

H Hospitalization (caused or prolonged)
P Permanent disability
G Congenital abnormality
L Life threatening

---

**SERIOUSNESS#**

1 No recurrence
2 Recurrence of event
3 No recurrence
4 Result unknown

---

**RECHALLENGES**

**LABORATORY & OTHER TESTS**

<table>
<thead>
<tr>
<th>Test</th>
<th>Date</th>
<th>Result (units)</th>
<th>Test</th>
<th>Date</th>
<th>Result (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Antibody</td>
<td>ALT</td>
<td>(SGPT)</td>
<td>CD4 Count</td>
<td>AST</td>
<td>(SGOT)</td>
</tr>
<tr>
<td>ESR</td>
<td>Lactic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WCC</td>
<td>Lipase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Chest X-Ray</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>Cavities (Y/N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Audiometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>Visual acuity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis markers</td>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**MEDITINES**

Anti-TB medicines taken since last interview

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Frequency</th>
<th>Route</th>
<th>Start date</th>
<th>Stop date</th>
<th>Continues</th>
<th>Reason(s) for stopping #</th>
<th>Action**</th>
</tr>
</thead>
</table>

Other medicines & traditional medicines taken since last interview

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Frequency</th>
<th>Route</th>
<th>Start date</th>
<th>Stop date</th>
<th>Continues</th>
<th>Reason(s) for stopping #</th>
<th>Action**</th>
</tr>
</thead>
</table>

---

[ ] More updated versions of this form may be published in future at www.who.int/challenges/pharmacovigilance/
Active TB drug-safety monitoring framework (5)
review form (2)

<table>
<thead>
<tr>
<th>Active TB drug-safety monitoring framework (5)</th>
<th>review form (2)</th>
</tr>
</thead>
</table>

### Instructions for the completion of the TREATMENT REVIEW FORM
A Treatment Review Form should be completed each time the patient is interviewed following commencement of treatment with the monitored medicine(s). This form represents a template and the programme may wish to adapt it according to its needs and preferences; it includes all of the essential data elements to be collected for the CEM of TB drugs as recommended by WHO.

**Patient ID**
Type of unique patient identification to be selected by country.

**Tick boxes (✓)**
Where there are tick boxes, please answer by placing a tick ✓ in the appropriate box.

### PATIENT DETAILS

**Patient initials**
Please use initials of given name(s) and family name.

**Date of birth**
If DOB is unknown, record the patient’s age (or estimated age if true age is unknown).

### TREATMENT PROVIDER

**Patient file number**
Record the file number used to identify the patient in your clinic.

### MEDICAL DETAILS

**Weight & height**
Record the patient’s current weight and height on the date of follow-up visit. Height should be recorded for children at treatment review, but is unnecessary for adults.

**Indication for treatment**
Please indicate whether the anti-tuberculosis therapy is to be used for the treatment of pulmonary TB, extra-pulmonary TB, MDR-TB or for prophylaxis. More than one box may be ticked.

**Pregnant**

### All NEW medicines (anti-TB & other) prescribed at this interview

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Frequency</th>
<th>Route</th>
<th>Start date</th>
<th>Expected stop date</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Reason for stopping

<table>
<thead>
<tr>
<th>Reason</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adverse event</td>
</tr>
<tr>
<td>2</td>
<td>Poor adherence</td>
</tr>
<tr>
<td>3</td>
<td>Course completed or cured*</td>
</tr>
<tr>
<td>4</td>
<td>Planned interruption</td>
</tr>
<tr>
<td>5</td>
<td>Planned medication change</td>
</tr>
<tr>
<td>6</td>
<td>No longer needed</td>
</tr>
<tr>
<td>7</td>
<td>Treatment failure*</td>
</tr>
<tr>
<td>8</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>9</td>
<td>Drug out of stock</td>
</tr>
<tr>
<td>10</td>
<td>Cost</td>
</tr>
<tr>
<td>11</td>
<td>Patient decision</td>
</tr>
<tr>
<td>12</td>
<td>Died*</td>
</tr>
<tr>
<td>13</td>
<td>Lost to follow-up*</td>
</tr>
<tr>
<td>14</td>
<td>Other (please specify)</td>
</tr>
</tbody>
</table>

### Action taken by clinician in case of suspected adverse event linked to a drug

- Dose not changed
- Drug withdrawn
- Not applicable
- Dose reduced
- Drug interrupted

### Outcome* (to be completed at the end of current treatment episode)

- Cured
- Completed
- Treatment failed
- Died
- Lost to follow up
- Not evaluated

---

[Follow the link for the full document](http://www.who.int/tb/stop-tb/2013_2014/en/)

---

Active TB drug-safety monitoring framework (6)

*create database*

- Build upon existing, functional e-register
- Good practices in data entry & transfer
- Simplicity for use and adaptation
- Interoperates with the global registries
Active TB drug-safety monitoring framework (7)

data analysis & identifying signals

• Checks & routines to validate the data
• Procedures
• Responsibilities
• Decision on signals and communication
Active TB drug-safety monitoring framework (8)

information cycle

1. DECISIONS ON PARAMETERS & IT SYSTEM
2. TRAINING
3. TESTING & DATA COLLECTION
4. DATA ENTRY
5. SUPERVISION
6. ANALYSIS, SIGNAL DETECTION
7. COMMUNICATION
### Active TB drug-safety monitoring framework (9)

**Expected intensity of work over time**

<table>
<thead>
<tr>
<th>Processes</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Define cohort</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do serial clinical &amp; lab tests</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Create expert group</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Create protocol</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manage &amp; supervise</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Train staff</td>
<td>+++</td>
<td>+</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Create data collection material</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Create e-database</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect &amp; enter data</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Identify signals and data analysis</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Elements</strong></td>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convene an expert group on aDMM</td>
<td>early; use existing body</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Develop aDMM plan / protocol</td>
<td>early; use local / international expertise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Define management and supervision roles and responsibilities</td>
<td>at start</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Train</strong> staff at different levels</td>
<td>before starting enrolment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Create standard data collection material</td>
<td>before starting enrolment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Define schedule and route for data collection and reporting</td>
<td>at start</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Create database with core elements</td>
<td>early</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Develop capacity for signal detection and data analysis</td>
<td>over time; engage local and international expertise</td>
<td></td>
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</tr>
</tbody>
</table>
Before starting active monitoring:
1. preparations for the collection of data (paper or electronic forms); and
2. staff properly trained to collect the data

Coordination ideally involves experts from relevant disciplines, convened by the NTP early on to steer the surveillance at national level (e.g. as one function of the MDR committee).
Active TB drug-safety monitoring framework (12)  

*training of staff*

- Different users; not all may be familiar with TB and TB drugs

- Trainees: health care providers (public / private; 1st ary health care / hospital), surveillance, IT specialists, regulatory, academia

- Find trainers & organise training ahead of start
Active TB drug-safety monitoring framework (13)
   steering group

- NTP assigns someone to coordinate the activities and to oversee active TB drug-safety surveillance
- Ensure that the two minimum elements are in place
- Develop a protocol and have it approved
- Integrated within an existing body (e.g. TB consilium)
- Constituencies represented: therapeutics, surveillance, regulatory, pharmacy, academia, research, ethics, finances, communication, patients and civil society
Active TB drug-safety monitoring framework (14)  
local adaptations

- Needs assessment: what gaps in TB drug-safety monitoring? ethics approval?
- Involvement of national drug-regulatory authority: expertise in causality assessment as per NTP demand and handle reporting of ADRs detected
- Agreement on how to respond to signals (threshold, communication of risk or detected harm ...)
- Human resources needed and budget
- Adjust the data management requirements to any existing system for TB/MDR-TB patient data
Immediate uses of the data

1. Causality assessment
2. Signal detection
3. Indicators
4. Drug-safety profiles
Data flows for active TB drug safety monitoring: processing, repository, analysis, action and communication.
**National TB Programme**

**PATIENT SAFETY & CARE**
- Treatment
- Patient questionnaires on symptoms
- Routine tests for TB drug safety monitoring

**DRUG SAFETY SURVEILLANCE**
- Deaths
- Serious adverse events
  
  **National and/or global Central database**
  - Signal detection
  - Causality assessment

**New Evidence**

**Inform treatment policy update**

**National Pharmacovigilance System**

**Further analysis & Communication**

**Inform drug safety profile update**

**Reporting within 24h**
In conclusion (1)

- Challenges posed by novelties in terminology, clinical testing (type and intensity), data collection & consolidation, national & supranational reporting, type of analysis
- However experience and best practices in active TB drug-safety monitoring using cohort approaches in MDR-TB patients at programme level is developing
In conclusion (2)

• More work needed to assist countries to
  • implement active TB drug-safety monitoring
  • implement the AE management component
  • define how to link records for signal detection (and contribute to supranational monitoring)
  • develop associated skills
• If the aDMM component is to develop and become a standard of TB patient care, fresh resources – domestic and donor (GF, USAID, UNITAID) - will be needed
Additional slides on technical detail
Which AE data to capture in the database?

- Exact value, even when normal (e.g. H’globin 14.2g/dL)
- Exact value, starting from mild severity
- Exact value, starting from moderate severity
- Indication of «not done/normal/mild/moderate/severe»
- Indication of «not done/normal/abnormal»
- Indication of «serious»
cutting down AE data: at what price?

Limiting event data...
(i) establish clinically significant trends (e.g. rising creatinine; decreasing haemoglobin; prolongation of QTc)
(ii) miss rare events which may not reach the seriousness or severity threshold because of dose-dependency
(iii) differentiate between a normal from a missing value
(iv) analysis of pooled data across projects may be complicated by variability in thresholds

Limiting cohort (e.g. sentinel surveillance)
(i) reducing the number of observations
(ii) different level of patient monitoring
Seriousness & severity (1)

Definitions

A serious reaction is one which involves any of the following: death or a life-threatening experience; hospitalization or prolongation of hospitalization; persistent significant disability; or congenital anomaly.

Severity reflects the intensity of an event.
• Subjective assessment of patient and/or HCW
• Impact on patient’s activities
• The underlying cause can be serious or not serious.
• Different scales to classify severity
Seriousness & severity (2)

Scales of severity

Simplest: a range from mild-> moderate-> severe

No detailed scales developed for TB: adapted from chronic disease (HIV or cancer)

ANRS: used by the multi-centric study of shorter regimens (with some adaptations)

Others: DAIDS, CTCAE grading system
### Seriousness & severity (3)  
DAIDS scale

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS**  
PUBLISH DATE: DECEMBER, 2004

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged QTc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adult &gt; 16 years</strong></td>
<td>Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval &lt; 0.03 sec above baseline</td>
<td>Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline</td>
<td>Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline</td>
<td>Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia</td>
</tr>
</tbody>
</table>

(accessed 10 July 2015)
Causality assessment

“Estimating the probability of a relationship between exposure to a medicine and the occurrence of an adverse reaction”
Causality assessment (1)

2 basic questions

- Is there a convincing *relationship* between the drug and the event?

- Did the drug *actually cause* the event?
Causality assessment (2)

*main things to look out for*

- Is the time to onset of the event compatible with the suspected cause (plausible time-frame)?
- Did the event occur after the start of some other medicine or new illness?
- Is the event plausible with what is known about the drug?
- Is there any other possible cause for the event?
- What is the response to withdrawal of the medicine (dechallenge)?
- What is the response to rechallenge?
- Is the event severe / serious (causality assessment prioritised)
### Causality assessment (3)

**approaches to assess causality**

<table>
<thead>
<tr>
<th>Method</th>
<th>Principles</th>
<th>+ / -</th>
<th>Reproducibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert opinion</td>
<td>Based on judgement of individual experts</td>
<td>Subjective</td>
<td>Low</td>
</tr>
<tr>
<td>Algorithms</td>
<td>Follows a decision tree defined by experts / pharmacology</td>
<td>More standardized than expert opinion</td>
<td>Low (subjective)</td>
</tr>
<tr>
<td>Probability assessment</td>
<td>Bayesian approach</td>
<td>Need special skills; numeric data</td>
<td>Considered «gold standard»</td>
</tr>
</tbody>
</table>

Adapted from R Benkirane (WHO-CC Morocco; 2014)
Causality assessment (4)

key data elements for causality assessment

- Medical history (incl. concomitant disease)
- Details of drugs taken: names, doses, routes
- Start and stop dates and indications for use
- Description of adverse event, including clinical description, laboratory results, and date of onset / end
- Evolution of event, severity/seriousness, outcome
Causality assessment (5)

categories of relationship

1. Certain
2. Probable
3. Possible
4. Unlikely
5. Unclassified (or conditional)
6. Unassessable
### Causality assessment (6)

**classification of relationship**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Exception: anaphylactic reaction</td>
</tr>
<tr>
<td>Probable</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No or ?</td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>Yes</td>
<td>No or ?</td>
<td>?</td>
<td>No or ?</td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>No</td>
<td>No or ?</td>
<td>No</td>
<td>No or ?</td>
<td>Suggestive if event resolves despite continued exposure</td>
</tr>
</tbody>
</table>
Signal

“Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”
Signal detection (1)

*principles*

- usually >1 event with a similar, strong relationship to a medicine ("certain" or "probable"). Events coded as "possible" can be used as supporting evidence.

- a cluster of unexpected deaths coded as "possible" forms an exception to this general rule and will need to be taken seriously.

- occasionally a single event ("certain" or "probable") - notable for its severity, seriousness or distinctiveness - can be regarded as a signal.
Signal detection (2)

Pointers to events to investigate

- Data are reliable
- Several reports show a credible and strong relationship between event and drug
- The event is of sufficient importance or interest:
  - to require regulatory action
  - to require advice to prescribers
  - for scientific / clinical purposes
Signal detection (3)

methods of signal identification

1. Clinical assessment of individual events
2. Clinical review of collated events
3. Record linkage (eg, with mortality register)
4. Automated signal detection
Signal detection (4)

clinical assessment of individual events

• Standardized assessment of individual reports with alertness to the possibility of a signal
• If new type of ADR is suspected, search for other similar events in references eg, Martindale, Micromedex, Physicians Desk Reference
• If there is no reference to the occurrence of the event as an ADR -> investigate
## Drug safety profile

### Draft framework for the summarization of added benefit and risk associated with an intervention

<table>
<thead>
<tr>
<th>The benefit: toxicity profile of the baseline MDR-TB regimen</th>
<th>The MDR-TB regimen which constitutes the most widely used standard of care is described in terms of its effectiveness and associated harms; this dimension of the profile uses information originating from the published literature; trials (un-/published); observational studies and cohorts (including nested case-controls); prospective CEM data and also other PV findings based on spontaneous reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety concerns associated with a specific drug or regimen</td>
<td>The characteristics (organ class), risk, severity, drug-drug interactions (DDI) and other safety concerns are summarized from the literature as well as local data (including CEM). The known concerns are described, such as increased mortality or prolonged QTc in Bdq users; suspected reasons for lack of efficacy such as resistance or drug quality issues</td>
</tr>
<tr>
<td>Quantifying risk &amp; benefit</td>
<td>As much as possible the safety concerns are also expressed in terms of risk, such as per 100 or 1000 exposures and as relative risks. The effectiveness is generally expressed in terms of % successful outcome or cure</td>
</tr>
<tr>
<td>Risk factors</td>
<td>These include host-related predispositions to harms, such as comorbidities, severity of TB disease, DDI, subpopulations (age-group/sex). These could form the basis of contraindications or caution in use of the regimen or drug</td>
</tr>
<tr>
<td>Signal detection</td>
<td>The procedure followed for relationship and causality assessments and detection of signals in the cohort is described and any departures from agreed methodologies described. Signal detection is attempted both at country- and supranational level. Any preliminary signals are discussed with the regulators and manufacturer before wide communication</td>
</tr>
<tr>
<td>Preventive measures</td>
<td>Advice on avoidance of harm/toxicity, precautions, contraindications</td>
</tr>
</tbody>
</table>
## Indicators (1)

<table>
<thead>
<tr>
<th>CLASS</th>
<th>IMPORTANCE</th>
<th>INDICATOR NUMBER AND NAME</th>
<th>CALCULATION</th>
<th>STRATIFICATION</th>
<th>EXPRESSED AS</th>
<th>DATA SOURCES</th>
<th>LEVEL</th>
<th>PERIOD OF ASSESSMENT</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage (process)</td>
<td>Essential</td>
<td>1) Target RR-/MDR-TB patients included in cohort event monitoring</td>
<td>Numerator: Number of TB cases started on target treatment included in CEM during the period of assessment. Denominator: Number of TB cases started on target treatment during the period of assessment and who were eligible for CEM.</td>
<td>None</td>
<td>Absolute numbers, proportion</td>
<td>Numerator: CEM register. Denominator: Second-line TB treatment register.</td>
<td>National; CEM centre</td>
<td>3 months</td>
<td>To be computed during the period of recruitment but not in the post-treatment observation phase</td>
</tr>
<tr>
<td>Completeness (process)</td>
<td>Optional</td>
<td>2) Time to stopping target drug</td>
<td>The difference in days between the date of start of treatment with a target drug and the date of the stopping the target drug. The calculation is done for each member of the cohort.</td>
<td>Reason for stopping</td>
<td>Number of patients included in the calculation; median interval and interquartile range in days</td>
<td>CEM register</td>
<td>National; CEM centre</td>
<td>12 months</td>
<td>Stratify by reason for stopping (e.g. success, died, treatment failed, loss to follow up, exclusion criterion developing after start of treatment such as pregnancy).</td>
</tr>
</tbody>
</table>
## Indicators (2)

<table>
<thead>
<tr>
<th>CLASS</th>
<th>IMPORTANCE</th>
<th>INDICATOR NUMBER AND NAME</th>
<th>CALCULATION</th>
<th>STRATIFICATION</th>
<th>EXPRESSED AS</th>
<th>DATA SOURCES</th>
<th>LEVEL</th>
<th>PERIOD OF ASSESSMENT</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>Essential (but stratification optional)</td>
<td>3) RR/ MDR-TB patients included in CEM with any serious adverse event</td>
<td>Numerator: Number of TB cases included in CEM during the period of assessment with one or more serious adverse events. Denominator: Number of TB cases included in CEM during the period of assessment.</td>
<td>By organ group; by outcome</td>
<td>Absolute numbers, proportion</td>
<td>Numerator: CEM register. Denominator: CEM register.</td>
<td>CEM centre</td>
<td>3 months</td>
<td>To be computed during the period of patient recruitment and during the post-treatment observation phase. Indicate outcome (deaths, hospitalisations, disability)</td>
</tr>
<tr>
<td>Adverse reactions associated with target treatment</td>
<td>Optional</td>
<td>4) Frequency of ADRs associated with the target treatment</td>
<td>Numerator: Number of ADRs attributed to target treatment among patients on CEM. Denominator: Number of TB cases included in CEM during the period of assessment.</td>
<td>By organ group; by seriousness/severity</td>
<td>Absolute numbers, proportion</td>
<td>CEM register. CEM centre</td>
<td>3 months</td>
<td>To be computed during the period of patient recruitment and during the post-treatment observation phase. Only to be reported after causality assessment (e.g. dechallenge, rechallenge) suggests the target treatment as the causative agent (certain, probable or possible). The same patient may have several ADRs (therefore the unit of measurement is the ADR and not the patients).</td>
<td></td>
</tr>
</tbody>
</table>
## Indicators (3)

<table>
<thead>
<tr>
<th>Class</th>
<th>Importance</th>
<th>Indicator number and name</th>
<th>Calculation</th>
<th>Stratification</th>
<th>Expressed as</th>
<th>Data sources</th>
<th>Level</th>
<th>Period of assessment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reactions associated with target treatment</td>
<td>Optional</td>
<td>5) Time to development of ADRs associated with the target treatment</td>
<td>The difference in days between the date of start of the target treatment and the date of the first detected onset of the ADR attributed to it</td>
<td>By organ group</td>
<td>Number of ADRs included in the calculation; median interval and interquartile range in days</td>
<td>CEM register</td>
<td>CEM centre</td>
<td>6 months</td>
<td>To be computed during the period of patient recruitment and during the post-treatment observation phase. The calculation is done for each reaction attributed to the target treatment; the same patient may have several ADRs computed (the unit of measurement is the ADR and not the patients); if a particular ADR recurs in the same patient during the CEM it is not calculated again. Only to be reported after causality assessment (e.g., dechallenge, rechallenge) suggests the target treatment as the causative agent (certain, probable or possible).</td>
</tr>
</tbody>
</table>


Commissioning electronic systems according to needs

WHO/HTM/TB/2011.22

whqlibdoc.who.int/publications/2012/9789241564465_eng.pdf