Active TB drug-safety management & monitoring

Global TB Programme, WHO, Switzerland

6 August 2015

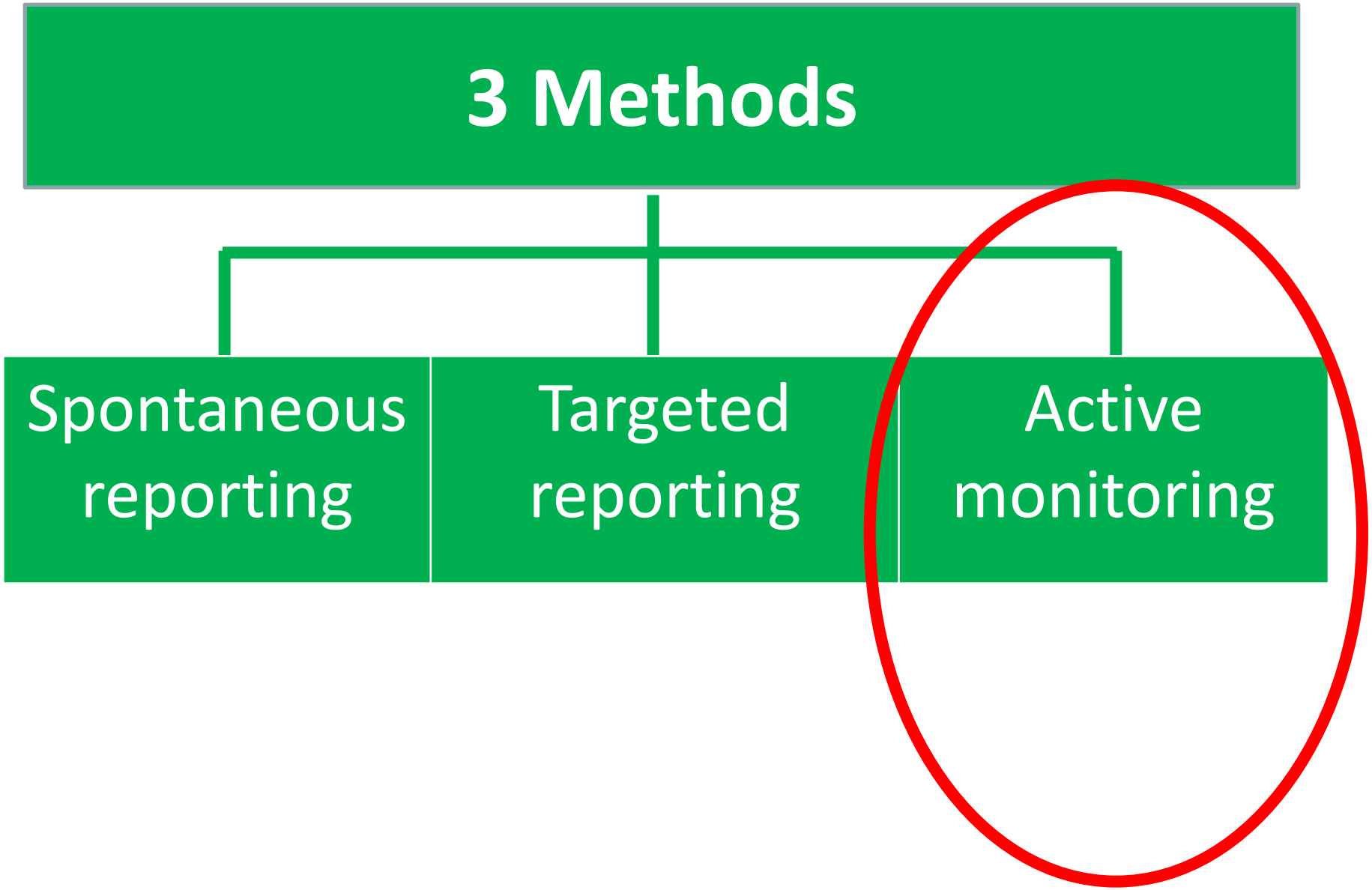
World Health Organization

GLOBAL TB PROGRAMME

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

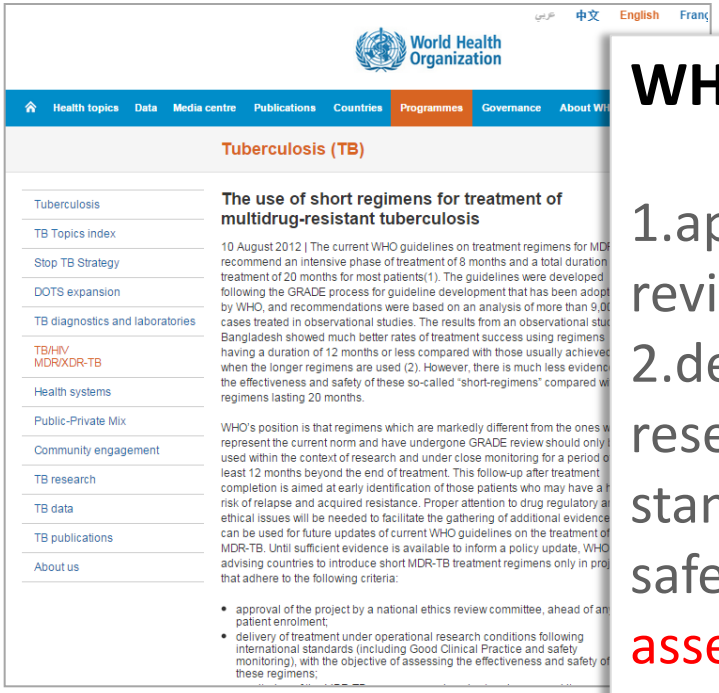
Active drug-safety monitoring (1)

- 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

Shorter regimens for MDR-TB (1)



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.

Shorter regimens for MDR-TB (2)

Global Drug-resistant TB Initiative
Accelerating the response

Stop TB Partnership

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

Stop TB Partnership

Global Drug-resistant TB Initiative (GDI)

Global Drug-resistant TB Initiative
Accelerating the response

Home | Mission | Terms of Reference | Governance | Task Forces | Meetings | Resources | Links | Join

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Task Forces

1. Taskforce for Patient-centred Programmatic Management of Drug-resistant Tuberculosis (PMDT)
2. Taskforce for Drug-resistant Tuberculosis Research
3. Taskforce on Advocacy for PMDT

Taskforce for Drug-resistant Tuberculosis Research

DR-TB research agenda

The update of the research agenda was prepared by members of the former Research Subgroup of the MDR-TB Working Group of the Stop-TB Partnership, RESIST-TB (Research Excellence to Stop TB Resistance) and the Global Drug-Resistant TB Initiative. The group first reviewed the 2008 research agenda on PMDT to determine whether the priorities published there had been resolved, partially resolved or unresolved. In addition, other relevant resources including publications, guidelines, documents, and websites published before August 2013 were identified by literature search and suggestion, and reviewed to identify knowledge gaps. Group members split into five teams according to the focused research areas in the 2008 research agenda on PMDT (Laboratory support, treatment strategy, programmatically relevant research, epidemiology and management of contacts). The knowledge gaps were then translated into research questions. A survey on the relative priority of the research questions was distributed to PMDT research stakeholders, through email to contact lists of relevant organizations including RESIST-TB, Treatment Action Group, TB CARE I, TB TEAM, and the Stop TB Partnership's New Diagnostics Working Group and MDR-TB Working Group. An estimated 500 email links to the survey were sent; 133 surveys were returned with responses to at least one question. Analysis of results is complete and manuscript development is underway. Submission of the manuscript for publication is expected in the second quarter of 2015.

Overview of ongoing DR-TB research activities

In the last quarter of 2014, an overview was developed of ongoing DR-TB research activities. This information was collected through a questionnaire sent out to a broad group of people, and asking for more contacts of people / groups doing relevant

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)

	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M15	M21	M27	M33
Clinical Evaluation	x	x	x	x	x	x	x	x	x	x	x	X	x	x
Sputum Smear	x	x	x	x	xx	(xx)	x	x	x	xx	x	X	x	x
Sputum Culture	x	x	x	x	x	x	x	x	x	x	x	X	x	x
Audiogram	x				x									
Chest X-ray	x									x				
Hemogram	x													
Serum Creatinin	x	x	x	x	x									
Serum Potassium	x	x	x	x	x									
TSH	x						x							
SGOT, SGTP	x	x	x	x	x		x							
ECG*	xx													
Pregnancy test	x													
HIV test	x													

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

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. Rayon'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

APID: ☐☐☐☐☐☐☐☐☐

Patient's name (surname, name): _____

Date form completed: ☐☐-☐☐-☐☐☐☐

Month of treatment: _____

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

General:
- ○ systemic allergic reaction GRADE ☐
- ○ arthralgia GRADE ☐
- ○ rash; GRADE ☐
- ○ prutitis; GRADE ☐

Mental health:
- ○ Depression; GRADE ☐
- ○ Psychosis; GRADE ☐
- ○ Anxiety; GRADE ☐

Other, specify
_____

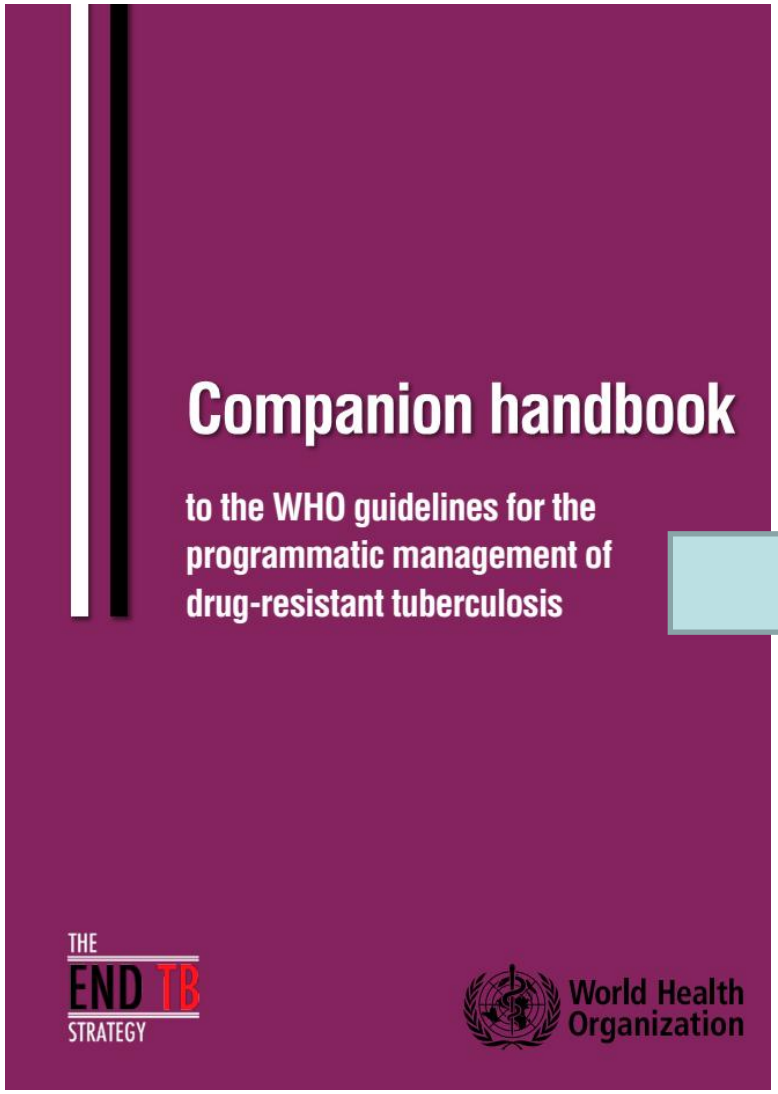
Gastrointestinal
- ○ Anorexia; GRADE ☐
- ○ Nausea; GRADE ☐
- ○ Vomiting; GRADE ☐
- ○ Abdominal pain; GRADE ☐
- ○ Diarrhoea; GRADE ☐
- ○ Constipation; GRADE ☐
- ○ Dysphagia ; GRADE ☐

_____

Neurological:
- ○ Headache; GRADE ☐
- ○ Decreased hearing; GRADE ☐
- ○ Ringing in the ears; GRADE ☐
- ○ Decreased vision; GRADE ☐
- ○ Seizures; GRADE ☐
- ○ Insomnia; GRADE ☐
- ○ Neuromuscular weakness; GRADE ☐
- ○ Neurosensory alteration; GRADE ☐
- ○ Vertigo GRADE ☐

August 2014
(update April 2015)

pp339ff



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 pre-clinical *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

THE END TB STRATEGY

World Health Organization

pp145-177

pp439-447

CHAPTER 11

Management of adverse effects and pharmacovigilance

ANNEX 11.1

Treatment initiation form – CEM for TB drugs[5]

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

ANNEX 11.2

Treatment review form – CEM for TB drugs[6]

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

Prophylaxis

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

A. Data collected at single time point (at start of treatment with drug/regimen of interest)

Data element	Categories or values (*when applicable*)
Facility information	
Interview date	DD-MMM-YYYY
Country	Country lookup list
Facility name and address	free text
Reporter	free text
Scale used for grading of severity of AEs*	No scale; CTCAE grading system; DAIDS AE Grading Table; Other
Patient information	
Patient ID	free text
Patient name	free text
Date of birth	DD-MMM-YYYY
Sex	M; F
Height	###.#
Height Unit	cm; IN
Weight**	###.#
Weight Unit**	kg; LB
Weight Date**	DD-MMM-YYYY
Pregnancy Status**	Y; N; U; NA
Pregnancy Status recording date**	DD-MMM-YYYY
If pregnant, gestation week**	##
Breastfeeding mother	Y; N; U; NA

Meeting of technical agencies on
active TB drug-safety management and monitoring

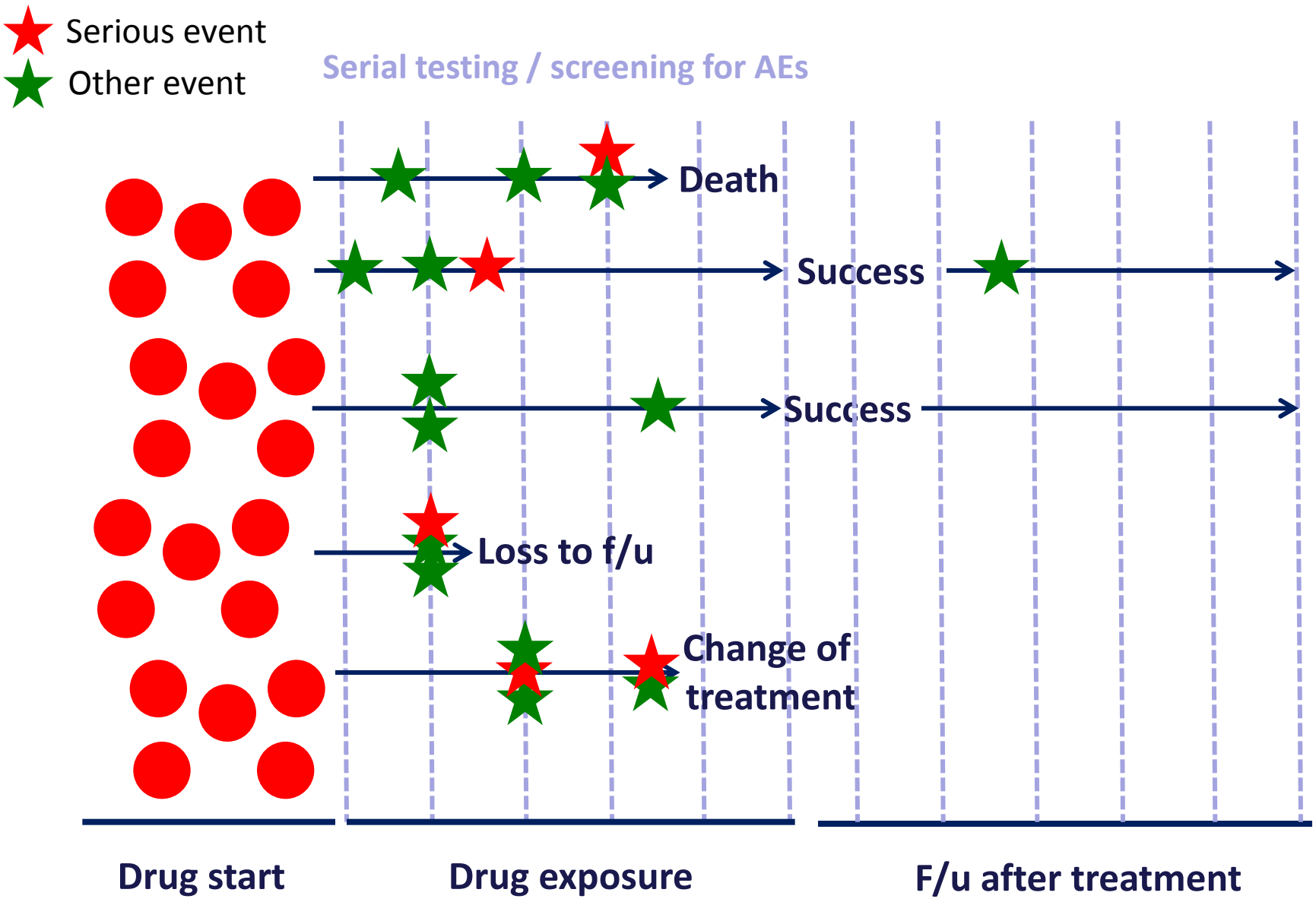
Geneva, 28-29 July 2015

- 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)



Active TB drug-safety monitoring framework (2)

organising the cohort

- 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

Active TB drug-safety monitoring framework (3)

initiation form

ANNEX 11.1

Treatment initiation form – CEM for TB drugs[5]

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)	Date of onset	Date of recovery	Continues
			☐
			☐
			☐
			☐
			☐
			☐
			☐
			☐

[5] More updated versions of this form may be published in future at www.who.int/tb/challenges/pharmacovigilance/

LABORATORY & OTHER TESTS.
Include laboratory tests taken at any time during the PAST 30 DAYS

Test	Date	Result (units)	Test	Date	Result (units)
Sputum smear			ESR		
Sputum culture			Total WBC		
Drug susceptibility*			Haemoglobin		
Line probe assay			ALT (SGPT)		
Nucleic acid testing			AST (SGOT)		
Tuberculin Test			Creatinine		
HIV Antibody			Creatinine Clearance		
CD4 Count			Glucose		
Chest X Ray		Cavities (Y/N)	Thyroid function (TSH)		
Audiometry			Electrocardiogram		QTc
Visual acuity			Other		
Hepatitis markers			Other		

MEDICINES

Medicines & traditional medicines taken at any time in PAST 30 DAYS	Indication	Dosage	Frequency	Route	Start date	Stop date	Continues
							☐
							☐
							☐
							☐
							☐
							☐
							☐
							☐

* 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), capreomycin, ofloxacin (or ciprofloxacin), levofloxacin and moxifloxacin

All NEW anti-TB medicines prescribed at this interview	Indication	Dosage	Frequency	Route	Start date	Anticipated Stop date

All other NEW medicines prescribed at this interview	Indication	Dosage	Frequency	Route	Start date	Anticipated Stop date

Active TB drug-safety monitoring framework (4)

review form (1)

Treatment review form – CEM for TB drugs[6]

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

Events	AE MedDRA / WHO-ART code*	Record all NEW EVENTS or CHANGES in pre-existing conditions since last interview					
		Date onset	Date resolved	Outcome**	Severity†	Seriousness†	Rechallenge§

* to be completed by PV centre after data collection (see also Instructions for completion)

OUTCOME**
R1 Recovered/ resolved
R2 Recovering/resolving
S Recovered with sequelae
N Not recovered/not resolved
D Died
U Unknown

MAXIMAL SEVERITY†
1 Mild
2 Moderate
3 Severe

SERIOUSNESS†
N Not serious
H Hospitalization (caused or prolonged)
P Permanent disability
C Congenital abnormality
L Life threatening
D Death

RECHALLENGE§
1 No rechallenge
2 Recurrence of event
3 No recurrence
4 Result unknown

Scale used for grading of severity of AEs:
☐ Clinician's judgement ☐ CTCAE grading system ☐ DAIDS AE Grading Table ☐ Other (specify): _____

[6] More updated versions of this form may be published in future at www.who.int/tb/challenges/pharmacovigilance/

LABORATORY & OTHER TESTS

Test	Date	Result (units)	Test	Date	Result (units)
HIV Antibody			ALT (SGPT)		
CD4 Count			AST (SGOT)		
ESR			Lactic acid		
Total WBC			Lipase		
Haemoglobin			Chest X-Ray		Cavities (Y/N)
Creatinine			ECG		QTc
Creatinine Clearance			Audiometry		
Glucose			Visual acuity		
Hepatitis markers			Other		
TSH			Other		

MEDICINES

Anti-TB medicines taken since last interview	Dosage	Frequency	Route	Start date	Stop date	Continues	Reason(s) for stopping #	Action**
						☐		
						☐		
						☐		
						☐		
						☐		
						☐		

Other medicines & traditional medicines taken since last interview	Dosage	Frequency	Route	Start date	Stop date	Continues	Reason(s) for stopping #	Action**
						☐		
						☐		
						☐		
						☐		
						☐		
						☐		
						☐		

Active TB drug-safety monitoring framework (5)

review form (2)

All NEW medicines (anti-TB & other) prescribed at this interview	Dosage	Frequency	Route	Start date	Expected stop date	Indication

REASON FOR STOPPING#

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

**** 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	☐ Loss to follow up	☐ Not evaluated

If the end of the treatment episode, treatment outcome date: dd/mmm/yyyy

* as per Definitions and reporting framework for tuberculosis – 2013 revision (WHO/HTM/TB/2013.2). Geneva, World Health Organization; 2013. Available from: www.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf

Name of the Reporter: _____

Please give this form to the CEM Focal Person

Focal Person: _____ Phone: _____

Date of next appointment: dd/mmm/yyyy _____

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

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)

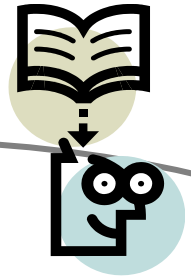
data analysis & identifying signals

- 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

Processes	***Q1***	***Q2***	***Q3***	***Q4***
Define cohort	++	+		
Do serial clinical & lab tests	++++	+++	+++	+++
Create expert group	++			
Create protocol	++			
Manage & supervise	++	+	+	+
Train staff	+++	+	+/-	
Create data collection material	++			
Create e-database	++	+		
Collect & enter data	++	++	++	++
Identify signals and data analysis		+/-	+/-	+

Active TB drug-safety monitoring framework (10)

key steps

Elements	***Stage***
Convene an expert group on aDMM	early; use existing body
Develop aDMM plan / protocol	early; use local / international expertise
Define management and supervision roles and responsibilities	at start
Train staff at different levels	before starting enrolment
Create standard data collection material	before starting enrolment
Define schedule and route for data collection and reporting	at start
Create database with core elements	early
Develop capacity for signal detection and data analysis	over time; engage local and international expertise

Active TB drug-safety monitoring framework (11)

things to have in place before starting

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; 1^{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

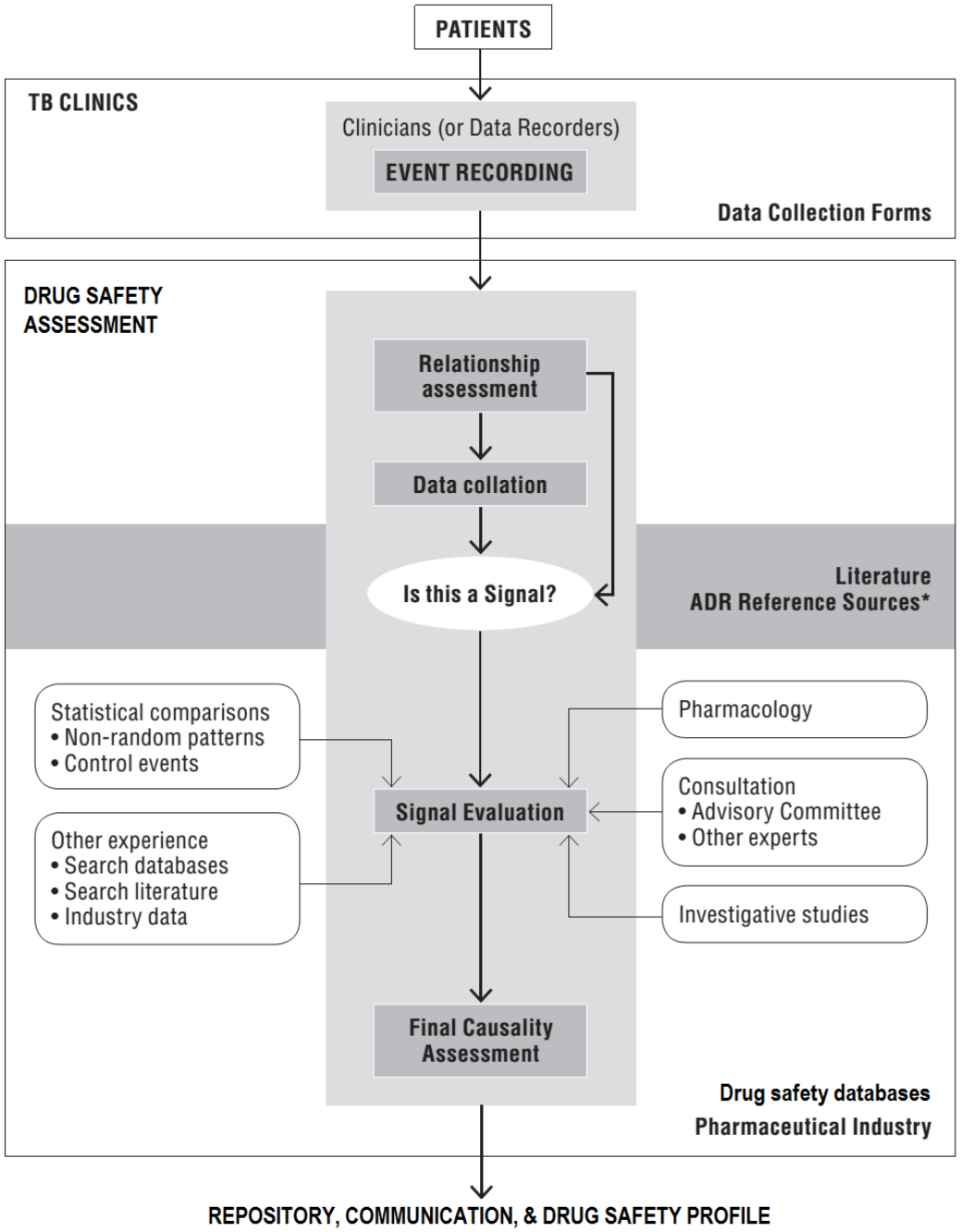
Active TB drug-safety monitoring framework (14)

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

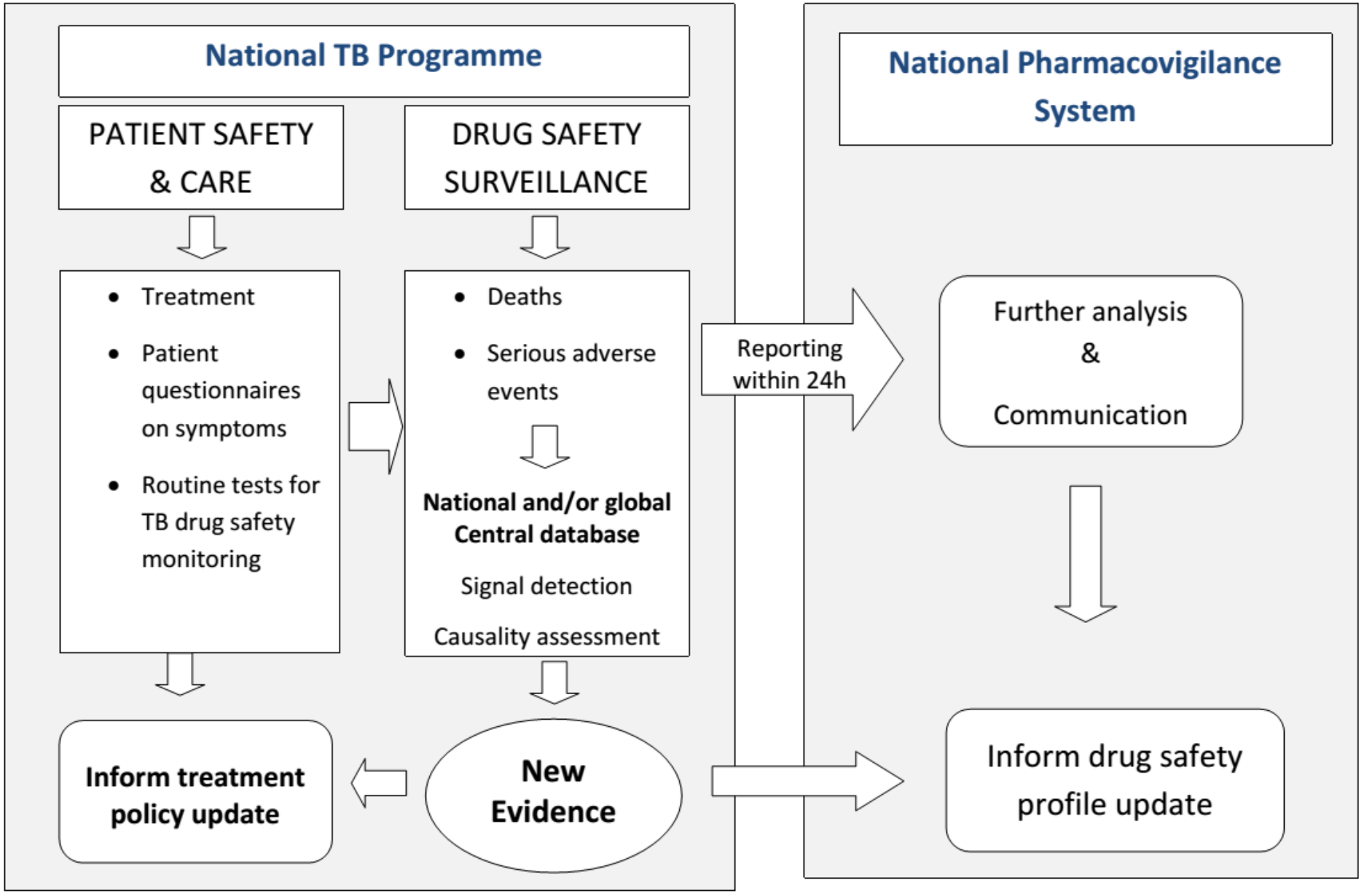
Immediate uses of the data

1. Causality assessment
2. Signal detection
3. Indicators
4. Drug-safety profiles



Adapted from WHO 2012 (www.who.int/entity/medicines/publications/pharmacovigilance_tb/)

Data flows for active TB drug safety monitoring: processing, repository, analysis, action and communication


National TB Programme
PATIENT SAFETY & CARE
DRUG SAFETY SURVEILLANCE
Treatment
Patient questionnaires on symptoms
Routine tests for TB drug safety monitoring
Deaths
Serious adverse events
National and/or global Central database
Signal detection
Causality assessment
Inform treatment policy update
New Evidence
Reporting within 24h
National Pharmacovigilance System
Further analysis & Communication
Inform drug safety profile update

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

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia

http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/daidsaegradingtable.pdf
(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

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

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

Category	***Time to event plausible?***	***Other explanation excluded?***	***Recovery after withdrawal?***	***Recurrence after rechallenge?***	***notes***
Certain	Yes	Yes	Yes	Yes	Exception: anaphylactic reaction
Probable	Yes	Yes	Yes	No or ?	
Possible	Yes	No or ?	?	No or ?	
Unlikely	No	No or ?	No	No or ?	Suggestive if event resolves despite continued exposure

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

The benefit: toxicity profile of the baseline MDR-TB regimen	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
Safety concerns associated with a specific drug or regimen	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
Quantifying risk & benefit	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
Risk factors	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
Signal detection	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
Preventive measures	Advice on avoidance of harm/toxicity, precautions, contraindications

Indicators (1)

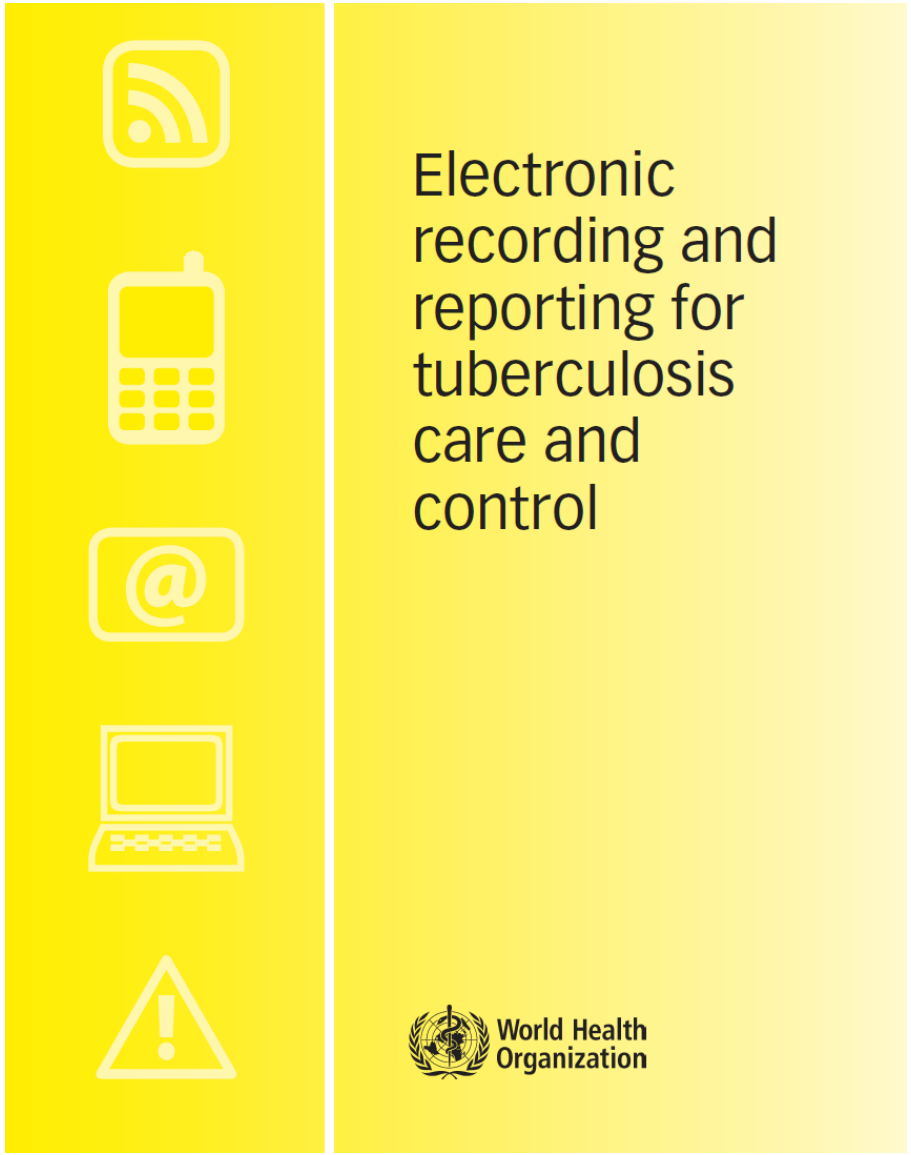
CLASS	IMPORTANCE	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Coverage (process)	Essential	1) Target RR-/MDR-TB patients included in cohort event monitoring	Numerator: Number of TB cases started on target treatment included in CEM during the period of assessment. Denominator: Number of TB cases started on target treatment during the period of assessment and who were eligible for CEM.	None	Absolute numbers, proportion	Numerator: CEM register. Denominator: Second-line TB treatment register.	National; CEM centre	3 months	To be computed during the period of recruitment but not in the post-treatment observation phase
Completeness (process)	Optional	2) Time to stopping target drug	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.	Reason for stopping	Number of patients included in the calculation; median interval and interquartile range in days	CEM register	National; CEM centre	12 months	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).

Indicators (2)

CLASS	IMPORTANCE	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Serious adverse events	Essential (but stratification optional)	3) RR-/ MDR-TB patients included in CEM with any serious adverse event	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.	By organ group; by outcome	Absolute numbers, proportion	Numerator: CEM register. Denominator: CEM register.	CEM centre	3 months	To be computed during the period of patient recruitment and during the post-treatment observation phase. Indicate outcome (deaths, hospitalisations, disability)
Adverse reactions associated with target treatment	Optional	4) Frequency of ADRs associated with the target treatment	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.	By organ group; by seriousness/ severity	Absolute numbers, proportion	CEM register.	CEM centre	3 months	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 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).

Indicators (3)

CLASS	IMPORTANCE	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Adverse reactions associated with target treatment	Optional	5) Time to development of ADRs associated with the target treatment	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	By organ group	Number of ADRs included in the calculation; median interval and interquartile range in days	CEM register	CEM centre	6 months	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 as the causative agent (certain, probable or possible).



Commissioning electronic systems according to needs

WHO/HTM/TB/2011.22

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