April 2017

Presentations from the Asia Regional Pharmacovigilance Workshop: Implementation of active TB drug-safety monitoring and management for new drugs and treatment regimens for multidrug-resistant tuberculosis

Hosted by USAID Control and Prevention of Tuberculosis Project (CAP-TB) and FHI 360

25-27 April 2017
Bangkok, Thailand

fhi360
THE SCIENCE OF IMPROVING LIVES

USAID Bedaquiline Donation Program
Asia Regional Pharmacovigilance (PV) Workshop: Implementation of active TB drug-safety monitoring and management (aDSM) for New Drugs and treatment regimens for MDR TB

Edmund Rutta, MD, MPH
Senior TB Technical Advisor
Bangkok, Thailand, April 25-27

Workshop Objectives

- Engage TB stakeholders of participating countries on the need for stronger PV systems to ensure patients safety and appropriate utilization of ND&STR
- Discuss on introduction of WHO-recommended aDSM framework as part of ND&STR introduction
- Identify opportunities and consensus for drug National Drug Regulatory Agency (NDRA) and national TB programs (NTP) for effective collaboration and joint implementation of aDSM activities
- Present and share experiences/lessons learned from countries that have implemented aDSM as part of the introduction of ND/STR
- Develop country's roadmaps for aDSM implementation

Expectations and Outcome

- Clear understanding of application and implementation of aDSM framework at the country level in order to strengthen national PV system related to ND&STR
- Consensus achieved on the reporting mechanisms of adverse drug reactions, including Serious Adverse Events (SAEs), from the patient level to the level of National Drug Regulatory Agencies and the international community
- Implementation roadmap, concrete steps and actions identified for all organizations involved in aDSM implementation for achieving international standards in PV

USAID Vision

- Introduce BDQ as part of strengthening the quality of the management of MDR TB
- Countries have the responsibility to ensure that all required elements from the WHO Policy Implementation package are in place and being implemented
- Technical assistance and support will be provided to assist countries with the rapid implementation of the required elements and prevent any delay to accessing BDQ

Technical Assistance

USAID direct support

- Challenge TB
- SIAPS (ending)
- Bilateral projects
- Independent MDR TB Consultants
- Advisors

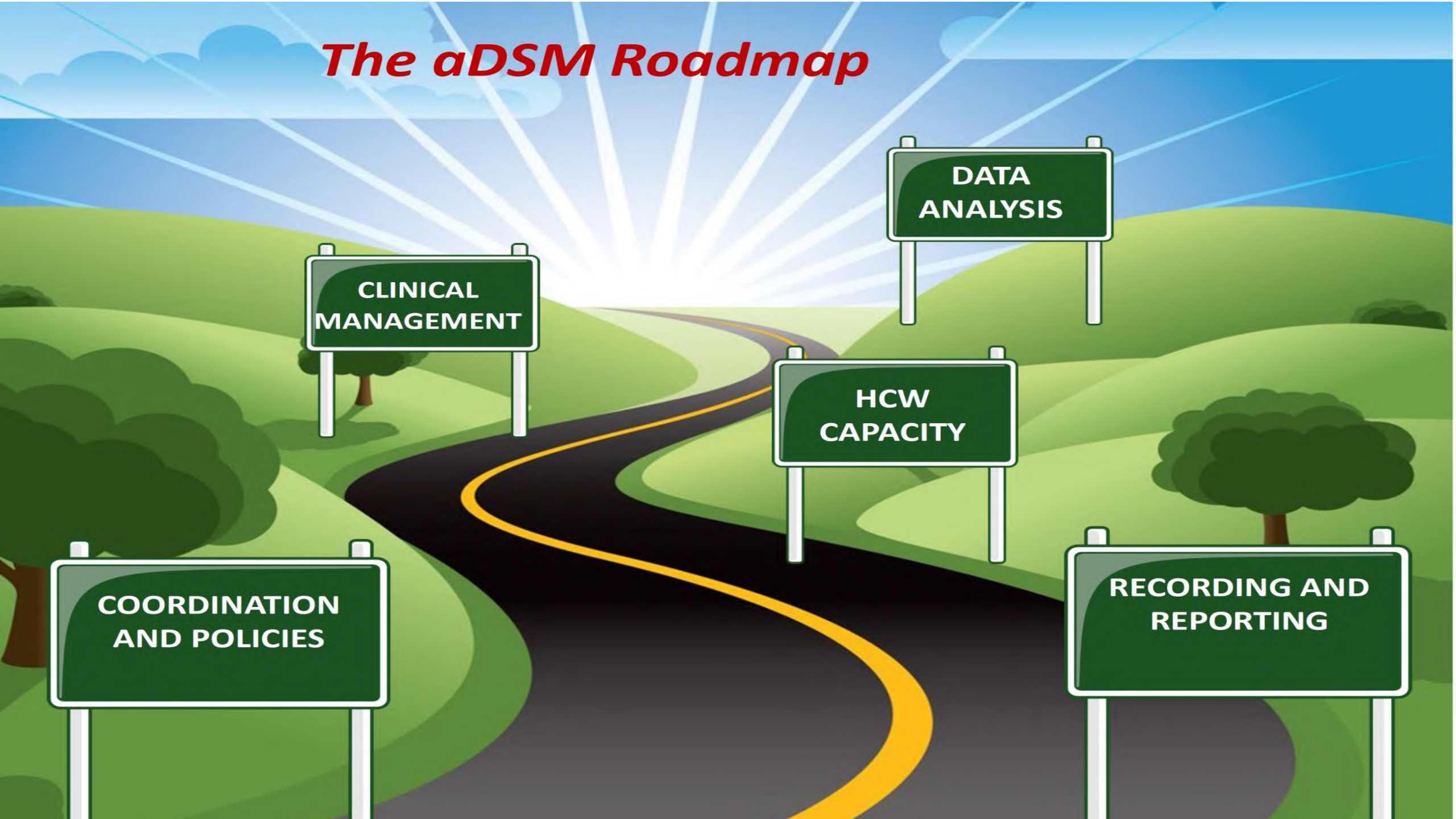
Collaboration with Partners

- EndTB Project (MSF/PIH/IRD) in 14 countries
- The UNION

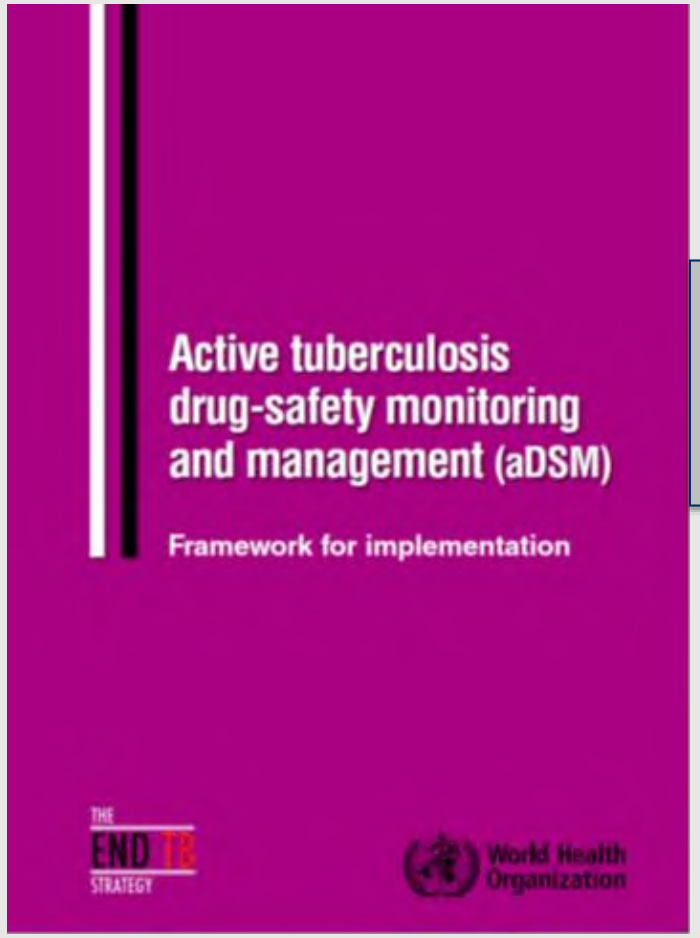
Collaboration with WHO

- WHO/rGLC could play an important role

The aDSM Roadmap

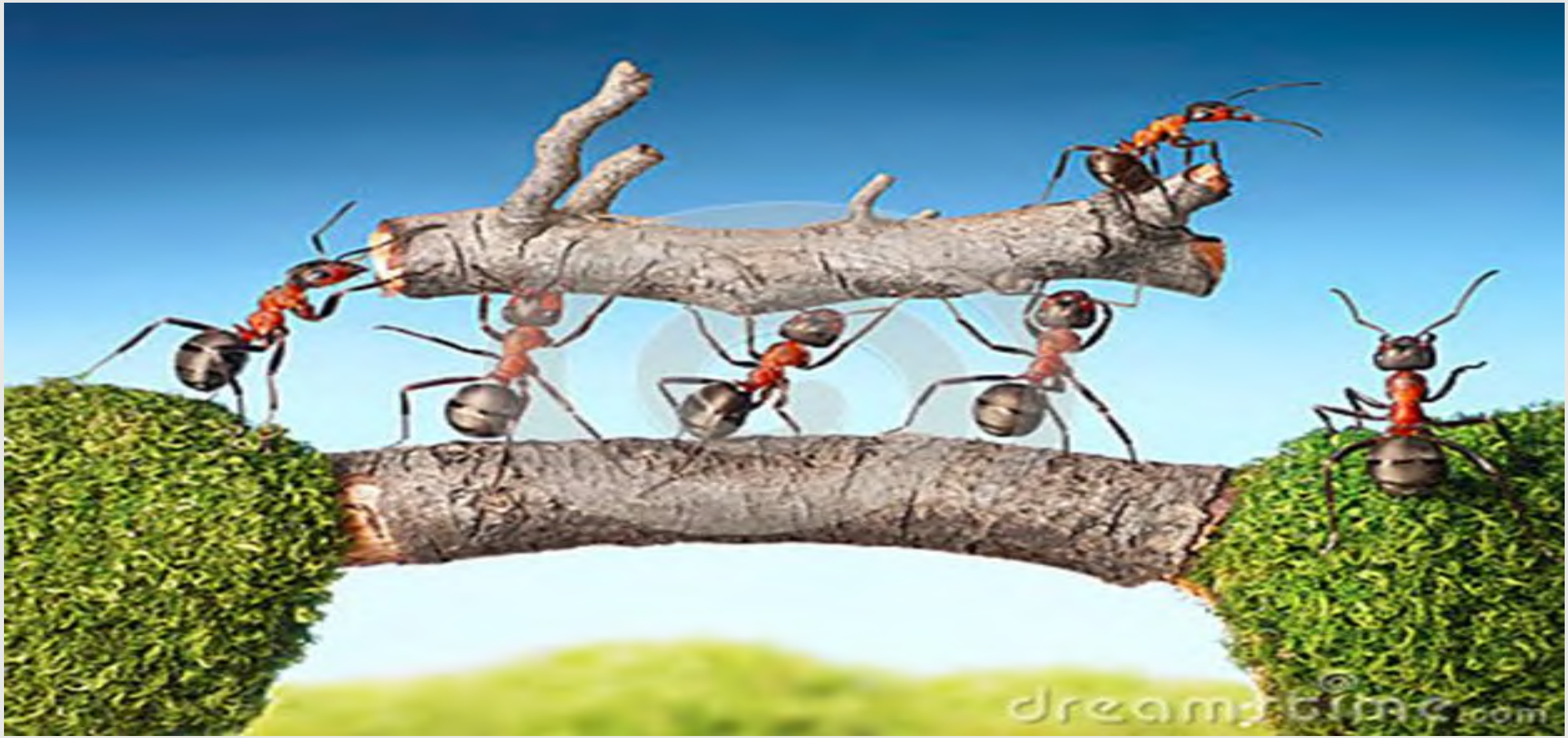


Components of aDSM Roadmap
(adapted from WHO aDSM framework)



- National coordination, policy, guidelines and implementation plan development
- Recording and reporting
- Health care workers capacity development
- Clinical management
- Data management and analysis

Let's work together!



Acknowledgements:

https://www.usaid.gov/what-we-do/global-health/tuberculosis

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Introduction to PV: application for roll out of new drugs and shorter treatment regimen for DR-TB treatment

April 25, 2017

Alexander Golubkov, MD, MPH

Sr. TB Technical Advisor. USAID/W

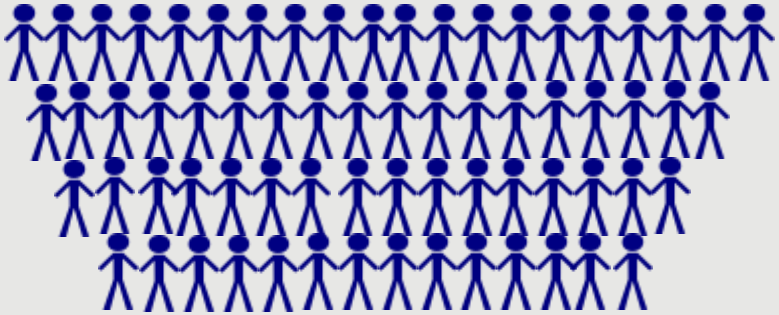
Welcome to this amazing PV workshop!

Presentation Outline

1. Why MDR-TB is important to USAID
2. Updates on shorter treatment regimen
3. Where we are with new TB drugs – BDQ and DLM
4. Why do we need pharmacovigilance?
5. Basics of PV and the concept of aDSM
6. Q&A

The DR-TB Challenge

Problem 1: ~20% OF ALL ESTIMATED MDR TB ARE STARTED ON TREATMENT



580,000 people fell ill with DR-TB in 2015

125,000 started on DR-TB treatment in 2015

52% treatment success in DR-TB patient starting treatment in 2013

Problem 2: ~50% of MDR TB started on treatment have an unfavorable treatment outcomes

USG Global TB Strategy

IMPACT	A World Free of TB
Long term outcomes	Reduce TB incidence rate by 90% by 2035 Reduce TB mortality rate by 95% by 2035
Medium term outcomes	During 2015-2019: Reduce TB incidence rate by 25% Maintain treatment success rate > 85% Successfully treat 13 million patients **Initiate treatment for 360,000 DR-TB patients** Provide ART for 100% of TB/HIV patients
Objectives	**Improved access to high quality, TB services** / **Prevention of transmission and disease progression** / **Strengthened TB platforms** / **Accelerated research**

MDR-TB NAP target to initiate additional 200,000 DR patients on treatment

National Action Plan For Combating MDR-TB

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NIH National Institute of Allergy and Infectious Diseases

CDC

MDR-TB NAP Vision and Goals

Vision: *The United States will work domestically and internationally to contribute to the prevention, detection, and control of multidrug-resistant tuberculosis in an effort to avert tuberculosis-associated morbidity and mortality and support a shared global vision of a world free of tuberculosis.*

Goals:

1. Strengthen domestic capacity to combat MDR-TB
2. Improve international capacity and collaboration to combat MDR-TB
3. Accelerate basic and applied research and development to combat MDR-TB

MDR-TB NAP Targets

By 2016

- Initiate appropriate treatment in 25% of patients with MDR-TB in 10 countries with the highest burdens of MDR-TB.

By 2018

- Initiate appropriate treatment in 35% of patients with MDR-TB in 10 countries with the highest burdens of MDR-TB.

By 2020

- Reduce by 15% the number of cases of MDR-TB in the United States.
- Initiate appropriate treatment in 50% of patients with MDR-TB in 10 countries with the highest burdens of MDR-TB.
- Reduce global TB incidence by 25% compared to 2015 levels.
- Successfully treat at least 16 million TB patients in high-burden countries.
- Achieve and maintain treatment success rates of 90% for individuals in high-burden countries with drug-susceptible TB.

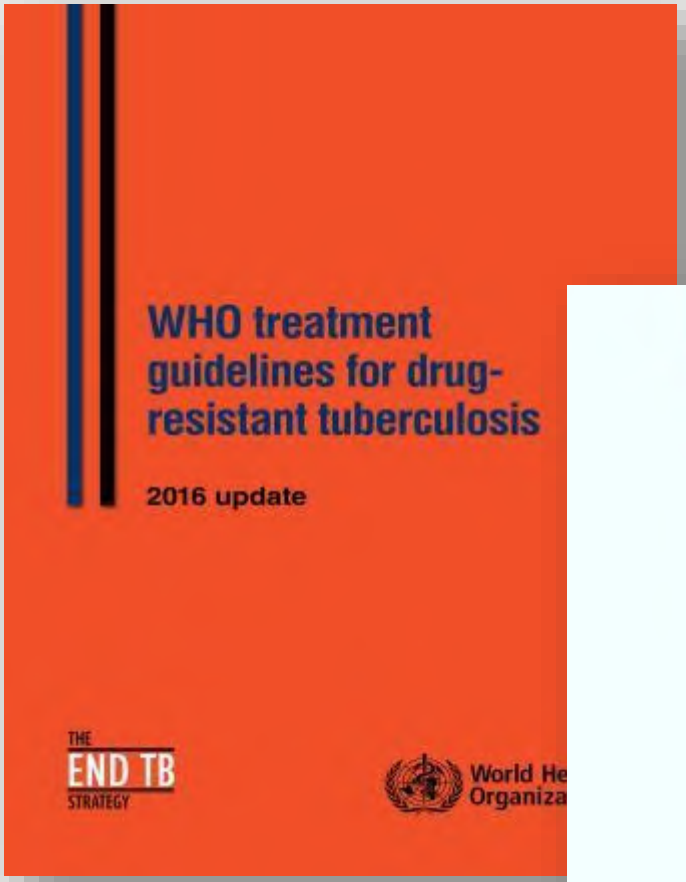
MDR-TB NAP – Scope

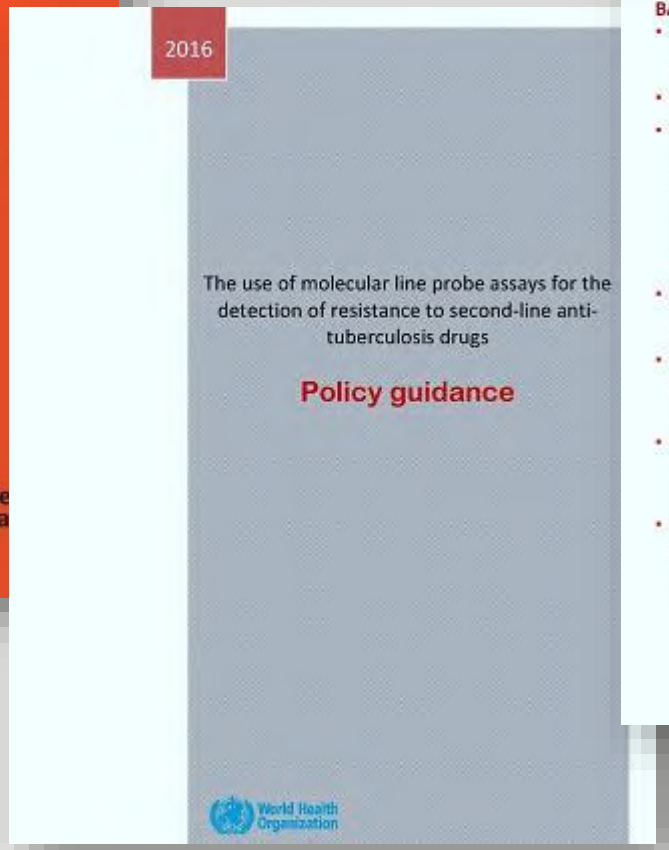
- Timely – Impact within 3-5 years
- Strengthen existing efforts, collaborations, and programs
- Increase options for preventing Mtb infection, transmission, and TB disease
- Improve the diagnosis of TB: latent infection; drug-sensitive (DS) TB, multidrug-resistant (MDR-TB), and extensively drug-resistant (XDR-TB)
- Improve treatment options for individuals with DS and M/XDR-TB
- Increase the capacity of TB endemic countries to conduct biomedical and clinical research in TB

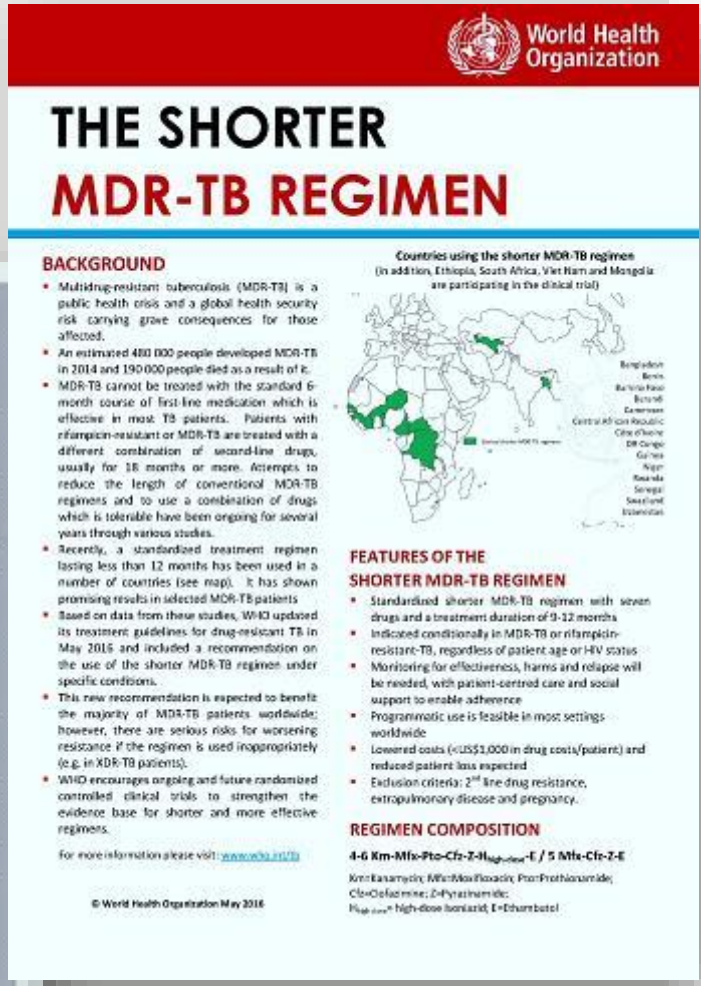
NAP Activities for ND and STR

- Number of NAP milestones focused on introduction of new drugs, shorter treatment regimen and pharmacovigilance
- Many targets set for Y1 and Y3 (2016-2018)
- Focus for the NAP is 10 priority countries: Burma, China, India, Indonesia, Kazakhstan, Nigeria, Pakistan, South Africa, The Philippines and Ukraine
- There are limited progress so far and ambitious and rapid scale up of interventions are needed

WHO approval for STR on 5/12/16







Shorter MDR-TB regimen (1)

Recommendation

In patients with rifampicin-resistant TB or MDR-TB, who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of a conventional regimen

WHO slides are courtesy of Dr.Dennis Falzon

Shorter MDR-TB regimen (2)

Main remarks

- **Standardized regimen; limited modifications permissible**
- **4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E**
- **Recommendation applies to adults, children, PLHIV**
- **Ideally, patients are tested for resistance to fluoroquinolones and second-line injectable drugs; not recommended in case of 2nd line drug resistance, extrapulmonary disease and pregnancy**

Shorter MDR-TB regimen (3)

Main remarks

- **Monitoring for effectiveness, relapse, and harms (active TB drug safety monitoring and management (aDSM))**
- **Trials (e.g. STREAM) expected to provide high-certainty evidence**
- **Lowered costs (<US$1,000 in drug costs/patient)**

USAID and Global Fund responses

- In mid-2016, USAID has developed a Guide for missions and implementing partners to quickly scale up the STR globally
- WHO and GF has issued a memo in March 2017 supporting STR and asking for urgent scale up within the new funding cycle
- Starting 2017, many countries planned to initiate patients on STR with rapid scale up in 2018

USAID Guidance for the Implementation of Shorter Treatment Regimens for Persons with MDR-TB | 2016

USAID
FROM THE AMERICAN PEOPLE

Developed by USAID/GH/HIDN/ID

Version 1. June 6, 2016

USAID guidance for the implementation of shorter treatment regimens for persons with multidrug-resistant tuberculosis (STR-MDR)

I. AUDIENCE AND AIM OF THIS DOCUMENT

World Health Organization

Dr Mark Dybul
Executive Director
The Global Fund to Fight AIDS, Tuberculosis and Malaria
Chemin de Blandonnet 8
CH- 1214 Vernier

20 March 2017

Dear Dr Dybul,

Support for countries to accelerate the transition to new tools to fight tuberculosis (TB), including paediatric and drug-resistant TB

BDQ Donation Program

BEDAQUILINE DONATION PROGRAM

- December 11, 2014: MOU between USAID and Janssen signed
- March 6, 2015: Gift Agreement signed
- April 1, 2015: BDQ donation program was launched

The purpose of the BDQ donation and Gift Funds is to assist governments and patients in combatting MDR-TB by ensuring access to the appropriate medicines for the management of MDR TB

Bedaquiline Donation Program: At a Glance

- Four-year program
- Up to 30,000 treatments for eligible patients
- 100 low and middle income countries
- Appropriate use in accordance with WHO Guidelines
- Removal of price as potential barrier to MDR-TB scale-up
- Gather evidence on its use and impact in a real world setting

General Provisions

BEDAQUILINE DONATION PROGRAM

Eligibility

All countries on Global Fund 2016 Eligibility List

As well as eligible for U.S. foreign assistance

Access

BDQ is available through the Stop TB Partnership's Global Drug Facility (GDF)

Countries are responsible for estimating the number of patients eligible for BDQ

Adverse Events

USAID and Janssen will collaborate with countries and partners to advance early detection and timely **reporting of severe adverse events (SAEs) related to BDQ**

BDQ Updates: Order Status and Registration

- 50+ countries have ordered BDQ from the GDF
- As of March 31, 2017, 8,599 BDQ dozes have been ordered. Of these, 3,100 have been successfully completed
- As of 1 May 2016, BDQ was registered with 12 regulatory authorities (Armenia, the European Union, India, Macau, Peru, Philippines, Russia, South Africa, South Korea, Taiwan, Turkmenistan, the United States, and Uzbekistan)
- Dossiers have been submitted to an additional 17 countries

Delamanid Updates

- Effective from 1 March, 2016 delamanid has been available for purchase via the Stop TB/GDF
- Price USD 1,700 for a full treatment course (6 months), has a 2-Year Shelf Life
- Over 100 countries eligible for TB Financing by the Global Fund can access delamanid via the GDF at this price
- Delamanid has been added to GDF Strategic Rotating Stockpile
- Same order process as BDQ
- Same aDSM requirements as BDQ, reports need to be filed via GDF

Five conditions for the inclusion of bedaquiline or delamanid in the adult treatment regimen of MDR-TB

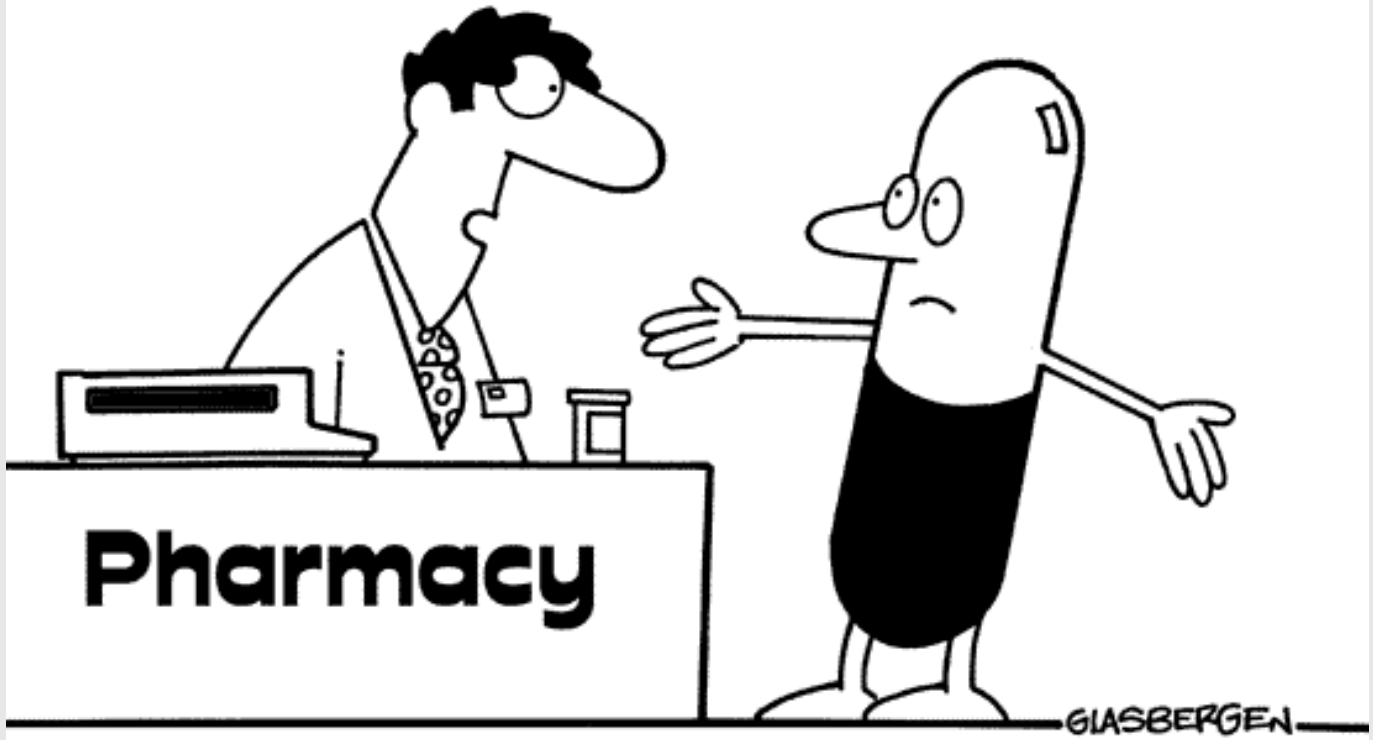
- Treatment is administered under closely monitored conditions
- Proper patient inclusion
- Patient informed consent obtained
- Adherence to principles of designing a WHO-recommended MDR-TB regimen
- Pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions

Updated Guideline for BDQ in 2017

- adult MDR-TB patients not eligible for the newly WHO-recommended shorter regimen.
  - patients with additional resistance or intolerance to fluoroquinolones or second line injectable drugs,
  - those with extended pulmonary lesions, advanced disease and others deemed at higher baseline risk for poor outcomes,
  - XDR-TB.
- when an effective WHO-recommended longer regimen containing at least four second-line drugs in addition to pyrazinamide cannot be designed.

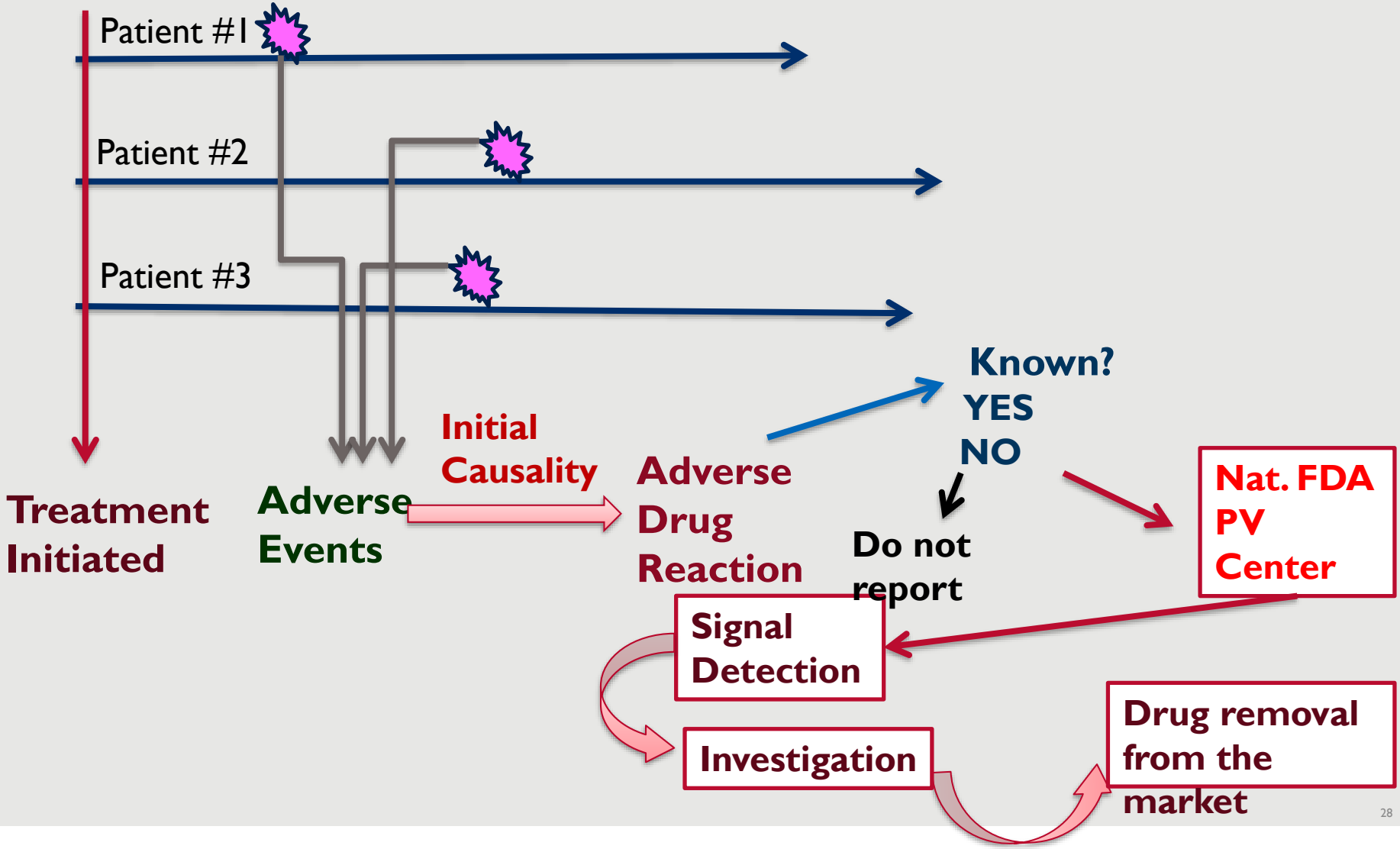
Updated Guideline for BDQ in 2017 [2]

- Bedaquiline must *not* be added alone to a failing regimen
- Bedaquiline shall be used for a duration of 6 months
  - limited evidence, so far, to warrant its use beyond 6 months
- Bedaquiline has been used in adolescents - data are insufficient to make any recommendation.
- Drug safety monitoring and management (aDSM) shall be in place
- Clinical monitoring and management of co-morbidities (especially cardiac and liver disease) should be in place
- Baseline testing and monitoring for QT prolongation and for dysrhythmias are imperative.



"Well there's a side effect I've never seen before!"

Example of PV in practice



How aDSM was created

- Initially WHO proposed to use CEM for new drugs introduced in the countries
- A large group of international TB experts pushed back on CEM concept as well as some NTPs
- On **28-29 July 2015** WHO convened a small expert group meeting to refine and re-discuss the concept PV for DRTB
- A new concept – aDSM was born

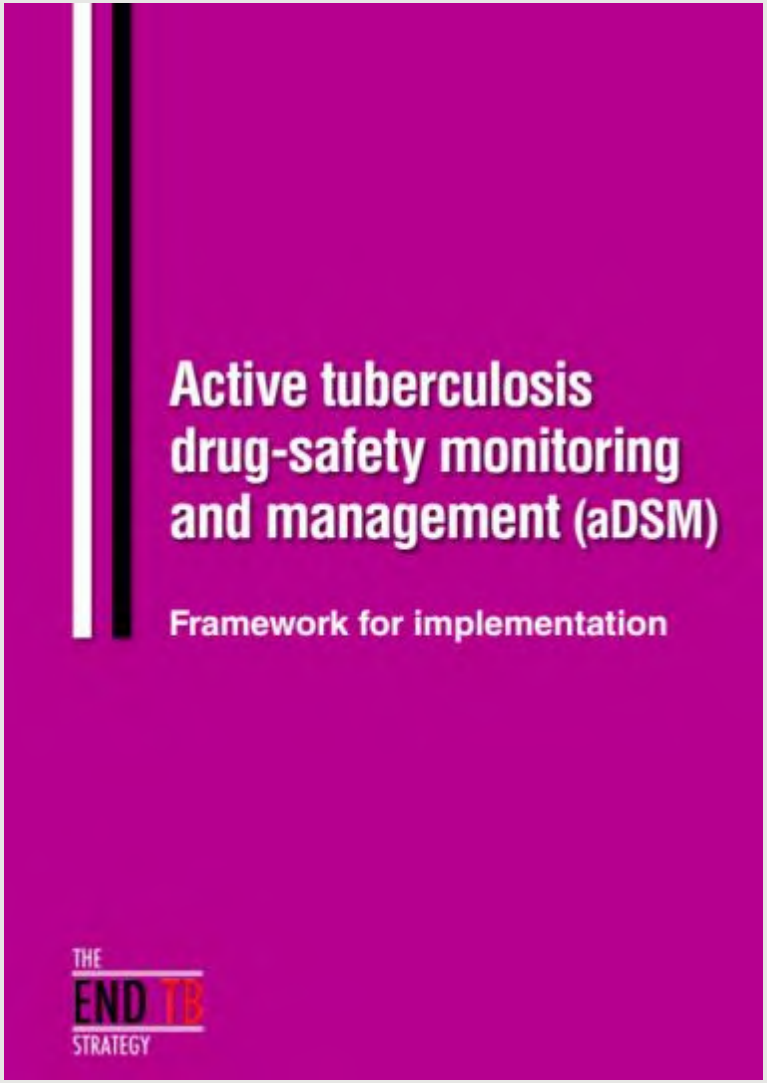
aDSM basics:

- aDSM: **a**ctive TB **d**rug **s**afety **m**onitoring and **m**anagement
- Goal of aDSM - to ensure the safety of patients on second-line treatment for drug-resistant TB
- aDSM - the active and systematic clinical and laboratory assessment of patients while on treatment
- Active and systematic clinical and laboratory assessment of patients:
  - Proper and regular laboratory tests
  - Clinical evaluation
  - Detection and management of ADR
  - Recording and reporting ADRs

"I stopped taking the medicine because I prefer the original disease to the side effects."

aDSM basics:

- Three levels:
  1. Core package: requiring monitoring and management of all SAEs
  2. Intermediate package: includes SAEs as well as AEs of special interest
  3. Advanced package: includes all AEs of clinical significance



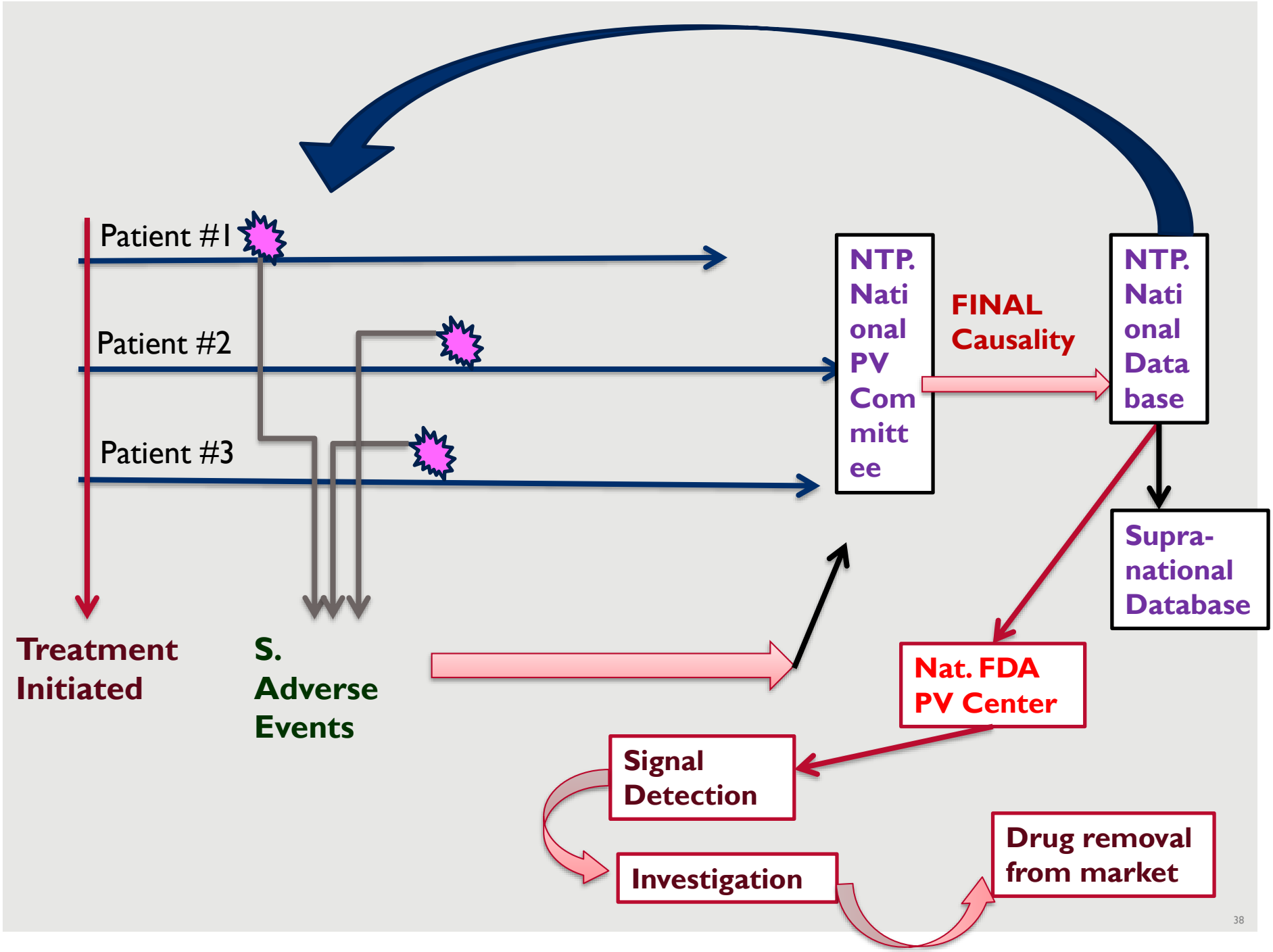
Serious adverse events are:

Any untoward medical occurrence that at any dose:

1. Results in death
2. Is life threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly or birth defect
6. Is medically significant or requiring intervention to prevent the above

aDSM applies to

1. MDR-TB and XDR-TB patients treated with new medicines, such as bedaquiline or delamanid, or
2. with novel regimens, such as shorter treatment regimen;
3. all other XDR-TB patients on second-line treatment

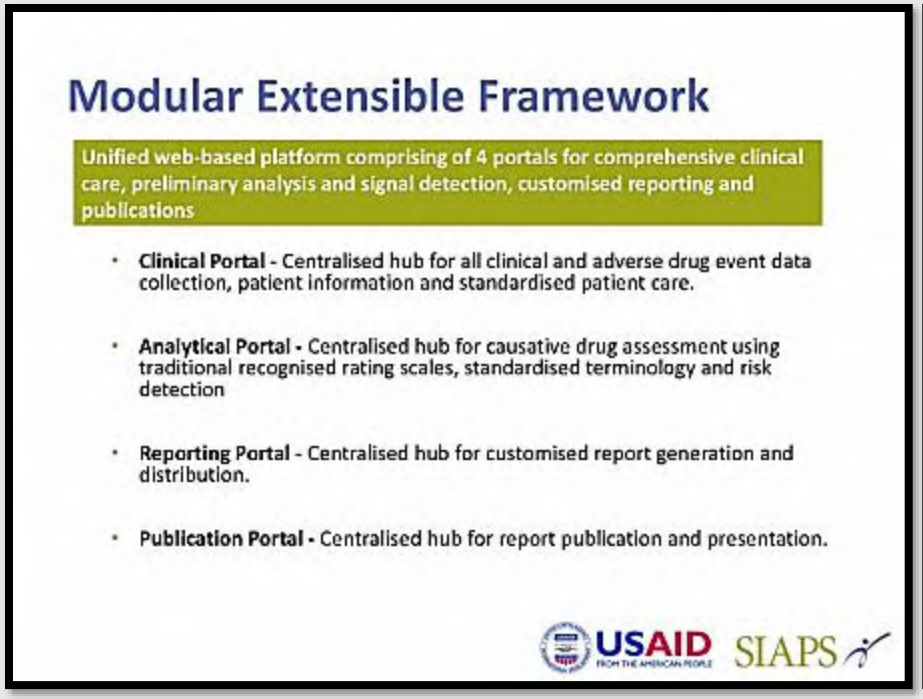

Patient #1
Patient #2
Patient #3
Treatment Initiated
S. Adverse Events
NTP. National PV Committee
FINAL Causality
NTP. National Database
Supra-national Database
Nat. FDA PV Center
Signal Detection
Investigation
Drug removal from market

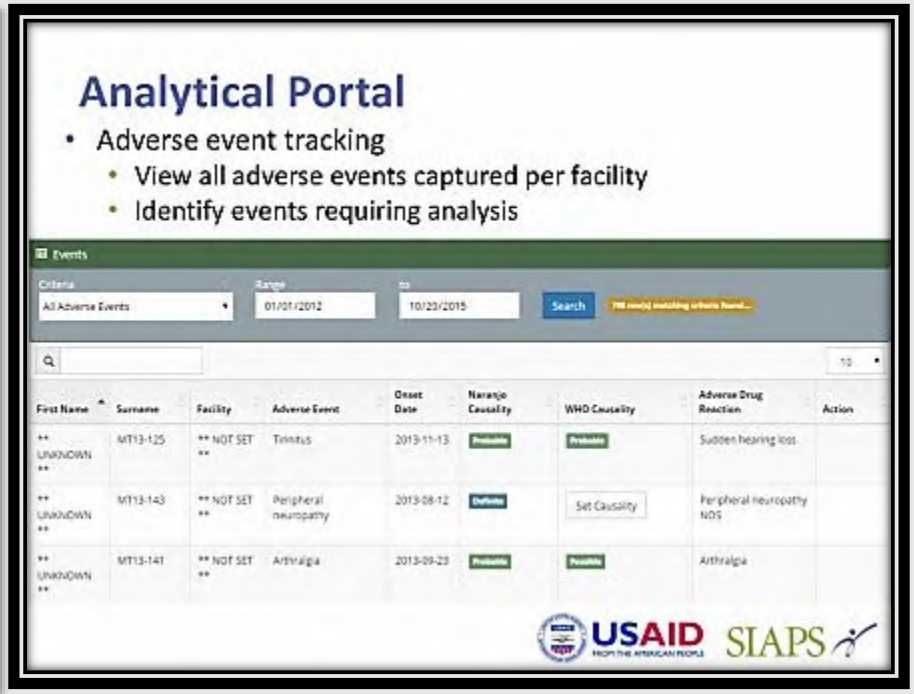
What is National PV Center?

- It's could be local FDA (drug regulatory agency)
- Or NTP central unit
- Or MDR-TB *concilium* at the national level enhanced with FDA staff

National aDSM database

- Updating the existing one (like e-TB manager)
- Or developing new
  - PVIMS example from MSH/SIAPS





U.S. Agency for International Development
1300 Pennsylvania Avenue, NW
Washington, DC 20523
www.usaid.gov

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WHO recommendations on active drug safety management and monitoring (aDSM) for new drugs and regimens

Dennis FALZON, MD
WHO/HQ Global TB Programme, Geneva

USAID Bedaquiline Donation Program
Asia Regional Pharmacovigilance (PV) Workshop

Thailand - 25 April 2017

THE END TB STRATEGY

World Health Organization

Objective of the presentation

- Outline the main components of the WHO framework for active TB drug-safety monitoring and management (aDSM)

WHO guidance on treatment & management of drug-resistant TB, 1996-2016

Choosing the treatment regimen in patients with confirmed MDR/RR-TB

- Confirmed susceptibility or presumed effectiveness to all medicines in the shorter MDR-TB regimen (isoniazid resistance excepted)
- No exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for ≥1 month
- No intolerance to any medicine in the shorter MDR-TB regimen and no risk of toxicity (e.g. drug-drug interactions)
- Pregnancy excluded
- Only pulmonary disease
- All medicines of the shorter MDR-TB regimen available to the programme

YES

Shorter MDR-TB regimen

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF AN EXCLUSION CRITERION

NO

Longer (individualized) MDR-TB regimens

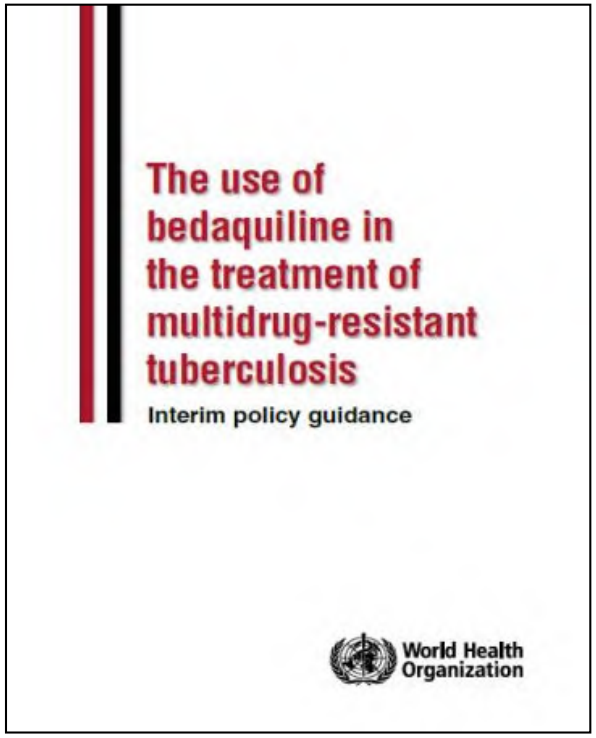
BEDAQUILINE : WHO interim policy guidance (June 2013)

"Bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB"

conditional recommendation, very low confidence in estimates of effect

Subject to the following 5 conditions:

1. Treatment under close monitoring
2. Proper patient selection
3. Patient informed consent
4. Treatment as per WHO recommendations
5. Active pharmacovigilance in place



DELAMANID : WHO interim policy guidance (October 2014)

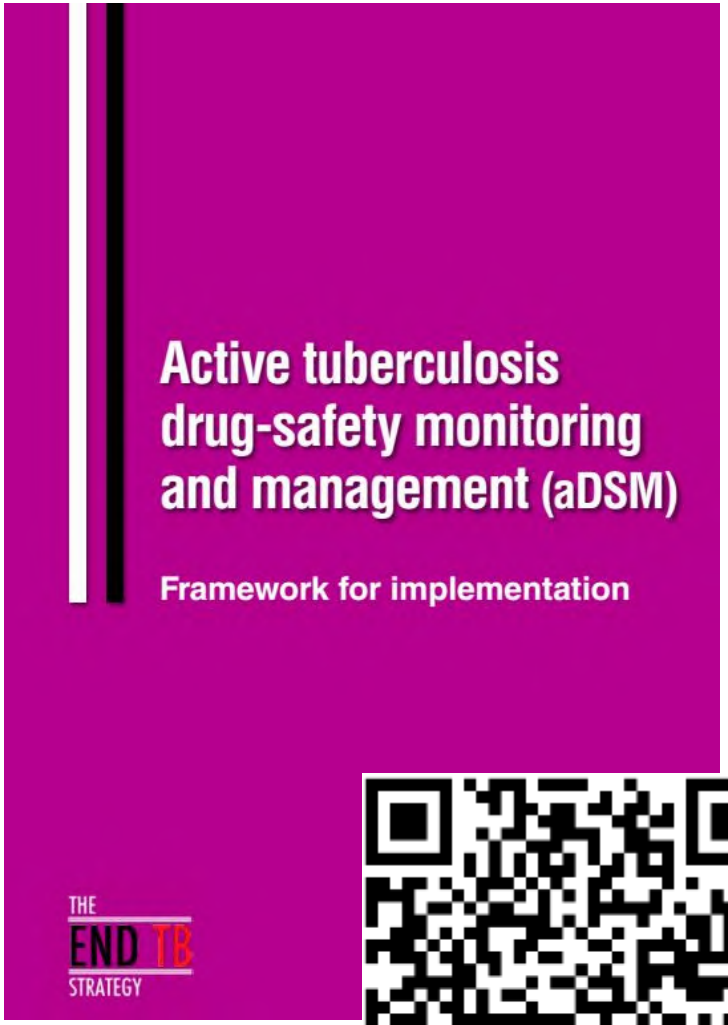
"Delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB"

conditional recommendation, very low confidence in estimates of effect

Subject to the following 5 conditions:

1. Proper patient inclusion
2. Treatment as per WHO recommendations
3. Treatment is closely monitored
4. Active pharmacovigilance in place
5. Patient informed consent obtained

-> October 2016 : may be used in patients 6-17 years



aDSM

"active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities"

apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf

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 "packages"

1. **Core:** requiring monitoring for and reporting of all serious adverse events (SAEs)

2. **Intermediate:** includes SAEs as well as AEs of special interest

3. **Advanced:** includes all AEs of clinical significance

aDSM eligibility

aDSM applies primarily to the following:

1. MDR-TB patients treated with bedaquiline, delamanid and other new medicines;

2. MDR-TB patients enrolled on treatment with novel regimens (including the shorter MDR-TB regimen);

3. All XDR-TB patients on second-line treatment, as these regimens usually include multiple repurposed drugs

Once coverage of these patient groups is reached, aDSM can extend to other MDR-TB patients on treatment

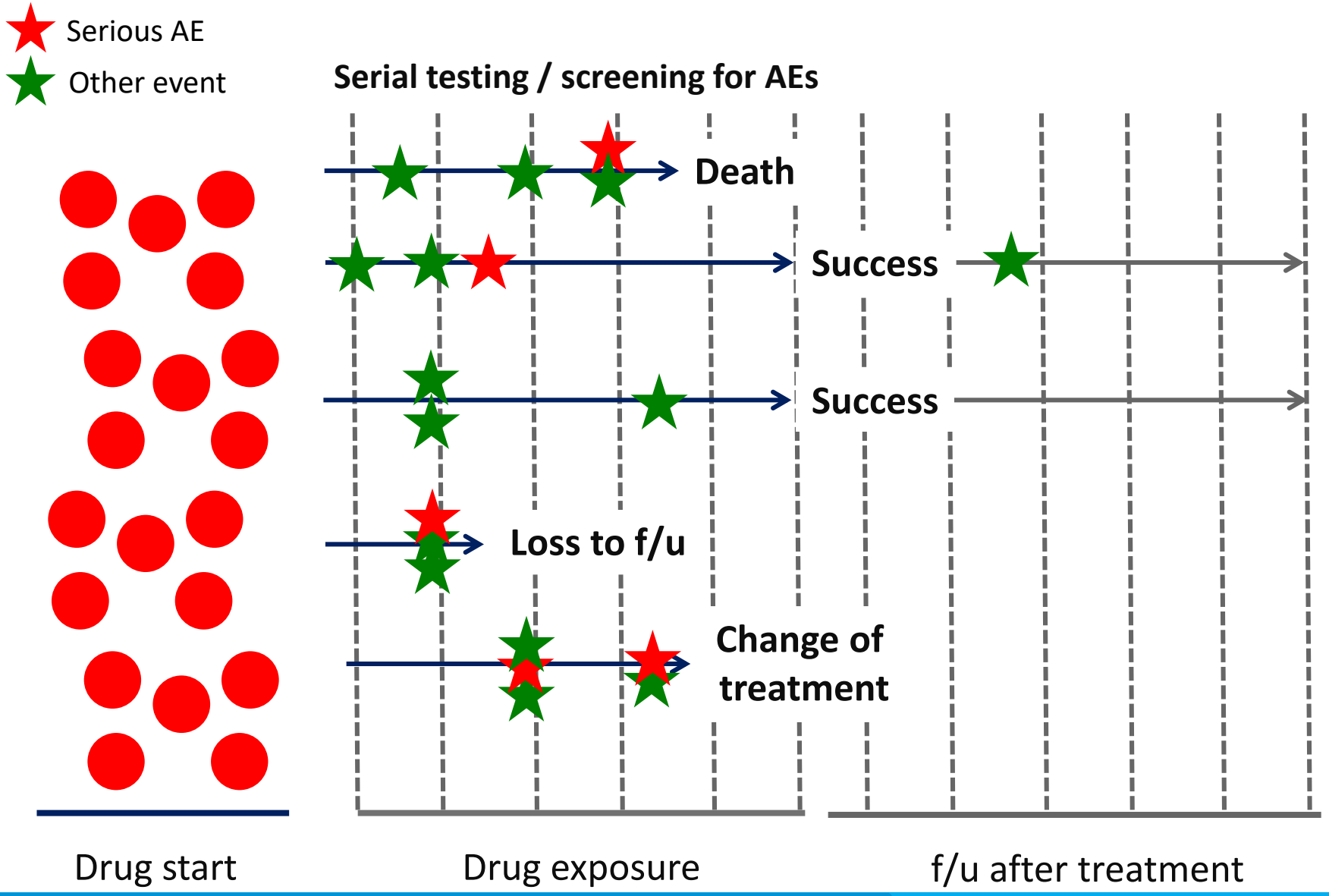
Seriousness

Seriousness involves any of the following:

- death or a life-threatening experience;
- hospitalization or prolongation of hospitalization;
- persistent or significant disability;
- congenital anomaly.

Events which do not result immediately in one of these outcomes but which might require an intervention to prevent it from happening may also be considered serious

aDSM : cohort-based approach



Clinical and laboratory testing schedule for aDSM

To be adapted to the treatment regimen and national policy[1]

	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
Date																									
Clinical screen																									
Visual acuity																									
Simple hearing test																									
Audiogram																									
Neuro & psychiatric investigations																									
Serum creatinine																									
ALT (SGPT)																									
AST (SGOT)																									
Bilirubin																									
Alkaline phospatase																									
γGT																									
ECG																									
Lipase																									
Amylase																									
Potassium																									
Magnesium																									
Calcium																									
Albumin																									
CBC																									
Blood glucose																									
Thyroid tests: TSH																									

[1] *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (WHO/HTM/TB/2014.11). Geneva, World Health Organization. 2014

Shade cells for the months when the test will not be done.

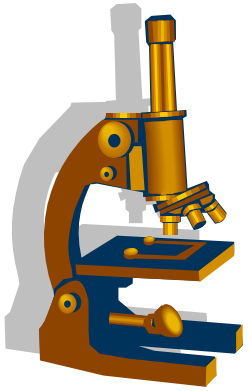
Notation for marking the cells: 0= screen/test not done 1=screen/test done; result pending 2=screen/test done; no SAE 3=screen/test done; SAE detected

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase);

CBC=complete blood count; ECG=electrocardiogram; γGT=gamma glutamyl transferase; TSH=thyroid stimulating hormone.

PATIENT HISTORY

CLINICAL TESTS



SAE

notification

DATA ENTRY

GLOBAL aDSM DATABASE

Data elements list – DRAFT sample

Data	Category labelling	Remarks
Facility information		
Country	string to be coded	Can use the country code or Iso code
Facility name or site identifier	string to be coded	Need to check in the agreement of sharing data which level of confidentiality is required.
Nature of the AEs reported	AE, SAE	Depending on what "package" is implemented at the site or country level
Coding use for AE/SAE terminology	WHOART, MedDRA, None	To be discussed if we agree that None is acceptable as well (in this case the coding need to be done by a service provider), I think we can cover that cost for the initial phase, piloting, but in the future, to be considered in term of sustainability
Scale used for grading of severity of AEs/AEs	string to be coded	(WHO scale; CTCAE grading system; DAIDS AE Grading Table; Other; None)
scale used to describe the degree of causality between drug and AE/SAE	string to be coded	Depending on what is chosen by the site, the option for reporting on causal relationship will be displayed differently (2

Global aDSM database

- A global aDSM database was created in 2016
- Coordinated by the Special Programme for Research and Training in Tropical Diseases at WHO Headquarters (TDR) and the WHO/GTB
- The Luxembourg Institute of Health (LIH) is responsible for its day-to-day management
- National programmes and other bodies can report AEs to the database for patients treated with medicines which are new or repurposed for an indication other than TB
- Belarus has started to report

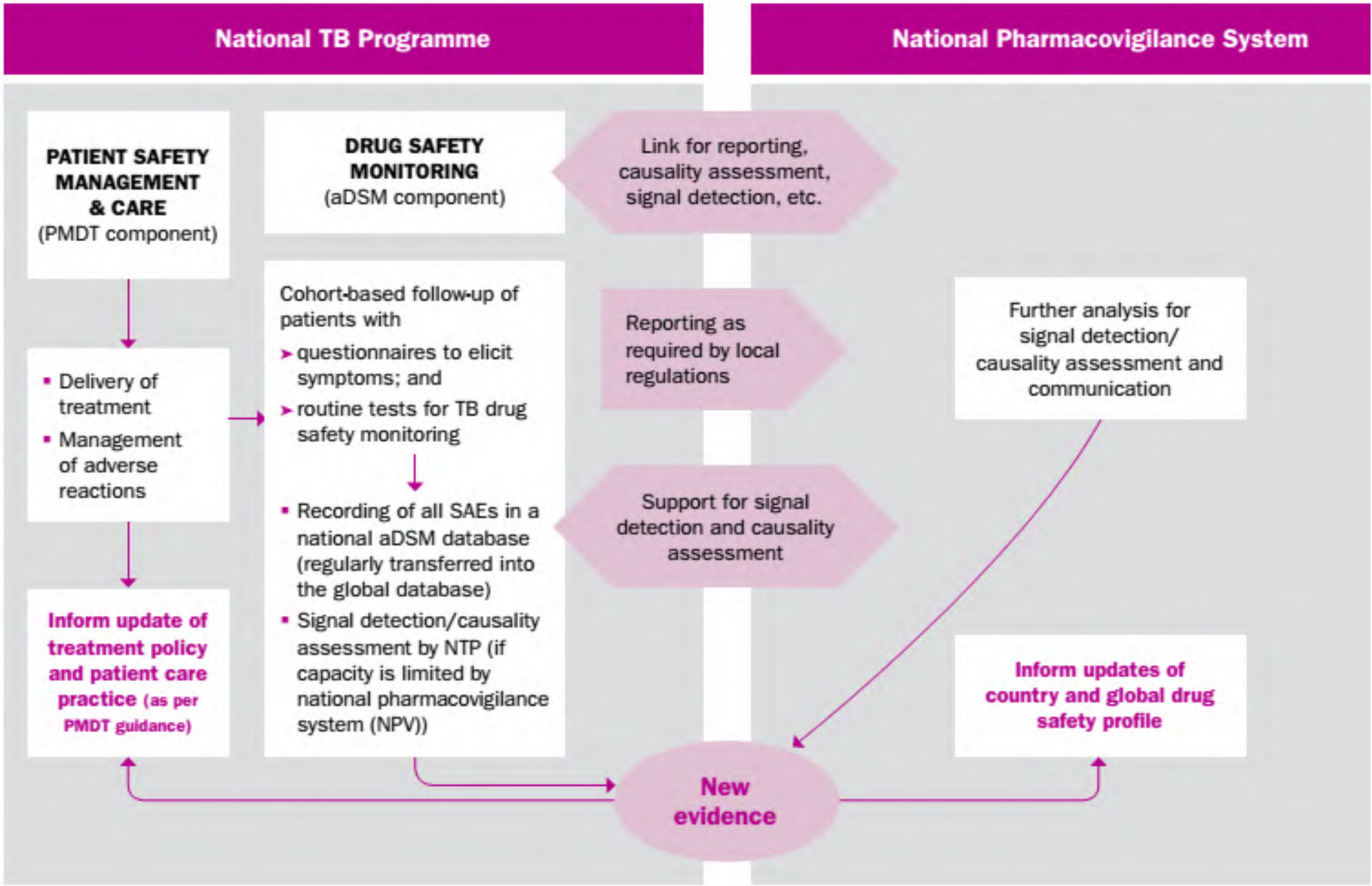
www.who.int/tdr/research/tb_hiv/adsm/en/

What happens to the data ?

- Programme indicators
- Causality assessment
- Signal detection
- Drug-safety profiles

Key steps in aDSM implementation

- Create a national coordinating mechanism for aDSM
- Develop a plan for aDSM
- Define management and supervision roles and responsibilities
- Create standard data collection materials
- Train staff on the collection of data
- Define schedules and routes for data collection and reporting
- Consolidate aDSM data electronically
- Develop capacity for signal detection and causality assessment


National TB Programme
National Pharmacovigilance System
PATIENT SAFETY MANAGEMENT & CARE (PMDT component)
DRUG SAFETY MONITORING (aDSM component)
Link for reporting, causality assessment, signal detection, etc.
Cohort-based follow-up of patients with
questionnaires to elicit symptoms; and
routine tests for TB drug safety monitoring
Delivery of treatment
Management of adverse reactions
Reporting as required by local regulations
Further analysis for signal detection/ causality assessment and communication
Recording of all SAEs in a national aDSM database (regularly transferred into the global database)
Signal detection/causality assessment by NTP (if capacity is limited by national pharmacovigilance system (NPV))
Support for signal detection and causality assessment
Inform update of treatment policy and patient care practice (as per PMDT guidance)
Inform updates of country and global drug safety profile
New evidence

www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/

www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/en/

Search

Health topics | Data | Media centre | Publications | Countries | Programmes | Governance | About WHO | Search

Tuberculosis (TB)

- Tuberculosis
- The End TB Strategy
- Areas of work
  - Detection and diagnosis
  - Treatment and care
  - Preventive care
  - Drug-resistant TB
    - MDR-TB surveillance
    - Treatment of drug-resistant TB
    - Public-private mix for drug-resistant TB
  - TB and HIV
  - TB and children
  - Addressing needs of vulnerable populations
  - Technical support to countries
  - Community engagement:

Treatment of drug-resistant TB

Resistance to TB drugs is a formidable obstacle to effective TB care and prevention globally. Multidrug-resistant TB (MDR-TB) is multifactorial and fuelled by improper treatment of patients, poor management of supply and quality of drugs, and airborne transmission of bacteria in public places. Case management becomes difficult and the challenge is compounded by catastrophic economic and social costs that patients incur while seeking help and on treatment.

Key topics

Active drug-safety monitoring and management | Short regimens | Treatment guidance for DR-TB

Active TB drug-safety monitoring and management (aDSM)

The term active TB drug-safety monitoring and management (abbreviated as aDSM) describes a new TB programme component to provide for the active and systematic clinical and laboratory assessment of patients on treatment for XDR-TB, or with new TB drugs or novel MDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.

In conclusion

- The WHO DR-TB treatment policy updates aim to improve the assignment of patients to treatment regimens which can increase the likelihood of cure
- Important uncertainties remain on the effectiveness and safety of the treatment options, both regarding older and newer medications
- More evidence will be needed and new studies to ensure that treatment is better targeted according to the patient profile
- aDSM and the global aDSM database aim to document signals of previously unknown or poorly documented adverse events in patients on new drugs or novel MDR/XDR-TB regimens

Question to countries

How far are you from having aDSM up and running?

What main barriers have you encountered (if any)?

Would you consider reporting to the global aDSM database?

Programmatic introduction of newer drugs for drug-resistant tuberculosis

Overview, clinical considerations, ethical issues, and informed consent

Dr. Vivian Cox and Dr. Sein Sein Thi

USAID StopTB Partnership MDR TB Clinical Consultants

25 April 2017

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Outline

- Background on newer drugs
- Global access
- Re-purposed drugs for DR-TB
- WHO recommendations
- “Triage” approach
- Publications
- Ethics considerations and informed consent
- Clinical considerations

Background and global access to newer drugs

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Bedaquiline

- Diarylquinoline: inhibits mycobacterial ATP synthase
- Approved by the US FDA Dec 2012, EMA in 2013; WHO interim guidelines June 2013
- Janssen donation: 30,000 courses to GDF in Dec 2014
- For GFATM countries: tiered pricing (900/3000/10000 USD)
- Dose: 400mg once daily for 2 weeks, followed by 200 mg thrice weekly for 22 additional weeks
- Half life 5.5 months; shelf life 24 months
- Cross-resistance seen with clofazamine

Bedaquiline

- Evidence of efficacy: study C208 (RCT phase ll)

  NEJM, 2014;371:723-732

  Other drugs used: ETO, PAS, CS, PZA, LFX, LZD, INH, CFZ
- Evidence of safety: studies C208/C209 (open label, one arm pre-XDR/XDR)
- BDQ + ART: EFZ dec BDQ, LPV/r inc BDQ J Antimicrob Chemother 2016;71:1037-1040; NVP or RAL preferred
- STREAM 2 will serve as the phase III trial (enrolling in May 2016)
- Key component of most planned combination clinical trials
- Registered in 12 countries, dossiers submitted in 17 countries

Bedaquiline: evidence of efficacy

- Median time to culture conversion 83 days (BDQ) versus 125 days (placebo) ($p<0.0001$)
- Rates of culture conversion at 6 months are 78.8% in BDQ group versus 57.6% in placebo group ($p=0.008$)
- 120 week follow-up showed 62.1% patients with culture conversion in BDQ arm compared with 43.9% in placebo arm ($p<0.035$)
- Proportion cured 57.6% in BDQ arm versus 31.8% placebo ($p<0.003$)
- Final culture conversion 72% (73.1% MDR/70.5% pre-XDR/62.2% XDR)

Bedaquiline	58	37	25	12	7	3
Placebo	61	53	40	30	22	5

The NEW ENGLAND JOURNAL of MEDICINE

Bedaquiline: evidence of safety

- Median grade 3 and higher AEs similar in both groups
- Higher rates of hepatic AEs in BDQ group (8.8% versus 1.9%)
- QTc values > 450ms higher in BDQ group (26.6% versus 8.6%)
- Increase of > 60msec higher in BDQ group (9.1% versus 2.5%)
- No cases of torsades or sudden death
- Of 12 deaths seen in the study, 10 occurred in BDQ group and 2 in the placebo group - none felt to be drug-related

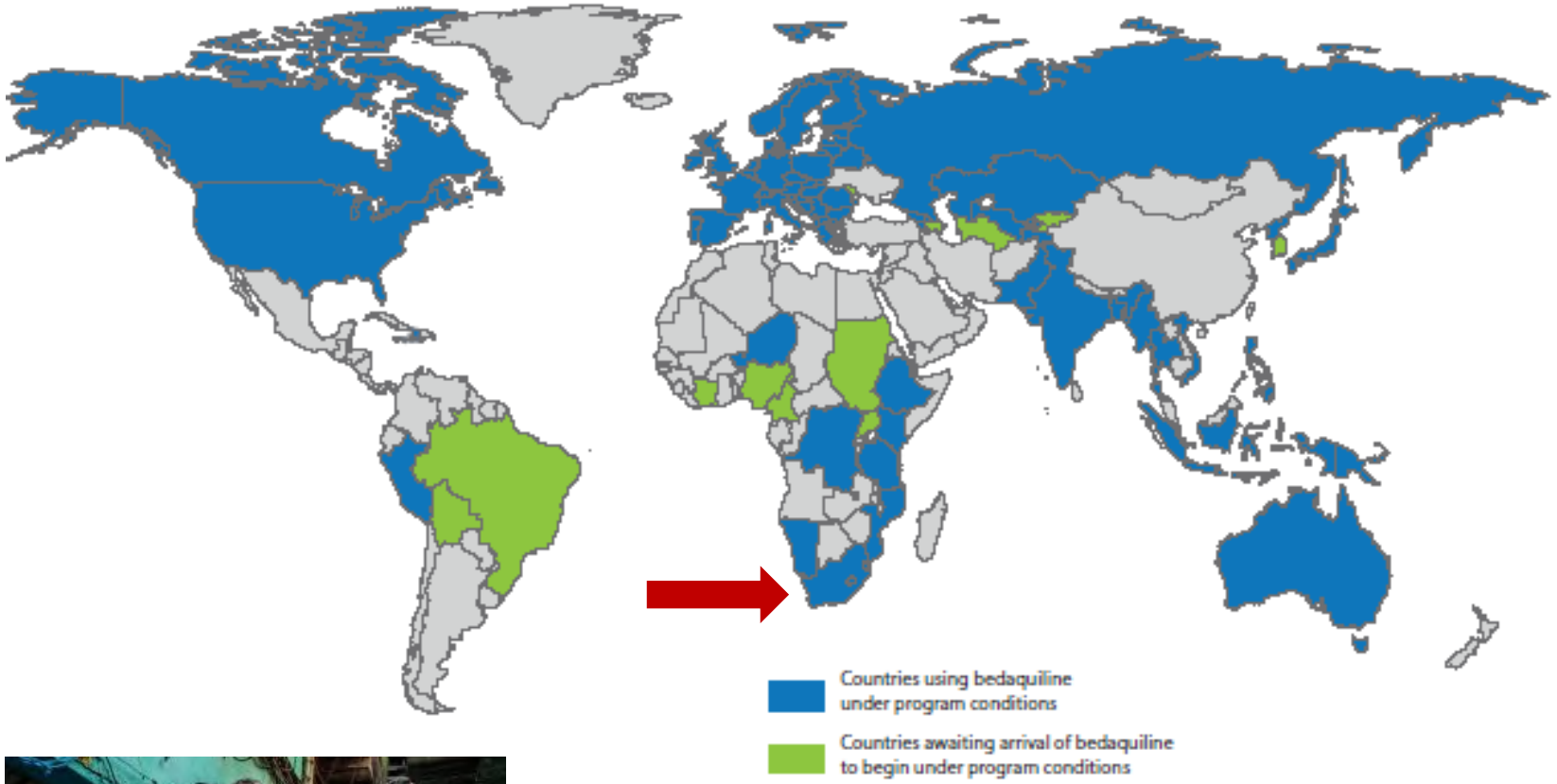
Table 2. Adverse Events during 120 Weeks in the Intention-to-Treat Population.*

Hyperuricemia	20 (25)	27 (33)
Hemoptysis	16 (20)	14 (17)

* There were no significant differences between the two groups in any category as calculated by means of Fisher's exact test in a post hoc analysis.
† Events were graded according to the Division of Microbiology and Infectious Diseases criteria.[14]
‡ Two serious adverse events were considered by the investigator to be possibly related to a study drug, including 2 events of acute pancreatitis in 1 patient in the bedaquiline group and spontaneous abortion in 1 patient in the placebo group.

The NEW ENGLAND JOURNAL of MEDICINE

Global BDQ implementation



- 8874 patients receiving BDQ end March 2017 through programmatic use
- Observational cohorts demonstrate results hold outside clinical trials - CID 2015;60:188-194; IJTLD 2015;19:979-985

Delamanid

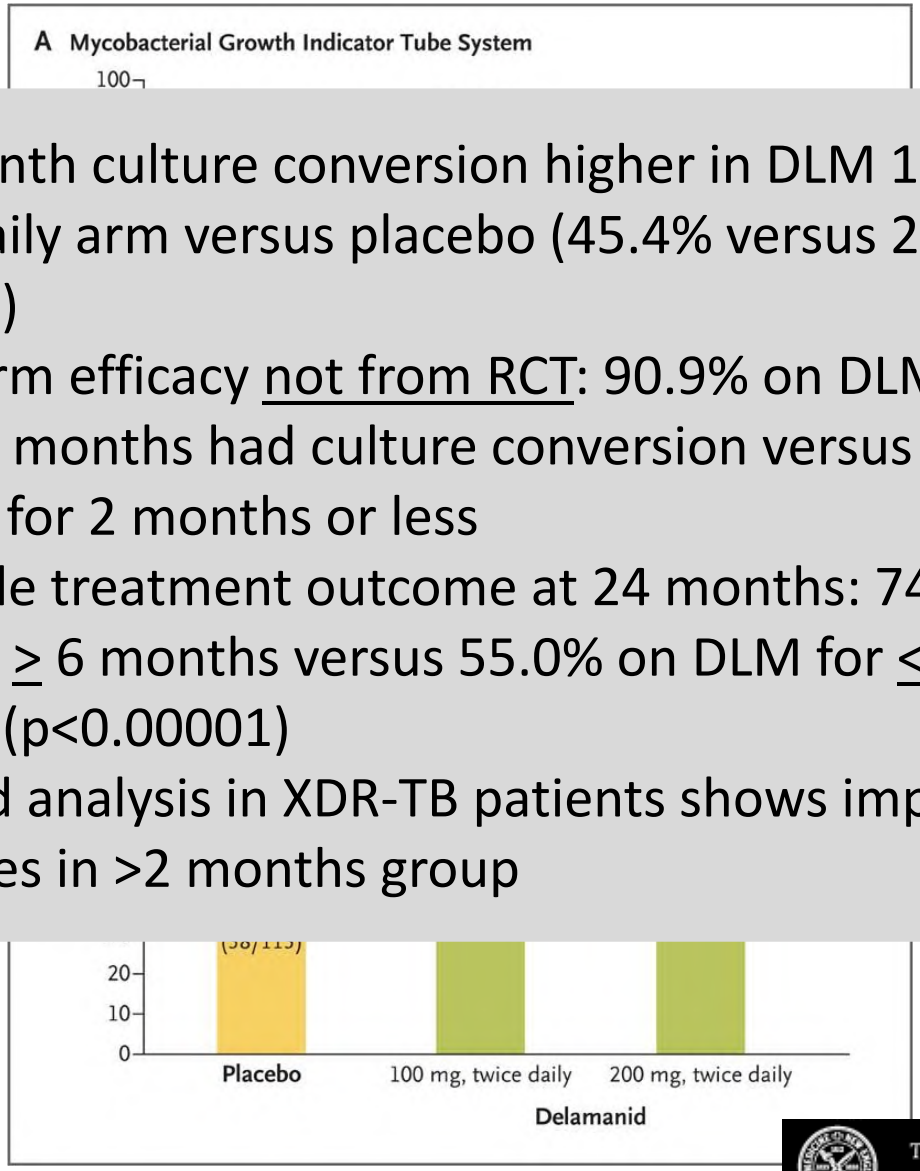
- Nitroimidazole: inhibits synthesis of mycobacterial cell wall
- Trial 204 (phase IIb) – 8 weeks RCT; trial 208 - 6 month open label extension; study 116 – observational, long term outcomes (Gler MT et al. NEJM 2012;366:2151-2160)
- Conditional approval: EU and Japanese Regulatory Authority in 2013; EMA 2014
- WHO interim guidelines October 2014; Otsuka donation program April 2015
- Phase lll RCT completed enrollment, outcomes 2017-2018 (RESIST-TB)

Delamanid

- Dose is 100 mg twice daily for 24 weeks
- Shelf-life 4 years; half-life 30-38 hours
- Cross-resistance with other nitroimidazoles (PA-824/pretomanid); cross-allergy with metronidazole
- Relatively low threshold to develop resistance
- DLM + ART: phase I showed no DDI with EFV, TDF, LPV/r
- Favorable safety profile in phase I/II clinical trials in children; WHO interim guidance in age 6 and older
- Registered in Japan, South Korea, Hong Kong, EU, endTB sites
- 1700 USD for 6 month supply

Delamanid: evidence of efficacy

- Two month culture conversion higher in DLM 100 mg twice daily arm versus placebo (45.4% versus 29.6%, p=0.008)
- Long-term efficacy not from RCT: 90.9% on DLM for 6 or more months had culture conversion versus 70.9% on DLM for 2 months or less
- Favorable treatment outcome at 24 months: 74.5% on DLM for ≥ 6 months versus 55.0% on DLM for ≤2 months (p<0.00001)
- Updated analysis in XDR-TB patients shows improved outcomes in >2 months group



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Delamanid: evidence of safety

- Pooled data from all DLM trials: drug relatively well tolerated with minimal adverse events
- QTc prolongation: 4.3% in DLM group versus 1.9% in placebo
- Risk may increase with low albumin - drug metabolized by albumin
- No torsades or sudden death reported
- Updated safety analysis: QTc prolongation very mild, even when used with other drugs

Table 2. Incidence of Adverse Events (Occurring in ≥10% of Patients in Either Delamanid Group and with Greater Frequency Than in the Placebo Group).*

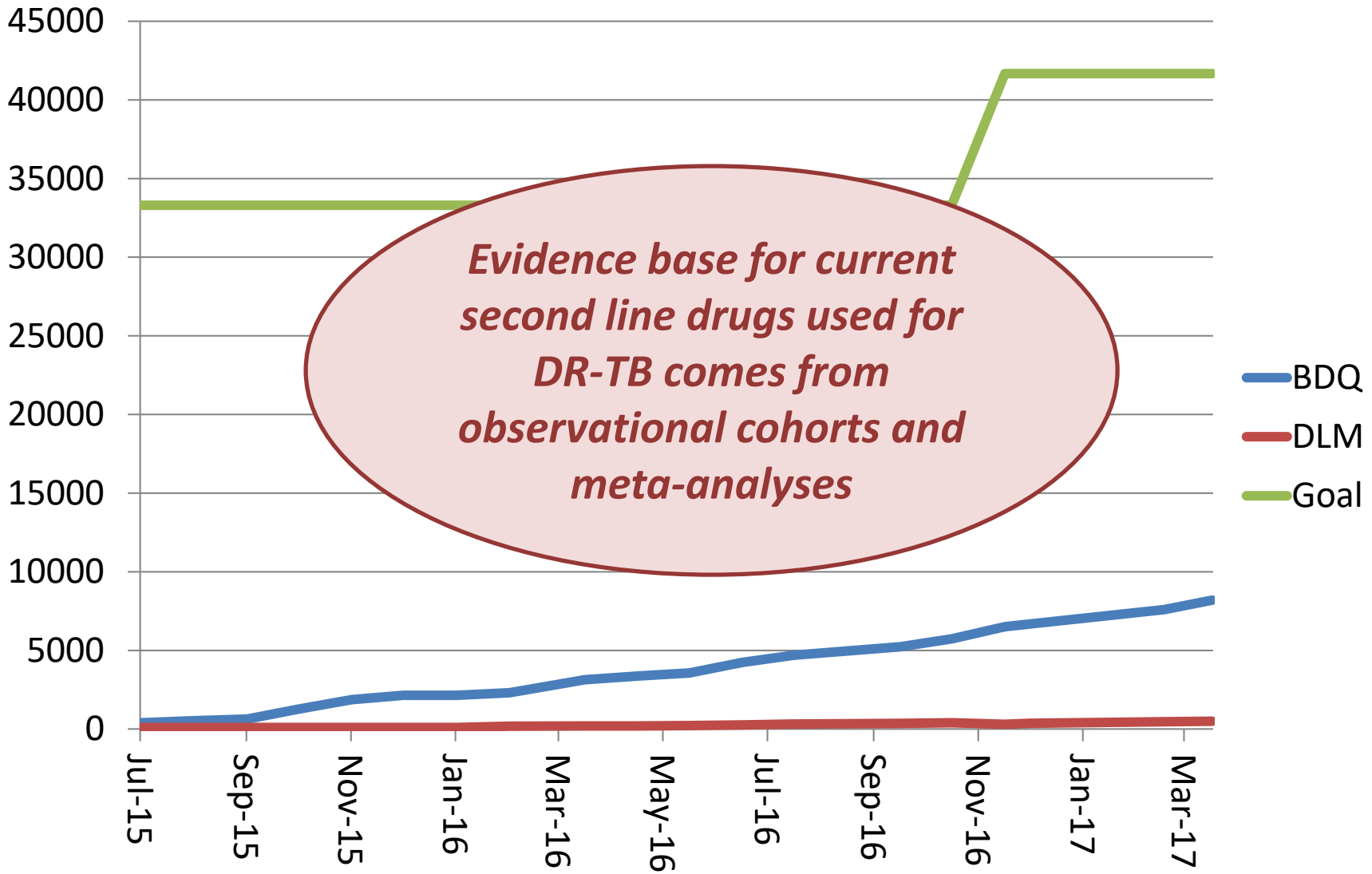
Malaise	12 (7.5)	16 (10.0)	12 (7.5)
Anorexia	23 (14.3)	34 (21.2)	24 (15.0)
Hyperhidrosis	9 (5.6)	17 (10.6)	8 (5.0)
Hyperuricemia	31 (19.3)	38 (23.8)	35 (21.9)
Hypokalemia	20 (12.4)	31 (19.4)	24 (15.0)

* With pairwise comparisons of the frequency of adverse events, only QT prolongation on electrocardiography (ECG) was significant (P=0.048 for the comparison of the 100-mg group with the placebo group and P=0.005 for the comparison of the 200-mg group with the placebo group). Furthermore, the Cochran–Armitage trend test used to evalu… for a dose-response trend in the incidence of adverse events across the three dose groups (0 mg, 100 mg, and 200 mg) yielded a P value of 0.004 for QT prolongation detected by means of ECG.

The NEW ENGLAND JOURNAL of MEDICINE

Global DLM implementation

- 564 patients receiving DLM end March 2017 through programmatic use
- Very little experience outside of clinical trials – majority of use is endTB/MSF



Cumulative delamanid and bedaquiline use over time compared with estimated need, July 2015 – March 2017

Re-purposed drugs for DR-TB

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Linezolid

- Oxazolidinone family: inhibits mycobacterial protein synthesis
- Other oxazolidinones: sutezolid, phase IIB for DS-TB
- Treatment of pneumonia, complicated skin/soft tissue infections, MRSA, VRE
- Available from Pfizer (very expensive but going off patent), generic from Hetero (still expensive); GDF
- Dosing: start at 600 mg daily, drop dose to 300 mg if toxicity seen
- NC-007: LZD optimization study (600/1200, 2/6 months)
- Shelf-life is 3 years; half life is 5 hours
- Suspension and IV formulations
- No effect on QT interval

Linezolid: evidence of efficacy

- Multiple observation studies showing culture conversion in XDR-TB patients
- Two meta-analyses: efficacy at 300mg once a day
- Systematic reviews: treatment success rates with LZD containing regimens for complicated MDR-TB equal to uncomplicated MDR-TB
- Randomized “delayed start” XDR-TB trial in South Korea (Lee et al NEJM, 2012)
  - Randomized 41 patients to 600 mg LZD immediately or after 2 months of background regimen
  - Faster culture conversion seen in early start
  - Most patients converted culture after 6 months
- LZD part of backbone for several all oral DR-TB trial regimens

Linezolid: evidence of safety

- Higher rates of AEs seen at a dose above 600mg daily
- Most common AEs: peripheral neuropathy (30%), bone marrow toxicity (10%%), optic neuropathy rare
- Avoid with serotonergic agents
- Monitor full blood count, visual acuity
- AEs in HIV-infected not higher than HIV un-infected DR-TB patients, manageable as outpatients (Hughes J et al ERJ 2015)
- Special populations:
  - can be given during pregnancy and breastfeeding (category C)
  - Well tolerated in children (Garcia-Prats AJ et al Tuberculosis 2014)
  - No interactions with ART in HIV positive patients

Imipenem-cilastatin/meropenem-clavulanate

- Broad spectrum carbapenem antibiotics
- In vitro activity – very little clinical experience
- Meropenem case control study (De Lorenzo et al ERJ 2013)
  - 37 patients with high-level resistance on regimen with LZD
  - 83.8% culture conversion versus 62.5% in controls (non-significant, p=0.06)
  - When XDR-TB excluded, statistically higher rate of culture conversion with mero/CLV plus LZD
- Used in CU/EA in Armenia and France
- Problems with drug delivery (IV or IM)
- Re-classified as D3 add on agent - consider in patients with high level resistance, no other options

Clofazimine

- Iminophenazine: binds preferentially to mycobacterial DNA, inhibits growth
- Commonly used in leprosy with dapsone/rifampicin
- EBA trials suggested efficacy
- RCT (Tang et al. CID 2015)
  - 105 patients
  - 100 mg daily for 21 months with background regimen
  - Treatment success: 73.6%, control group 53.8%, p=0.035)
- Component of STREAM trial and WHO shorter regimen
- Supply concerns (second supplier to GDF in 2017)
- Safety:
  - Skin pigmentation (slowly reversible)
  - QTc prolongation

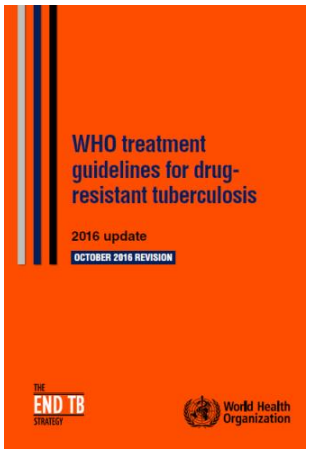
WHO recommendations and the triage approach

WHO guideline updates

May 2016

4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E

- 9-12 month regimen
- Reclassification (LZD/CFZ now group C, BDQ/DLM group D2)
- <u>Paediatrics: avoid injectable if no severe disease; DLM age 6 and above</u>
- Role of surgery in MDR-TB management
- RR-TB – treat as MDR regardless of INH resistance



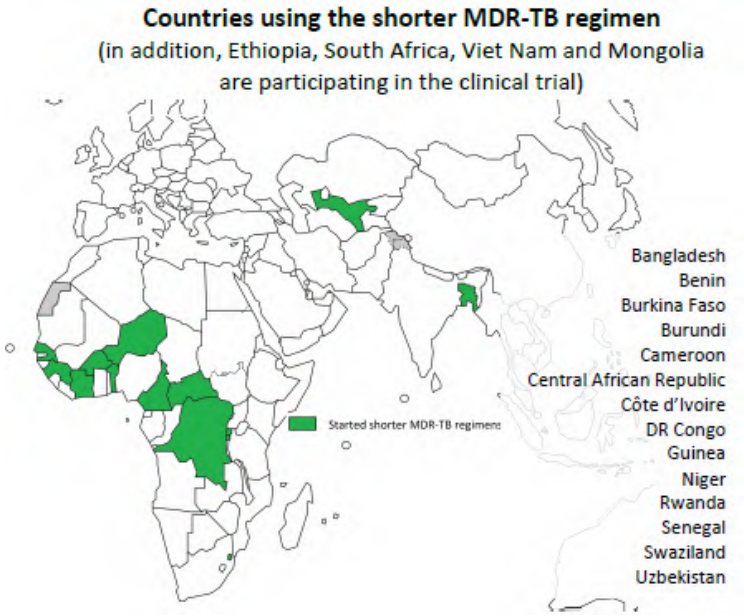
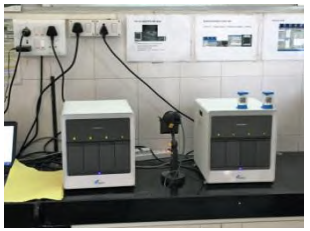


Table 6. Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB[1]

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)[3]	Am Cm Km (S)
C. Other core second-line agents[2]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid	Z E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	*p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)

“Triage” approach



CHOOSING THE MDR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

CRITERIA: Do any of the follo

- ✓ Confirmed resistance or suspe… medicine in the shorter MDR-TB regimen (except isoniazid r…
- ✓ Exposure to ≥1 second-line me… er MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the …orter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

SL LPA

NO

Shorter MDR-TB regimen

Intensive phase
Duration: 4-6 months
Composition: 4 second-line drugs

Continuation phase
Duration: 5 months
Composition: 2 second-line drugs

Supported by selected first-line TB drugs

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

YES

Individualised … (“conventio… MDR/RR-T…

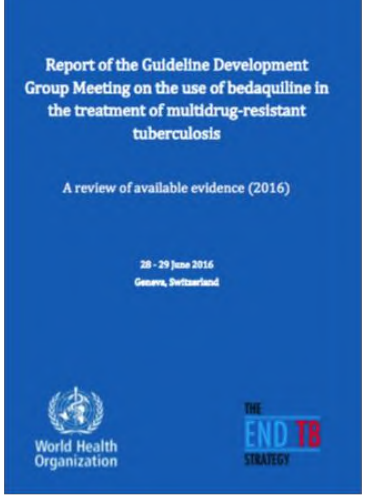
BDQ/ DLM

Intensive phase
Duration: Up to 8 months
Composition: 4 or more second-line drugs

Continuation phase
Duration: 12 months or more
Composition: 3 or more second-line drugs

Supported by selected first-line TB drugs

WHO GDG Meeting Report March 2017



- Bedaquiline recommended for:
  - persons who do not qualify for the SR
    - TB is resistant to a medicine in SR (not INH)
    - prior exposure for >1 month to a second line drug in SR
    - intolerance/increased risk of toxicity to 1+ drugs in SR
  - Continue to recommend bedaquiline for MDR-TB when a five drug regimen cannot be constructed for reasons of resistance or intolerance
- Downgrade of safety concerns: potential risks now “moderate” instead of “large”
- *Acknowledge that while the certainty of the evidence reviewed is low, the impact of bedaquiline on culture conversion and mortality was large enough to outweigh the harms for most patients*

WHO Meeting Report March 2017

Cohorts reviewed

HIV co-infected persons receiving antiretroviral therapy, who accounted for a quarter of patients

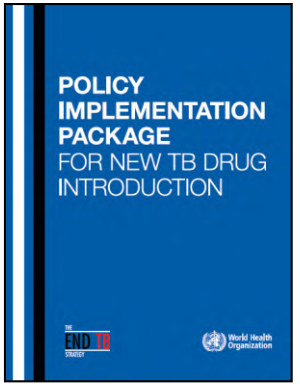
Adolescents, who made up 7% of the persons who received bedaquiline, although the numbers are small (39 adolescents)

Persons who had an extension of bedaquiline beyond 24 weeks, who represented 5.9% of persons in the analysis

Clarifications

- Use BDQ with caution in patients on lopinavir/ritonavir (due to QT prolongation effects), avoid with efavirenz (due to drug-drug interactions)
- BDQ safely used in large cohorts of people with HIV receiving ART
- aDSM – as opposed to Cohort Event Monitoring – should be used to ensure reporting of ADRs
- Informed consent policies should follow local practice for MDR-TB treatment in general

WHO approach



- Goal: support countries in preparing for new TB drugs and/or regimens, based on WHO policy guidance
- WHO recommendations for program conditions, not clinical trials (OR can be part of introduction)
- Country directed process: country will certify they meet WHO conditions
- Technical assistance can be provided to support countries to ensure drugs are used optimally
- *Structures and processes set up for BDQ and DLM will allow for optimal introduction of future new technologies, including drugs, regimens, and diagnostics*

Publications and programmatic experience with new drugs

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BQG and DLM: early publications

Infection and Drug R

Open Access Full Text Article

New develop
drug-resistan
of bedaquilin

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INT J TUBERC LUNG DIS 20(10):1282
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http://dx.doi.org/10.5588/ijtld.16.0522

Bedaquiline plus delamanid for XDR tuberculosis

We read with interest the co respondence by Caitlin Reed an colleagues, reporting a patient wit a severe case of extensively dru resistant (XDR) tuberculosis wh was treated with bedaquiline an subsequently denied delamani because of concerns over additiv cardiac toxic effects.[1] Here w report the case of a man with XD tuberculosis who was treated with regimen containing bedaquiline an delamanid in combination.

A 20-year-old man from Democratic Republic of the Congo was diagnosed with pulmonary tuberculosis in October, 2014. Sputum smears were positive. Cultures confirmed an XDR *Mycobacterium tuberculosis* strain. On the basis of genotypic and

routine-use programmatic conditions is scaled up, ensuring maximum benefit for patients and countries battling the MDR-TB crisis.

Keywords: MDR-TB, XDR-TB, tuberculosis drugs, group 5 drugs

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EDITORIAL

Using bedaquiline and delamanid in combination and safely

DESPITE GREAT STRIDES in global tuberculosis (TB) control over the past decade, drug-resistant TB remains a major threat both to individuals and to the prospects of eradicating TB as a public health problem. The World Health Organization (WHO) estimates that 3.3% of new TB cases and 20% of retreatment TB cases have multidrug-resistant TB (MDR-TB), and that globally cure rates are around 50%.[1] More worryingly, around 10% of MDR-TB cases have extensively drug-resistant TB (XDR-TB), with even lower cure rates. Therefore the recent development and introduction of two new highly effective drugs, bedaquiline (BDQ) and delamanid (DLM), for X/MDR-TB treatment is welcome, although expansion of use of these drugs into resource-poor settings with the highest burden of MDR-TB has been slow to date.

Interim guidance for the use of BDQ and DLM has been published by the WHO, and the place for use of these drugs as part of a regimen for X/MDR-TB is set out in new WHO guidelines. The two new drugs now have their own group, 'D2', and are considered as non-core add-on agents that can be added to a TB treatment regimen if a minimum number of five effective agents cannot be selected from the groups of

the national level,[4] and after patient's informed consent. Conditions for this combination use described by Alberto Matteelli and colleagues[2] were therefore fulfilled. Moreover, this combination was initiated under close cardiac monitoring and was

new drug will not be realised if added to a failing or inadequate regimen. Second, the clinical centre must be competent in the management of X/MDR-TB and have a pharmacovigilance system in place. The patient must give informed consent to the treatment. Also, appropriate independent expert advice should be sought from a body such as the WHO TB Consilium, not only on the use of the BDQ-DLM combination but also to ensure that an optimal background regimen with appropriate monitoring has been chosen.[5] Pending trial evidence it is essential that these conditions for combined use are applied to ensure that inappropriate use is minimised and subsequent development of resistance guarded against. Sadly, a case of TB resistant to both BDQ and DLM following sequential use with an inadequate background regimen has already been reported.[6]

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Qualitative assessment of TB programmes in which >5% of MDR patients received BDQ under programme conditions

Belarus, France, Georgia, South Africa, and Swaziland

Common factors:

- experience with compassionate use/expanded access
- support from implementing partners
- adequate national or donor-supported budgets

Barriers:

- restriction of BDQ to the in-patient setting
- lack of access to companion drugs
- development of aDSM systems

Other country experiences needed for country and global level evidence base

Ethics considerations and informed consent

Only when we put affected people at the center of our efforts, recognizing and protecting their rights, will we eradicate this millennia-old illness that has caused so much suffering.

– Hon M Kirby

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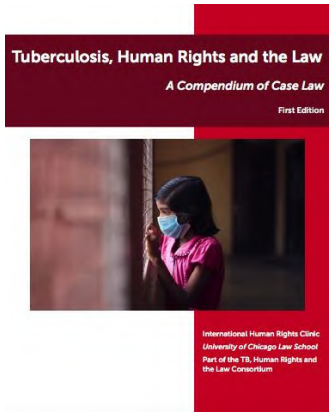
Ethics and informed consent

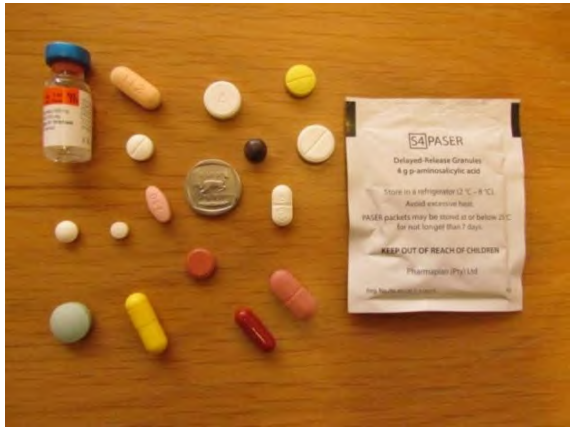


- Recognition of the rights of people living with and vulnerable to TB
- Reduce the socioeconomic and structural drivers of the epidemic – prioritize needs of key populations
- Ensure close participation of affected communities
- New drugs are being recommended for use under program conditions, not as a clinical trial
- Ethical issues/concerns arise from lack of long-term safety data, higher mortality rate seen with BDQ compared with placebo in the registration trial
- Ethical concerns must be placed in the context of current treatment of MDR-TB
  - poor outcomes
  - high rates of adverse events

Ethics and informed consent

- Obtain approval of protocols/guidelines from nationally recognized committees
- Provide informed consent (most patients sign form to receive DR-TB treatment)
  - Introduction of new drugs: catalyst for improving consent process overall, facilitate patient understanding
  - Ensure the new drugs are not “exceptionalized”
  - Include information, benefits/risks, side effects, confidentiality, right to withdraw, contact details
  - SHOULD NOT mirror consent forms used in clinical trials
- Core package of aDSM is in place – data collection and staff training
- What are the ethics of treating patients with a suboptimal regimen: 1/3 of 1539 cases in Mumbai can be treated with 4 or more DR-TB drugs (Udwadia FZ et al Lung India 2016)

Clinical considerations



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Important points

- BDQ/DLM tested and licensed as addition to backbone therapy for patients with MDR-TB
- Studies included: pulmonary disease, ages 18-65 years
- WHO recommend use with resistance or intolerance to SLDs
- Lack of data in other populations (children, pregnant women): use with caution
- New drugs should be introduced in the context of overall PMDT
- New drugs should be considered additional tools in the fight against DR-TB and parallel systems should not be created just for these drugs

Clinical considerations

1. Patient selection criteria
2. Regimen composition (multiple QT prolonging drugs, drug dosing)
3. Length of therapy: extension beyond 24 weeks
4. Inpatient or outpatient initiation
5. Combination of BDQ and DLM
6. Special populations
   - Children
   - pregnant women
   - HIV positive patients

1. Patient selection (1)

- Small number of absolute contraindications:
  - Refuses consent
  - Allergy
  - History of severe cardiac disease (torsades, arrhythmias)
- Shouldn't reserve new drugs only for patients failing MDR treatment or for "the most resistant" patients: poor outcomes, NOT the best way to maximize the benefits of these drugs
- Consider re-assessment after baseline abnormality (elevated QTc, lab value)
- Can be used with caution in special populations

1. Patient selection (2)

Second line drug resistance (FQ, AG, or both):

- Obtaining results from SL DST can take weeks to months
- Patients with documented RR-resistant TB: resistance testing should be done to at least AG/FQ
- Rapid testing is acceptable as a rule-in test
- Patients likely to have SLD resistance can be started on BDQ or DLM in the absence of confirmed DST
  - received these drugs in the past
  - contacts who are resistant to these drugs
  - failing MDR-TB treatment

1. Patient selection (3)

- Programs could consider adding new drugs in the setting of resistance to other SLDs, e.g high rates of ETO resistance, high rates of intolerance
- Balance electrolytes and correct albumin when possible
- “Intolerance:” at discretion of clinical team, shouldn’t wait until effect is severe or irreversible
- Patients with primary extrapulmonary DR-TB
  - not included in the registration trials
  - no reason to believe BDQ/DLM cannot be used in this population

2. Regimen composition

- Never add BDQ or DLM as single drug to a failing regimen
- If patient is culture negative, and the new drugs are being SUBSTITUTED for toxicity reasons, can make a single drug substitution
- XDR or failing MDR-TB regimen: need to add at least 3 new drugs, including BDQ or DLM, LZD, CFZ, PZA, +/- carbapenem
- Use with caution with other drugs that can prolong the QTc interval (MFX if evidence of suseptibility, CFZ)
- BDQ or DLM? No studies comparing the 2 drugs
  - Use other drug if history of use, allergy
  - DLM – no interactions with ART
  - DLM – paediatrics and adolescents (short term PK/safety data)

3. Length of therapy (extension beyond 24 weeks)

- Both DLM and BDQ were tested in 6 month trials and are recommended for 6 months of therapy
- 6 months chosen for ease of endpoint analysis
- In patients with high-level resistance or intolerance, drugs can be used for longer periods of time on a case-by-case basis
  - Long term follow up of 45 BDQ patients (Guglielmetti et al ERJ 2017)
    - 33 (73%) received BDQ > 190 days (median 361)
    - QTcF > 500 ms – 11%
    - Successful outcome – 80%
  - DLM has been given in research conditions for up to 8 months
- 6 month time period does not correspond with an 'intensive phase'

4. Inpatient or outpatient treatment initiation

- If hospitalizing for cardiac monitoring, consider that DLM takes 8 weeks to reach its peak and BDQ up to 16 weeks
- If hospitalizing for cardiac safety, ensure access to a defibrillator
- Ensure adherence support (nutrition, transportation support, community based care) and proper monitoring
- Transition from hospitalization for all patients starting new drugs to outpatient initiation of stable patients

5. Combination of BDQ and DLM

- Limited extent of programmatic use
- Multicentric cohort in MSF sites (Union, 2016):
  - 28 patients on combo median 16.8 weeks (IQR 5-34.6 weeks)
  - Number of drugs at start of combo: 7 (IQR 6-10)
  - Other QT prolonging drugs administered in 86% of cohort
    - 23 patients on CFZ or MFX
    - 1 patient on CFZ and MFX
  - 7 completed 24 weeks: 75% culture conversion
  - All QTc > 500 ms or >60 ms increase resolved without cardiac event
  - 1 fatality: multi-organ failure, hypoglycemia, seizure

6. Special populations (1): children and adolescents

- DLM is being tested for PK and safety in children ages 5 years and under
- Pediatric formulation of DEL is available (50 mg scored, dispersible)
- Recommended dosing becoming available (Am J Respir Crit Care Med 2017)
  - Delamanid: 20-34 kg: 50 mg BD, <20 kg and <6 yo: consult
  - Bedaquiline: >12 yo and >33 kg: 400 daily for 14 d, 200 TIW x 22 weeks
- Time for injectable sparing regimens for children

Paediatric DR-TB

CONCISE CLINICAL REVIEW

New/Repurposed Drugs for Pediatric Multidrug-Resistant Tuberculosis

Practice-based Recommendations

Elizabeth P. Harausz[1], Anthony J. Garcia-Prats[2], James A. Seddon[3], H. Simon Schaaf[2], Anneke C. Hesseling[2], Jay Achar[4], Jonathan Bernheimer[5], Andrea Cruz[6], Lia D'Ambrosio[7,8], Anne Detjen[9], Stephen M. Graham[10], Jennifer Hughes[5], Sylvie Jonckheere[11], Ben J. Marais[12], Giovanni Battista Migliori[7], Lindsay McKenna[13], Alena Skrahina[14], Marina Tadolini[15], Peyton Wilson[16], and Jennifer Furin[17]; on behalf of the Sentinel Project on Pediatric Drug-Resistant Tuberculosis

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Abstract

It is estimated that 33,000 children develop multidrug-resistant tuberculosis (MDR-TB) each year. In spite of these numbers, children and adolescents have limited access to the new and repurposed MDR-TB drugs. There is also little clinical guidance for the use of these drugs and for the shorter MDR-TB regimen in the pediatric population. This is despite the fact that these drugs and regimens are associated with improved interim outcomes and acceptable safety profiles in adults. This review fills a gap in the pediatric MDR-TB literature by providing practice-based recommendations for the use of the new (delamanid and bedaquiline) and repurposed (linezolid and clofazimine) MDR-TB drugs and the new shorter MDR-TB regimen in children and adolescents.

Keywords: multidrug-resistant tuberculosis; *Mycobacterium tuberculosis*; child; adolescent; pediatric

Paediatric DR-TB

S2213-2600(17)30078-4
Emargo: March 23, 2017—23:30 (GMT/BST)
Unlinked comment

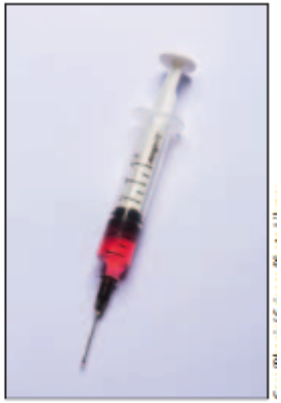
readability, reduce length, and achieve consistency with *Lancet* style]

The time has come: sparing injectables in paediatric MDR-TB

Proponents of critical thinking recount this fable: a daughter asks, "Mother, why do you cut the end off the holiday ham?" Her mother answers, "Because that's the way Grandma always did it." The daughter, an inquisitive sort, then asks her grandmother, "Grandma, why do you cut the end off of the holiday ham?" Her grandmother replies, "Because my pan is too small." In matters of medicine, progress demands that clinicians and investigators continuously challenge practices that are more aligned with convention than with strong scientific rationale. Nowhere is this more imperative than in cases where treatment dictated by long-standing practice carries with it a high prevalence of permanent harm. And when irreversible toxicities affect children, they cast a long and terrible shadow, because children are affected for their

this type of monitoring is resource intensive, infrequently available in settings where MDR tuberculosis is common, and challenging in young children. Daily intramuscular injections are programmatically challenging and painful, causing prolonged distress for children and their caregivers.

Second, the evidence that injectables provide meaningful microbiological activity to MDR tuberculosis treatment regimens is, at best, mixed. Given the high risk of serious permanent toxicity, the threshold for benefit should be high. However, in clinical studies of early bactericidal activity, amikacin as monotherapy at doses of 5–15 mg/kg per day had no measurable effect on sputum bacterial load, by contrast with all other tuberculosis drugs in use.[7] Notably, there have been no randomised trials of injectable-containing versus injectable-sparing regimens.[8] A



Lancet Respir Med 2017
Published Online
March 23, 2017

6. Special populations (2): pregnancy and breastfeeding

- No data on the safety of these drugs on developing fetus or breastfed children
- BDQ and DLM: pregnancy category B (most likely to be safe based on animal studies)
- Current DR-TB drugs: almost all either category C or D – more familiar, but more toxic
- Stopping the injectable during pregnancy is likely treating with a sub-standard regimen
- Birth control should be used as with routine PMDT
- DLM CU protocol allows use in pregnant women
- Must weigh the risks and benefits of using either of these drugs in pregnancy

6. Special populations (3): HIV/DR-TB co-infected

- Patients with HIV can be given BDQ or DLM: not included in significant numbers in registration trials, but high mortality
- Choice of ART
  - EFV lowers concentration of BDQ; use PI regimens with caution with BDQ
  - NVP or integrase inhibitor thus preferred with BDQ
  - DLM: can be used with most ART regimens
- Management
  - If patient not yet on ART, start BDQ regimen then start NVP-based ART regardless of CD4 count
  - If patient on NVP or lopinavir/ritonavir-based regimen, continue regimen and begin BDQ
  - If patient on EFV containing regimen, check VL: if VL LDL stop EFV and start NVP for duration of BDG; if VL detectable, stop EFV and start lopinavir/ritonavir-based regimen

Thank you
ขอขอบคุณ

'Chains of habit are too light to be felt until they are too heavy to be broken.'
Warren Buffet

Acknowledgements:
Edmund Rutta, Jennifer Furin

- New drugs are no longer new – safe, less toxic, and effective
- Use with minimal modifications to current PMDT clinical programs and as part of effective combination therapy
- Patients with resistance or intolerance to SLDs should be prioritized
- Most data on patients 18-65 with pulmonary disease, but can be used safely in other populations
- Plans for roll out of new drugs at country level are an essential component of improving DR-TB outcomes

Designing and implementing aDSM for new drugs under programmatic conditions: Georgia Experience

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Head of Surveillance and Strategic Planning Department

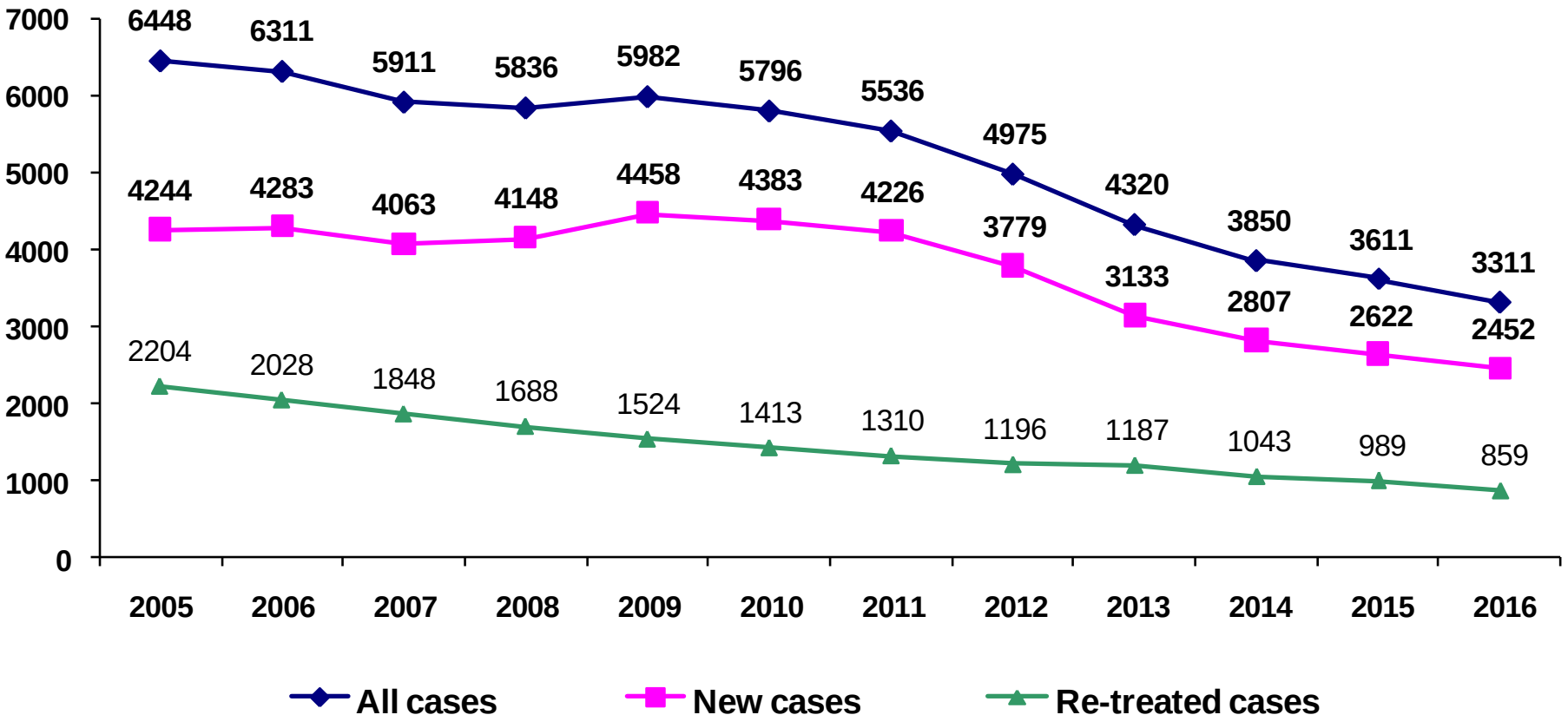
National Centre for Tuberculosis and Lung Diseases (NCTLD), Tbilisi, Georgia

Asia Regional Pharmacovigilance Workshop: Implementation of active TB drug-safety monitoring and management (aDSM) for New Drugs and Shortened Treatment Regimens for MDR TB

25-27 April, 2017

Bangkok, Thailand

Notified Tuberculosis cases in Georgia
(absolute numbers)



Country Context – MDR-TB

- **Georgia was a high MDR/XDR-TB burden country pre 2016**
- **In 2016 (preliminary):**

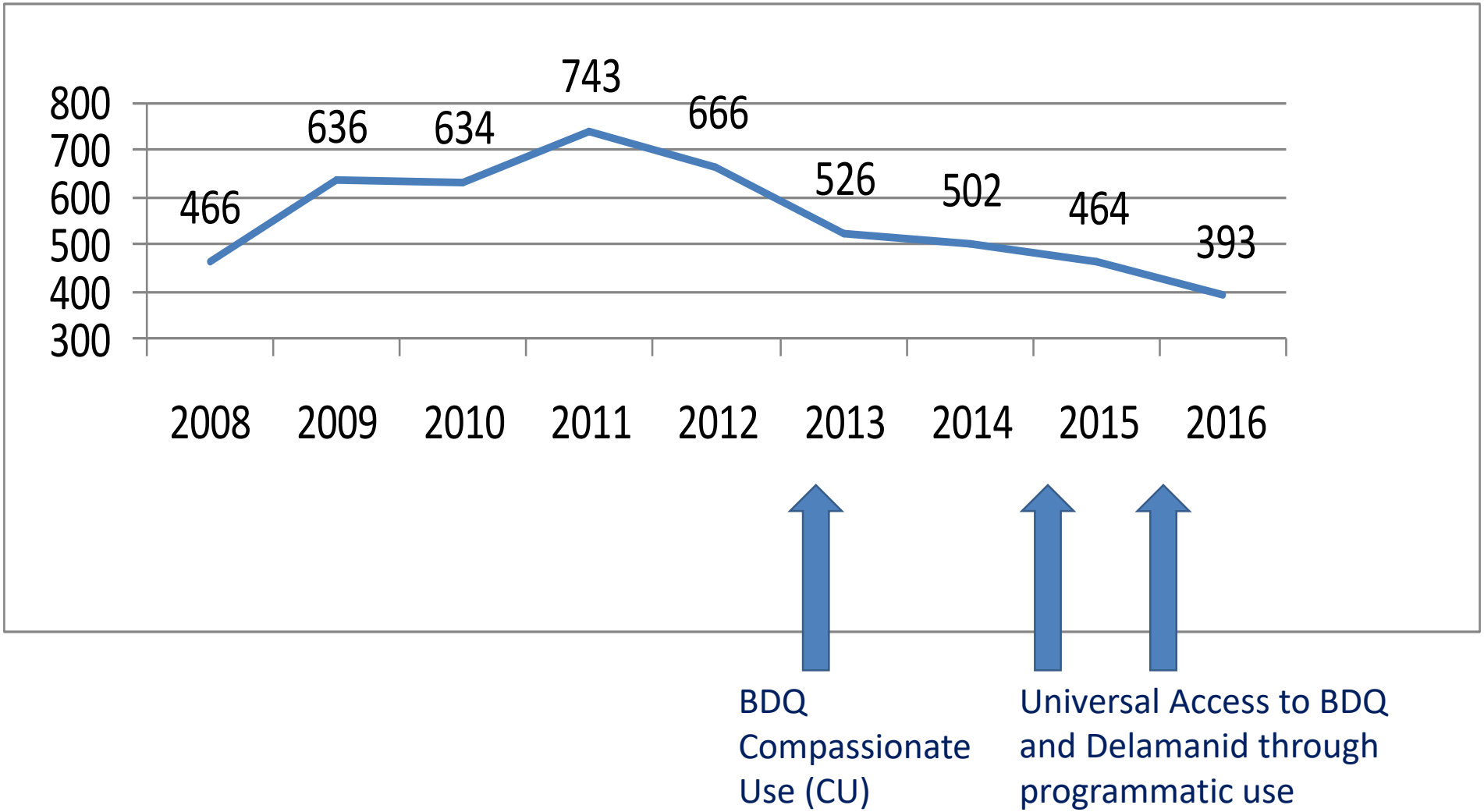
New MDR TB cases	Previously treated MDR TB cases	XDR-TB cases
9.8%	40.1%	18% XDR TB ➢ 36% any FQ resistance ➢ 38% any 2nd LI
(range 2005-16: 6.8%-11.6%)	(range 2005-16: 26.4%-40.3%)	(range XDR 2009-16: 9%-20%) (range FQ 2009-16: 12%-36%)

- **In 2013 cohort:**
  - ➢**RR-TB** treatment success rate **44%** (range 2008-13: 56%-44%)
  - ➢**XDR-TB** treatment success **21%** (range 2008-13: 39%-21%)

Overall, ~36% of RR-TB patients annually (~150 patients) eligible for introduction of new TB drugs in Georgia.

Cases enrolled in 2nd line treatment in Georgia

(absolute numbers, > 5000 cases)



Chronology of access to New TB Drugs

2013

- **Start** BDQ Compassionate Use (CU) Program

From 2014

MSF supported **scale up** of CU & programmatic use of BDQ and CU of Delamanid

Aug 2015

Programmatic use of BDQ through **USAID Donation Program**

Nov 2015

- **Universal access** to diagnosis/treatment for TB including 'pre-XDR'/ XDR-TB
- **National TB guidelines**: up to date, endorsed by MoH, include M/XDR treatment regimens and new drug safety monitoring schedule (WHO guidance)

Chronology of Practical Steps Taken

2014

- **National BDQ Implementation Plan** developed with the USAID project
- Approved by National TB Council chaired by the Minister of Health himself

Jan 2015

Technical Working Group created to coordinate new drug implementation, including PV, led by NCTLD

March 2015

MoH-approved **new voucher funding** for safety monitoring linked with new drug use, incl. ECG investigations, etc

Apr2015

- Georgia became a primary Candidate to receive BDQ through **USAID & Janssen Therapeutics' donation** program followed by the ceremony of BDQ handover in Oct 2015

July 2015

- An innovative approach of **Mobile Consilium** was launched by the NCTLD with the support of the Global Fund TB Program

Indications for New TB Drug Regimens in Georgia

Eligible are patients with one or more of the following:

a. XDR-TB (resistance to a fluoroquinolone and at least one second-line injectable).

b. Pre-XDR-TB (resistance to a fluoroquinolone or to at least one second-line injectable, but not both) or intolerance to a fluoroquinolone and/or second-line injectable

c. Patients with two or more Group 4 drugs (Eto/Pto, Cs, PAS) compromised/resistant or with intolerance to them.

d. Patients with severe disease and a bad clinical prognosis.

Exposure to New Drugs - Georgia

Total of **361 Patients** enrolled on new treatments (as of **March 31st 2017**):

- **Bdq: 262 patients**
  - ❑ 20 through CU
  - ❑ 242 through programmatic use (drug source USAID donation and MSF)
- **Dlm: 99 patients** (CU)
  - ❑ 12 through CU
  - ❑ 87 through programmatic use (drug source MSF, and Global Fund program through GDF)

❑ **211 patients are still on treatment**

Pre-*aDSM* Pharmacovigilance (PV)

Pre 2014

- **PV "naïve"** country in any disease context.

May-Jul 2014

MSF supported **training on treatment of XDR-TB**

- Focus on monitoring & management of AEs and reporting of SAEs
- MSF managed SAE reporting and collection of non-serious AEs into MSF clinical database

May 2015

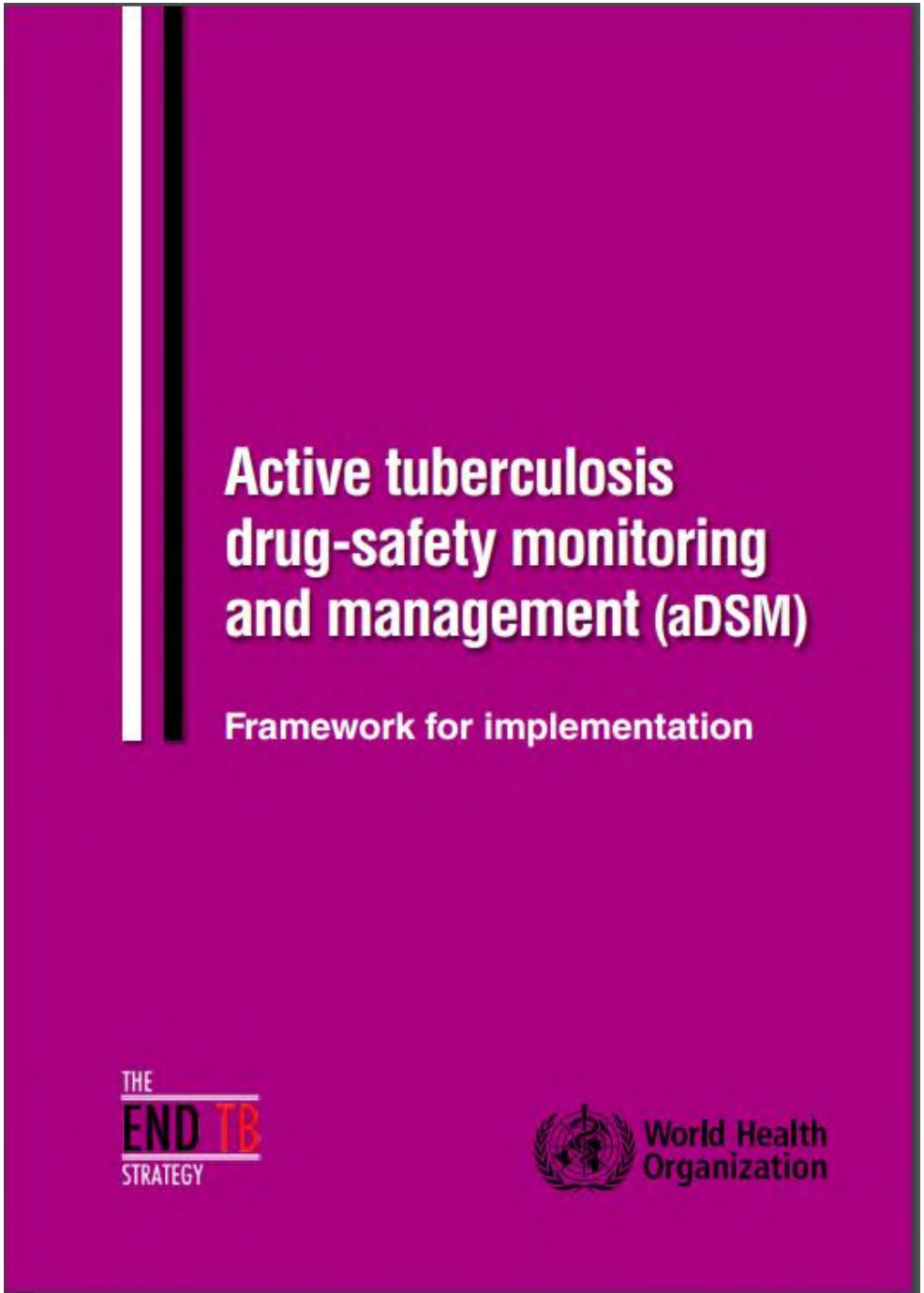
- **Technical assistance to establish a PV system:**
  - USAID donation program, through USAID/SIAPS

June-July 2015

- **Preparation of PV system within USAID/SIAPS TA:**
  - Decision to report <u>any AE</u> of clinical importance *(per "Companion Handbook" recommendations of CEM);* Development of comprehensive <u>baseline and monthly AE reporting</u> developed by USAID/SIAPS experts in collaboration with the NCTLD and MoH
  - *Not Implemented*

Aug 2015

- Training of trainers on clinical management of adverse events in line with the severity grading was conducted (USAID/SIAPS TA)



What happened AFTER the "Vigilant" Georgian TB society heard about aDSM decisions and recommendations from the July Geneva meeting …

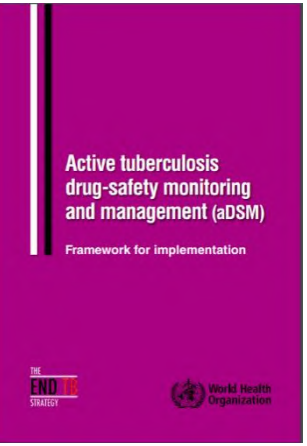
Post-*aDSM* PV Implementation

Sep 2015

Meeting of partners to **reassess TB PV needs** (NTP, USAID/SIAPS MSF, USAID/URC)

- ***Goal***: establish new framework for introduction of active TB drug safety management and monitoring (aDSM) for new anti-TB drugs - latest recommendations.

➢ **DECISIONS**:



1. **Core package**:
   - Requiring monitoring for and reporting of all **SAEs** among **all drug-resistant TB patients** being on treatment as part of routine programmatic practice,

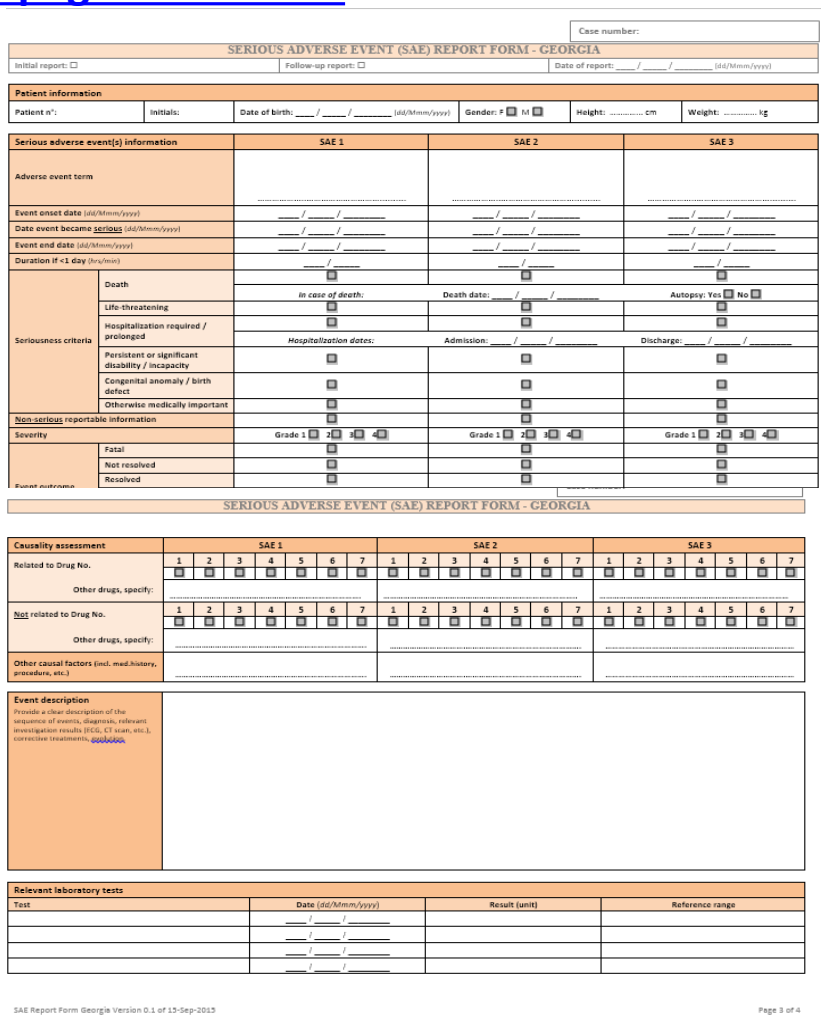
2. **Sentinel site**:
   - Through MSF endTB project for the collection of **intermediate & advanced packages** that includes **SAEs** as well as **AEs of clinical significance**.

➢ **A gradual takeover plan of intermediate & advanced package by TB program was established for after MSF leaves the country**

aDSM Implementation (I)

- Translation and adaption of SAE form, completion guidelines and severity grading scale from endTB for use at National Level

4 pages SAE Form:



Case number:

SERIOUS ADVERSE EVENT (SAE) REPORT FORM - GEORGIA

Initial report: ☐ | Follow-up report: ☐ | Date of report: ___ / ___ / _____ (dd/Mmm/yyyy)

Patient information

Patient n°: | Initials: | Date of birth: ___ / ___ / _____ (dd/Mmm/yyyy) | Gender: F ☐ M ☐ | Height: ..... cm | Weight: ..... kg

Serious adverse event(s) information		SAE 1	SAE 2	SAE 3
Adverse event term		.....	.....	.....
Event onset date (dd/Mmm/yyyy)		___ / ___ / _____	___ / ___ / _____	___ / ___ / _____
Date event became serious (dd/Mmm/yyyy)		___ / ___ / _____	___ / ___ / _____	___ / ___ / _____
Event end date (dd/Mmm/yyyy)		___ / ___ / _____	___ / ___ / _____	___ / ___ / _____
Duration if <1 day (hrs/min)		___ / ___	___ / ___	___ / ___
Seriousness criteria	Death	☐	☐	☐
		In case of death:	Death date: ___ / ___ / _____	Autopsy: Yes ☐ No ☐
	Life-threatening	☐	☐	☐
	Hospitalization required / prolonged	☐	☐	☐
		Hospitalization dates:	Admission: ___ / ___ / _____	Discharge: ___ / ___ / _____
	Persistent or significant disability / incapacity	☐	☐	☐
	Congenital anomaly / birth defect	☐	☐	☐
	Otherwise medically important	☐	☐	☐
Non-serious reportable information		☐	☐	☐
Severity		Grade 1 ☐ 2 ☐ 3 ☐ 4 ☐	Grade 1 ☐ 2 ☐ 3 ☐ 4 ☐	Grade 1 ☐ 2 ☐ 3 ☐ 4 ☐
Event outcome	Fatal	☐	☐	☐
	Not resolved	☐	☐	☐
	Resolved	☐	☐	☐

SERIOUS ADVERSE EVENT (SAE) REPORT FORM - GEORGIA

Causality assessment		SAE 1	SAE 2	SAE 3
Related to Drug No.	1 2 3 4 5 6 7	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐
	Other drugs, specify:	.....	.....	.....
Not related to Drug No.	1 2 3 4 5 6 7	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐
	Other drugs, specify:	.....	.....	.....
Other causal factors (incl. med.history, procedure, etc.)		.....	.....	.....

Event description

Provide a clear description of the sequence of events, diagnosis, relevant investigation results (ECG, CT scan, etc.), corrective treatments, outcome.

Relevant laboratory tests

Test	Date (dd/Mmm/yyyy)	Result (unit)	Reference range
	___ / ___ / _____		
	___ / ___ / _____		
	___ / ___ / _____		
	___ / ___ / _____		

SAE Report Form Georgia Version 0.1 of 15-Sep-2015 Page 3 of 4

Case number:

SERIOUS ADVERSE EVENT (SAE) REPORT FORM - GEORGIA

Suspected drug(s) *including all TB drugs & any other drug*	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
Suspected drug name (INN)	.....	.....	.....	.....	.....	.....	.....
Daily dose & route							
Batch number							
Treatment start date (dd/Mmm/yyyy)	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____
Treatment stop date (dd/Mmm/yyyy)	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____
Action taken in response to the event							
Dose maintained	☐	☐	☐	☐	☐	☐	☐
Dose reduced	☐	☐	☐	☐	☐	☐	☐
New daily dose							
On (dd/Mmm/yyyy)	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____
Drug permanently withdrawn	☐	☐	☐	☐	☐	☐	☐
On (dd/Mmm/yyyy)	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____
Drug interrupted	☐	☐	☐	☐	☐	☐	☐
From (dd/Mmm/yyyy)	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____
To (dd/Mmm/yyyy)	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____	___ / ___ / _____
Not applicable	☐	☐	☐	☐	☐	☐	☐
Event diminished after drug stopped/dose reduced?	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐
Event reappeared after drug/dose	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐	Yes ☐ / No ☐ / N/A ☐

Case number:

SERIOUS ADVERSE EVENT (SAE) REPORT FORM - GEORGIA

Concomitant medications

Drug name (INN)	Daily dose and route	Indication	Treatment start date (dd/Mmm/yyyy)	Treatment stop date (dd/Mmm/yyyy)	Continued
			___ / ___ / _____	___ / ___ / _____	☐ Yes ☐ No
			___ / ___ / _____	___ / ___ / _____	☐ Yes ☐ No
			___ / ___ / _____	___ / ___ / _____	☐ Yes ☐ No
			___ / ___ / _____	___ / ___ / _____	☐ Yes ☐ No
			___ / ___ / _____	___ / ___ / _____	☐ Yes ☐ No

Relevant medical history

Indicate relevant medical history, including prior diagnoses, past laboratory investigations, X-ray, ECG prior to treatment, previous procedures, and relevant past drugs.

Reporter

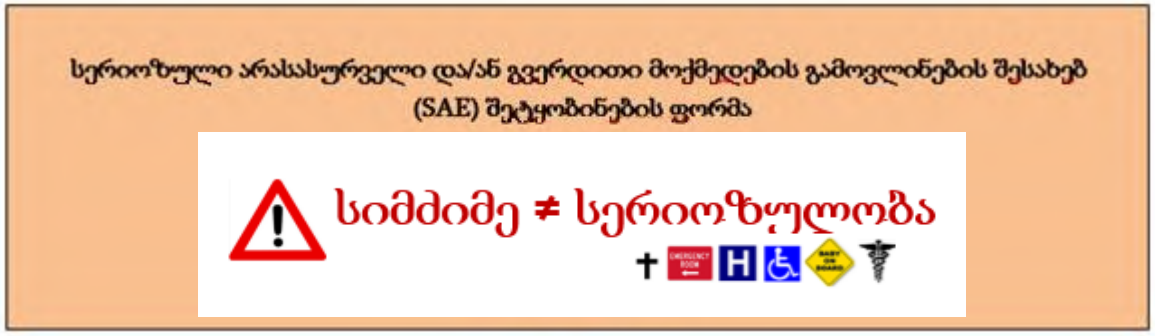
Name of reporter:	Role in trial/program:	Date of event's awareness:	Address:	Date and signature:
		ALL SAEs to be reported within 24 hrs of awareness ___ / ___ / _____	Email: Phone:	___ / ___ / _____

Further information on this SAE expected?	Any annex to this document? (e.g. discharge summary, autopsy report, lab results)
Yes ☐ No ☐ *If yes please send a follow up report once new information is available*	Yes ☐ No ☐ *If yes, list the annexes:*

SAE Report Form Georgia Version 0.1 of 15-Sep-2015 Page 4 of 4

aDSM Implementation (II)

- Translation and adaption of SAE form, completion guidelines and severity grading scale from endTB for use at National Level…
- **SAE Form Completion Guidelines:**



- **The Severity Grading Scale based on 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**

არასასურველი მოვლენის სიმძიმე

როგორ გამოვიყენოთ სიმძიმის ხარისხის შკალა?

- მოძებნეთ სიაში თქვენს მიერ დაფიქსირებული დიაგნოზი, ან ნიშანი/სიმპტომი:
- მაგ., პაციენტის ALT მომატებულია და არის 100 U/L (N <40)

მდგომარეობის დასახელება	ხარისხი 1	ხარისხი 2	ხარისხი 3	ხარისხი 4
ალანინ ამინოტრანსფერაზას მომატება (ALT ან SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN

- მაგ., პაციენტს აქვს შეუჩერებელი ღებინება 2 დღის მანძილზე, დეჰიდრატირებულია და საჭიროებს ჰოსპიტალიზაციას.

მდგომარეობის დასახელება	ხარისხი 1	ხარისხი 2	ხარისხი 3	ხარისხი 4
ღებინება	1 ეპიზოდი 24 საათის განმავლობაში	22-5 ეპიზოდი 24 საათში	>6 ეპიზოდი 24 საათში, ან ი/ვ სითხის მიწოდების საჭიროება	ფიზიოლოგიური შედეგები, რომელიც მოითხოვს ჰოსპიტალიზაციას ან პარენტერალ კვებას

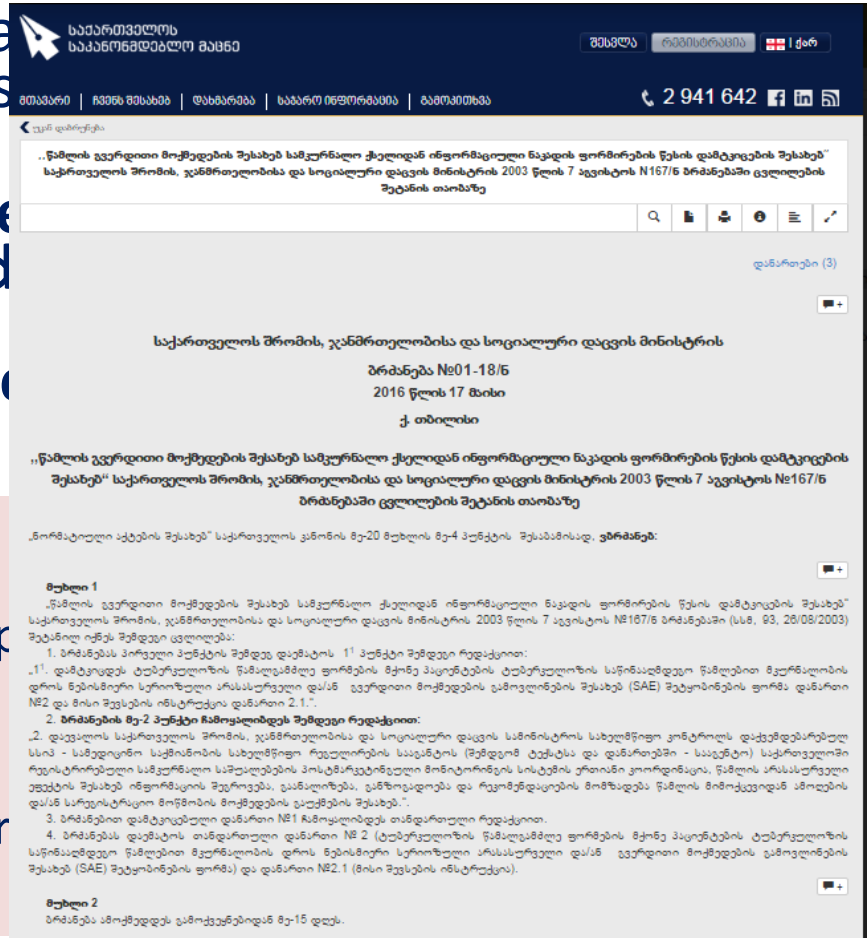
aDSM Implementation (III)

Oct 2015

- The National Center for TB and Lung Diseases (NCTLD) referred to the Minister of Health with a letter summarizing the need of the mandatory reporting rules and practices of SAEs for patients undergoing SLD TB treatment
- Already developed form a was provided to the Minis an attachment

May 2016

- **Permanent Ministerial De mandatory recording and all DR-TB patients issued went into force since Jun**


საქართველოს
საკანონმდებლო მაცნე

შესვლა | რეგისტრაცია | ქარ

მთავარი | ჩვენს შესახებ | დახმარება | საბარო ინფორმაცია | გამოკითხვა | 2 941 642

..წამლის გვერდითი მოქმედების შესახებ სამკურნალო ქსელიდან ინფორმაციული ნაკადის ფორმირების წესის დამტკიცების შესახებ" საქართველოს შრომის, ჯანმრთელობისა და სოციალური დაცვის მინისტრის 2003 წლის 7 აგვისტოს N167/ნ ბრძანებაში ცვლილების შეტანის თაობაზე

დანართები (3)

საქართველოს შრომის, ჯანმრთელობისა და სოციალური დაცვის მინისტრის

ბრძანება №01-18/ნ

2016 წლის 17 მაისი

ქ. თბილისი

,,წამლის გვერდითი მოქმედების შესახებ სამკურნალო ქსელიდან ინფორმაციული ნაკადის ფორმირების წესის დამტკიცების შესახებ" საქართველოს შრომის, ჯანმრთელობისა და სოციალური დაცვის მინისტრის 2003 წლის 7 აგვისტოს №167/ნ ბრძანებაში ცვლილების შეტანის თაობაზე

„ნორმატიული აქტების შესახებ" საქართველოს კანონის მე-20 მუხლის მე-4 პუნქტის შესაბამისად, **ვბრძანებ:**

მუხლი 1

„წამლის გვერდითი მოქმედების შესახებ სამკურნალო ქსელიდან ინფორმაციული ნაკადის ფორმირების წესის დამტკიცების შესახებ" საქართველოს შრომის, ჯანმრთელობისა და სოციალური დაცვის მინისტრის 2003 წლის 7 აგვისტოს №167/ნ ბრძანებაში (სსმ, 93, 26/08/2003) შეტანილ იქნეს შემდეგი ცვლილება:

1. ბრძანების პირველი პუნქტის შემდეგ დაემატოს 1[1] პუნქტი შემდეგი რედაქციით:

„1[1]. დამტკიცდეს ტუბერკულოზის წამალგამძლე ფორმების მქონე პაციენტების ტუბერკულოზის საწინააღმდეგო წამლებით მკურნალობის დროს ნებისმიერი სერიოზული არასასურველი დასნ გვერდითი მოქმედების გამოვლინების შესახებ (SAE) შეტყობინების ფორმა დანართი №2 და მისი შევსების ინსტრუქცია დანართი 2.1.".

2. **ბრძანების მე-2 პუნქტი ჩამოყალიბდეს შემდეგი რედაქციით:**

„2. დაევალოს საქართველოს შრომის, ჯანმრთელობისა და სოციალური დაცვის სამინისტროს სახელმწიფო კონტროლის დეპარტამენტს სსიპ - სამედიცინო საქმიანობის სახელმწიფო რეგულირების სააგენტოს (შემდგომ ტექსტსა და დანართებში - სააგენტო) საქართველოში რეგისტრირებული სამკურნალო საშუალებების პოსტმარკეტინგული მონიტორინგის სისტემის ერთიანი კოორდინაცია, წამლის არასასურველი ეფექტის შესახებ ინფორმაციის შეგროვება, გაანალიზება, განზოგადოება და რეკომენდაციების მომზადება წამლის მიმოქცევიდან ამოღების დასნ სარეგისტრაციო მოწმობის მოქმედების გაუქმების შესახებ.".

3. ბრძანებით დამტკიცებული დანართი №1 ჩამოყალიბდეს თანდართული რედაქციით.

4. ბრძანებას დემატოს თანდართული დანართი № 2 (ტუბერკულოზის წამალგამძლე ფორმების მქონე პაციენტების ტუბერკულოზის საწინააღმდეგო წამლებით მკურნალობის დროს ნებისმიერი სერიოზული არასასურველი დასნ გვერდითი მოქმედების გამოვლინების შესახებ (SAE) შეტყობინების ფორმა) და დანართი №2.1 (მისი შევსების ინსტრუქცია).

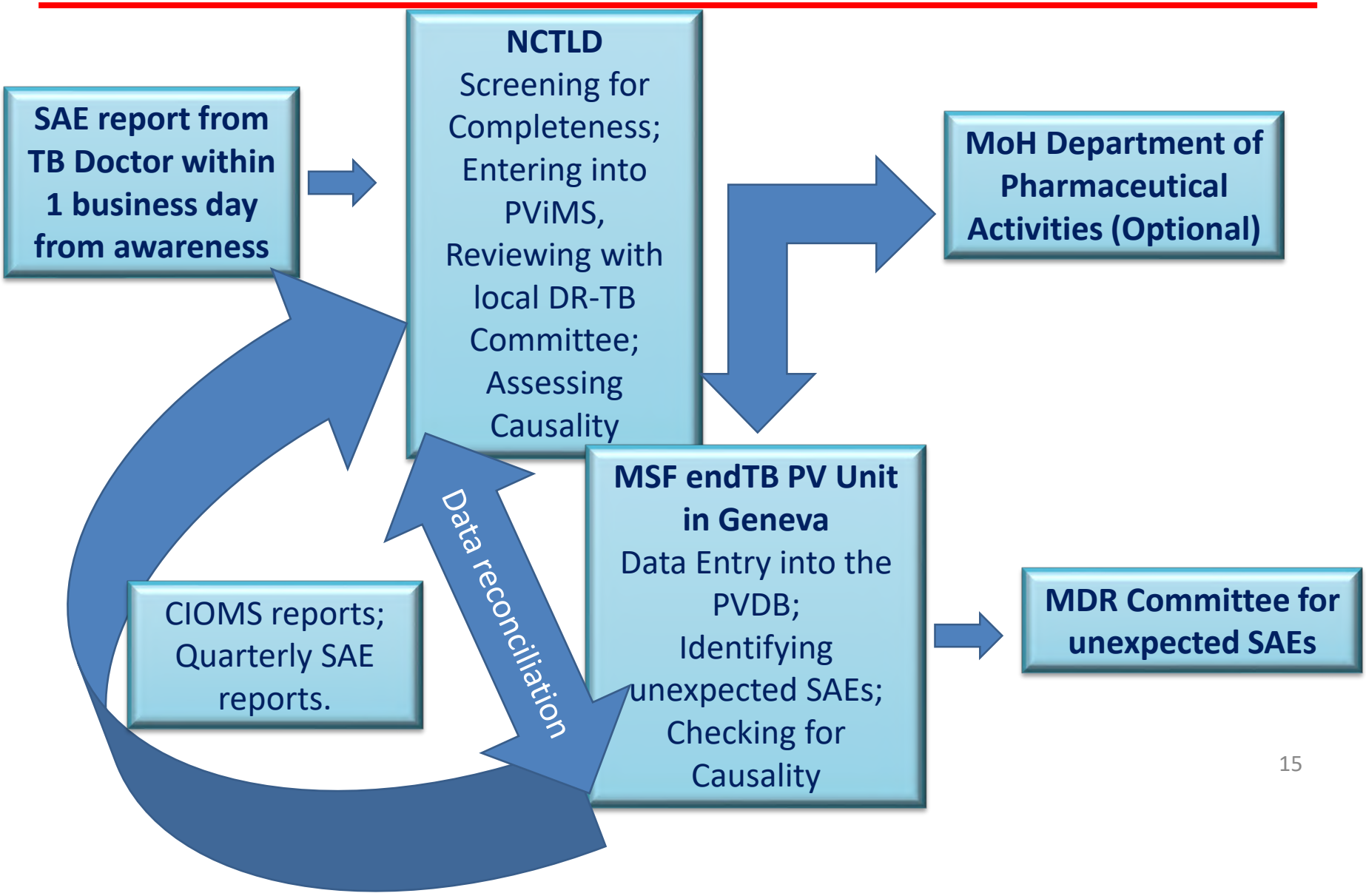
მუხლი 2

ბრძანება ამოქმედდეს გამოქვეყნებიდან მე-15 დღეს.

- Flow of safety data:
  - **SAEs** collected by doctors should be rep
    - Then reported to endTB PV unit
    - **Non SAE** data collected by endTB pr site

aDSM Implementation (V)

Flow of Data within the TB program and Externally



aDSM Implementation (VI)

PV Data Base (PViMS)

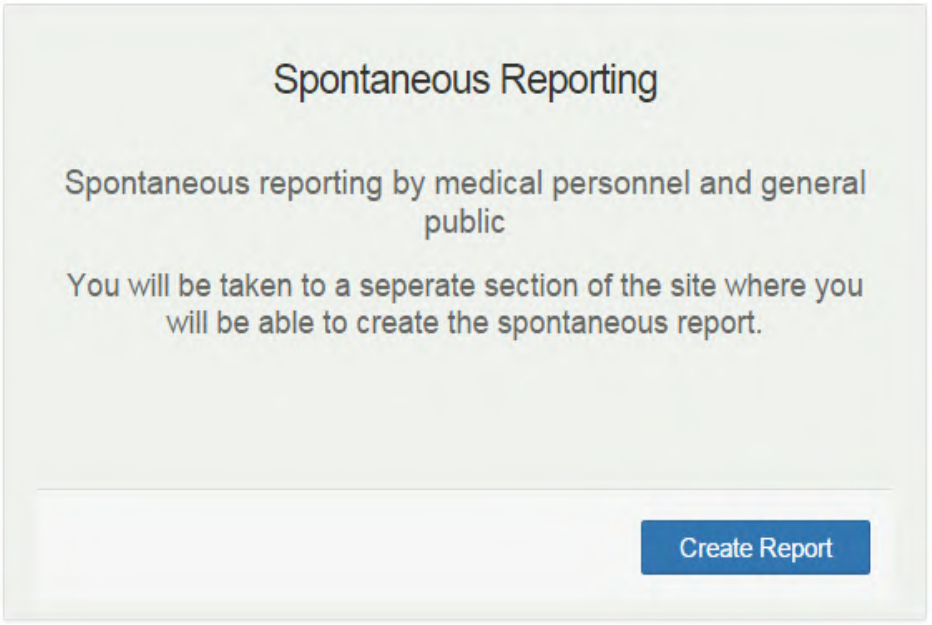
- USAID/SIAPS granted NCTLD an access to the Pharmacovigilance Monitoring System (PViMS)

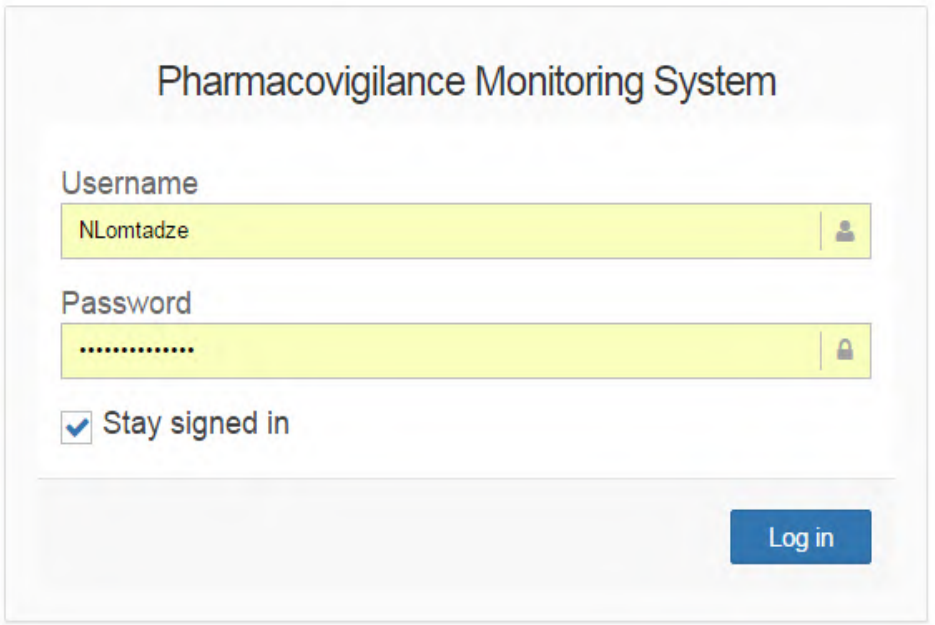
USAID FROM THE AMERICAN PEOPLE

SIAPS Systems for Improved Access to Pharmaceuticals and Services

PV|MS

Welcome to the SIAPS tool for strengthening pharmacovigilance services





aDSM Implementation (VII)

USAID/SIAPS TA

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SIAPS Systems for Improved Access to Pharmaceuticals and Services

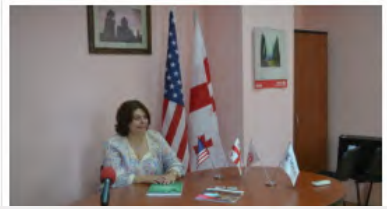
search

Home | About Us | How We Work | Health Areas | Where We Work | Tools and Guidance

SIAPS Launches Innovative Digital Health Tool in Georgia to Monitor Adverse Drug Reactions

JULY 25, 2016 PHARMACOVIGILANCE, SIAPS NEWS, TUBERCULOSIS

In April 2015, the US Agency for International Development (USAID) and Janssen Therapeutics officially launched the bedaquiline donation initiative. As part of this initiative, Janssen committed to providing bedaquiline at no cost to 30,000 patients with multidrug-resistant tuberculosis (MDR-TB) over a four-year period. Bedaquiline is the first anti-TB medicine to be approved by the U.S. Food and Drug Administration in more than 40 years and is considered a particularly significant development in the fight against MDR-TB. Georgia was the first country to request assistance from the bedaquiline donation program and required significant technical assistance to introduce this new medicine and active drug safety management.



The World Health Organization (WHO) emphasizes active pharmacovigilance in its companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (DR-TB) when treating patients with bedaquiline. An active pharmacovigilance regime helps ensure the safety of patients taking new medicines, and an active drug safety

ტუბერკულოზის ცენტრს ორგანიზაცია MSH-დან სტუმრობდნენ – ამერიკული გამოცდილების გაზიარება

July 11, 2016 | tbgeo | სიახლეები

პირველად საქართველოში, ტუბერკულოზისა და ფილტვის დაავადებათა ეროვნულ ცენტრს ორგანიზაცია MSH-დან სტუმრობდნენ. ჯილ პარამბირი, უფროსი ტექნიკური მრჩეველი და ანტონია ქვისიენი, ჯანმრთელობის მეცნიერებათა მენეჯერი, ცენტრის პერსონალის დასატრენინგებლად ჩამოვიდა.

aDSM Implementation (VIII)
Training

June 2016

- To facilitate the effective implementation of the Ministerial Decree regarding mandatory SAE reporting, a training materials and lectures were developed with participation of the NCTLD, USAID/SIAPS and MSF experts/consultants for TB doctors and programmatic staff

July 2016

- Within frames of the USAID/SIAPS program, implemented by MSH, the Phthisiologists and Pulmonologists Association of Georgia (GPPA), was engaged (Procurement Order No TRA103590) to conduct 3 days training of at least 200 Tuberculosis doctors and TB programmatic staff on active Drug Safety Monitoring and Management (aDSM)

Aug-Oct 2016

- By October 17th 2016, the training mission has been accomplished in Tbilisi and regions;
- Total of 275 TB doctors and PMDT staff have received the active PV training throughout the 16 training sessions of 3 days duration each covering the 100% of need;
- This is the first ever training on the topic of TB aDSM globally with the countrywide coverage of so many TB specialists.

aDSM Implementation (VIII)
Training

USAID FROM THE AMERICAN PEOPLE

SIAPS Systems for Improved Access to Pharmaceuticals and Services

CERTIFICATE OF TRAINING

To certify that

_____

Training Participant Name

Has successfully completed the training course on

"ACTIVE DRUG SAFETY MONITORING AND MANAGEMNET (aDSM): STANDARDIZED RECORDING AND REPORTING FOR SERIOUS ADVERSE EVENTS (SAE) AND ADVERSE EVENTS (AE) WITHIN TUBERCULOSIS PROGRAM IN GEORGIA"

Duration of the Training course from: ___/___/2016 to ___/___ /2016

Chinwe Owunna
Principal Technical Advisor for TB
Management Sciences for Health
US-VA-Arlington

Zaza Avaliani
Director
National Center For Tuberculosis and Lung Diseases
Tbilisi, Georgia

Lamara Vashakidze
Director
Association of Phthiziologists and Pulmonologists of Georgia

National Center for Tuberculosis and Lung Diseases

Reminder: Serious adverse event (SAE)

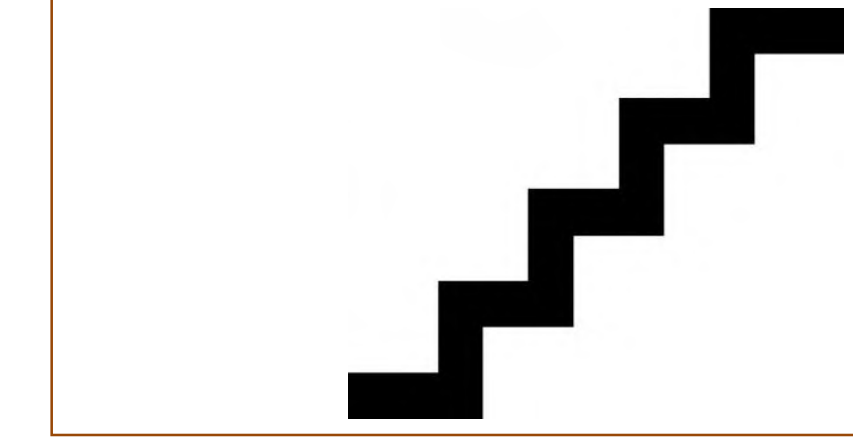
Any unfavorable or unintended sign/ symptom/ disease (incl. lab abnormality) that at any dose is:

	Fatal
	Immediately life threatening
	Leading to hospitalisation or prolongation of hospitalisation
	Leading to a significant disability / incapacity
	Birth defect or congenital anomaly
	Otherwise medically important, necessitating an intervention to prevent one of the above listed outcomes

If developed in a patent being on the SLD TB treatment is a subject to mandatory SAE reporting within 1 business day in Georgia

Reminder: Severity Grading Scale

SEVERITY= INTENSITY



SEVERITY ≠ SERIOUSNESS

How to use the Severity grading scale?

- Look for your diagnosis or your signs and symptoms in the list:
- e.g. Patient has ALT increase at 100 U/L (normal <40)

Condition term	Grade 1	Grade 2	Grade 3	Grade 4
Alanine Aminotransferase (ALT or SGPT) Increased	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN

- e.g. Patient presents vomiting continuously for 2 days, he is dehydrated and has to be hospitalized.

Condition term	Grade 1	Grade 2	Grade 3	Grade 4
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences requiring hospitalization or requiring parenteral nutrition

Severity General definition

Only use general score if the diagnosis or symptom is not found in the severity scale. If you are having trouble to decide which term to use - ask for help.

MILD Grade 1	MODERATE Grade 2	SEVERE Grade 3	Potentially LIFE-THREATENING Grade 4
• Transient or mild discomfort (<48 hours); • No medical intervention or therapy required.	• Mild to moderate limitation in activity, some assistance may be needed; • No or minimal medical intervention or 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 or therapy required, • Hospitalization or hospice care probable.

Source: DMID

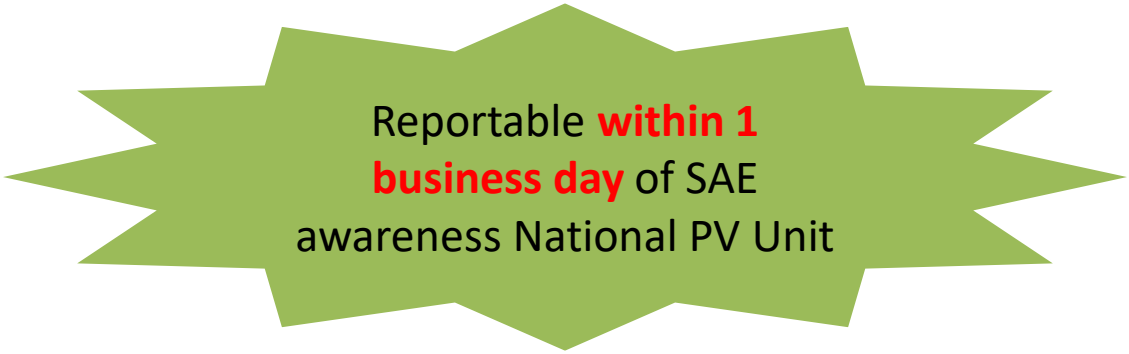
For labs and some medical conditions, detailed grading scales are available.

Medical judgment should always prevail!

SEVERITY = INTENSITY ≠ SERIOUSNESS

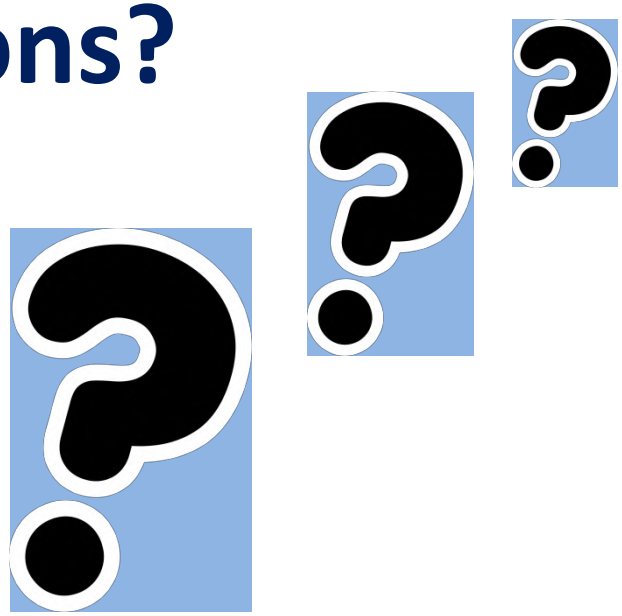
Medication errors

- Medication errors
  - Unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient.
  - (e.g. wrong drug prescribed, **overdose**).
- On an SAE Report Form.
- Associated or not with adverse events!



Thank you!

Questions?



Management of SAE data and causality analysis

Dr. Nino Lomtadze

USAID/Stop TB Partnership MDR-TB Clinical Consultant

Head of Surveillance and Strategic Planning Department

National Centre for Tuberculosis and Lung Diseases (NCTLD), Tbilisi, Georgia

Asia Regional Pharmacovigilance Workshop: Implementation of active TB drug-safety monitoring and management (aDSM) for New Drugs and Shortened Treatment Regimens for MDR TB

25-27 April, 2017

Bangkok, Thailand

Why do Causality Assessment?

- Assessment of the degree to which a reported event is causally associated with the suspected drug
- Causality Assessment considers the likelihood that the drug was responsible for causing the event

The logic of causality

For a 'perfect' causal relationship:

If A then B
If B then A

We can say:

It is raining, so my clothes are wet

But can we say:

My clothes are wet, so it is raining

Source of the slide: Geraldine Hill, Interregional PV Training, 3-5 March, 2014, Denmark

The logic of causality

It's raining; my clothes are wet.

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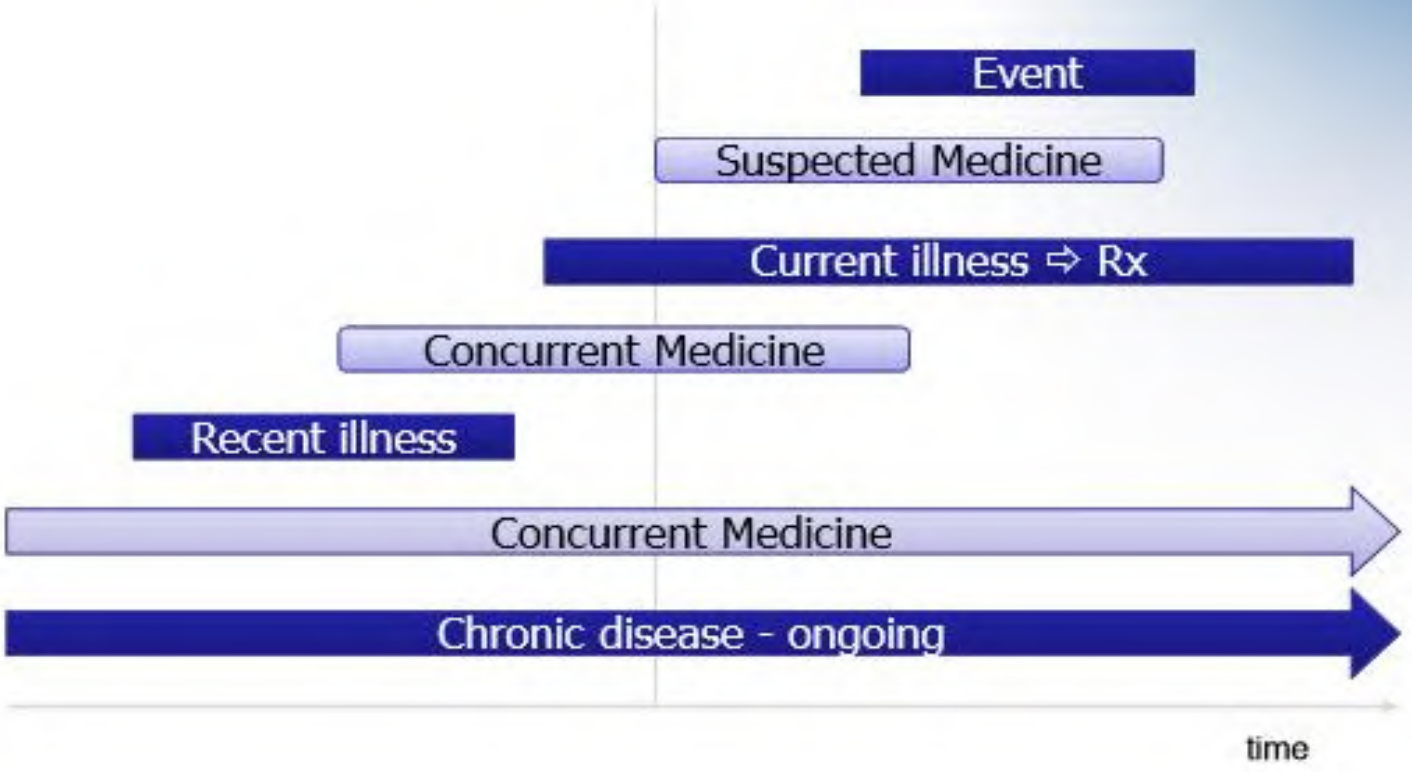
Source of the slide: Geraldine Hill, Interregional PV Training, 3-5 March, 2014, Denmark

Did the suspected medicine cause the event?



Source of the slide: Geraldine Hill, Interregional PV Training, 3-5 March, 2014, Denmark

How Causality Assessment is Accomplished

Naranjo algorithm

- Uses a series of 10 questions
- Questions can be answered as:
  Yes, *No* or *Do not know*
- Answers are weighted with scores ranging from -1 to +2
- Total score is ranked on a probability scale:

> 9	certain
5-8	probable
1-4	possible
0	unlikely

Naranjo algorithm

Naranjo, C. A., U. Busto, et al. (1981). "A method for estimating the probability of adverse drug reactions." Clin. Pharm. Ther. **30(2): 239-245.**

	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
Did the adverse reaction appear when the drug was readministered	+2	-1	0	
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
Did the reaction appear when a placebo was given?	-1	+1	0	
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0	
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score	

certain > 9; probable 5-8; possible 1-4; unlikely 0.

the UPPSALA MONITORING CENTRE

WHO-UMC Causality Categories

Event Parameters	Certain	Probable	Possible	Unlikely	Unclassified	Unassessable
Reasonable time relationship to drug exposure	+	+	+	-	Un-known	NA
No other explanation (drugs or disease)	+	+	-	-	Un-known	NA
Event is Definitive – Specific Problem	+	-	-	-	Un-known	NA
Positive De-challenge	+	+	Unclear	-	Un-known	NA
Positive Re-challenge	+	Unclear	Unclear	-	Un-known	NA

Causality Assessment Process

Check logic...

You should not assess...

Causality to be certain if:

- no rechallenge*, or outcome of rechallenge unknown

Causality to be probable if:

- there has been no dechallenge, or result of dechallenge is unknown
- outcome of event is unknown
- there are other possible causes of the event

*except where rechallenge is unnecessary to assign a 'certain' causal association e.g. anaphylaxis

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Source of the slide: Geraldine Hill, Interregional PV Training, 3-5 March, 2014, Denmark

Exceptions:

- Deaths

  Cannot be coded as probable because no opportunity to assess effect of dechallenge

  Possible

- Myocardial Infarction

  Many patients recover as part of the natural history of the disease; recovery is not a response to withdrawal of the drug, so dechallenge is meaningless

  Possible

- Stroke

  Variable natural outcomes; dechallenge meaningless

  Possible

- Anaphylaxis

  Obviously a direct relationship (without rechallenge!!!)

  Certain

Source of the slide: Geraldine Hill, Interregional PV Training, 3-5 March, 2014, Denmark

SUMMARY

- Use of a causality assessment method provides structured approach to assessing the relationship between drug and adverse event
- Causality assessment deals with probability
- There is no gold standard for causality assessment
- WHO-UMC method is widely used
- Depends on quality of the information
- Different assessors may draw different conclusions based on the same information

aDSM Preliminary SAE Results from Georgia

- Before mandatory SAE reporting (June 2016), the safety reports were being collected under MSF end-TB project output 1, staring April 2015 and reported to the NCTLD;

- As of September 2016 total number of **37 SAE** terms have been reported that have encountered to 23 out of 283 patients enrolled on new TB drugs, thus around 8% of patients developed at least one SAE;

- Out of the 23 SAE patients 8 were on Delamanid, with 10 SAEs and 15 were on Bedaquiline, with 27 SAEs

- Out of these 37 SAEs, 30 developed to males (81%) and 7 to females (19%);

- Age (years): Mean - 43, Median – 44, Mode – 38, Min-Max: 15 – 63;

aDSM Preliminary SAE Results from Georgia (Cont'd)

- **As of December 2016:**
- total number of 76 SAE terms have been reported that have encountered to 53 out of 353 patients enrolled on new TB drugs, thus around 15% of patients developed at least one SAE
- 40 SAE terms have been reported only within September 2016- March 2017, compared to just 37 SAE terms that have been reported from April 2015 to September 2016. So we observe greatly increased SAE recognition and reporting practices after countrywide aDSM training in Georgia that was conducted from August 24 to October 8th, 2016. Doctors have become much more alert on adverse events that would have been missed before training and underreported.
- Out of these 40 SAEs: 1 was fatal SAEs, compared to before training reported ones where the majority where death reports (again training effect on identifying SAEs other than death); 17 (42%) were hepatitis, 3 (7,5%) were QTc prolongation; 3 (7.5%) were peripheral neuropathy; 3 (7.5%) were acute GI events; 1 (2.5%) was facial burns, the remaining 11 SAEs were solitary cases of allergic reactions, delirium tremens, unstable angina, Bronchopneumonia, pruritus, pneumothorax, empyema, meningitis, Pompholyx, hyperbilirubinemia.

aDSM Preliminary SAE Results from Georgia: Reported SAE Terms

#	SAE term	Frequency	Percent
1	Acute kidney injury	1	2.70%
2	Asphyxia (DLM)	1	2.70%
3	Blood bilirubin increased	1	2.70%
4	Cardiac arrest (DLM)	1	2.70%
5	Cardiac failure	1	2.70%
6	Cardiogenic shock (DLM)	1	2.70%
7	Cardiopulmonary failure	1	2.70%
8	Completed suicide	2	5.40%
9	Concussion	1	2.70%
10	Death	2	5.40%
11	Dizziness (DLM)	1	2.70%
12	Electrocardiogram QT interval	1	2.70%
13	Electrocardiogram QT prolonged (DLM)	2	5.40%
14	Headache (DLM)	1	2.70%
15	Hepatic enzyme increased	1	2.70%
16	Hepatitis	1	2.70%

aDSM Preliminary SAE Results from Georgia: Reported SAE Terms (cont'd)

#	SAE term	Frequency	Percent
17	Hepatotoxicity	2	5.40%
18	Hyperbilirubinaemia	1	2.70%
19	Hypersensitivity	1	2.70%
20	Hypotension	1	2.70%
21	Infectious pleural effusion	1	2.70%
22	Leriche syndrome	1	2.70%
23	Metabolic encephalopathy	1	2.70%
24	Psychotic disorder	1	2.70%
25	Pulmonary haemorrhage (DLM)	1	2.70%
26	Pyo-pneumothorax (DLM)	1	2.70%
27	Renal failure	1	2.70%
28	Respiratory failure	3	8.10%
29	Road traffic accident	1	2.70%
30	Sudden death (DLM)	1	2.70%
31	Vomiting	1	2.70%
	Total	37	100.00%

aDSM Preliminary SAE Results from Georgia: Criteria for Seriousness*

	Fatal	26	70%
	Immediately life threatening	3	8%
	Leading to hospitalisation or prolongation of hospitalisation	13	35%
	Leading to a significant disability / incapacity	0	0%
	Birth defect or congenital anomaly	0	0%
	Otherwise medically important, necessitating an intervention to prevent one of the above listed outcomes	6	16%

***The Initial and follow up SAE reports received for some patients were qualifying more than one seriousness criteria**

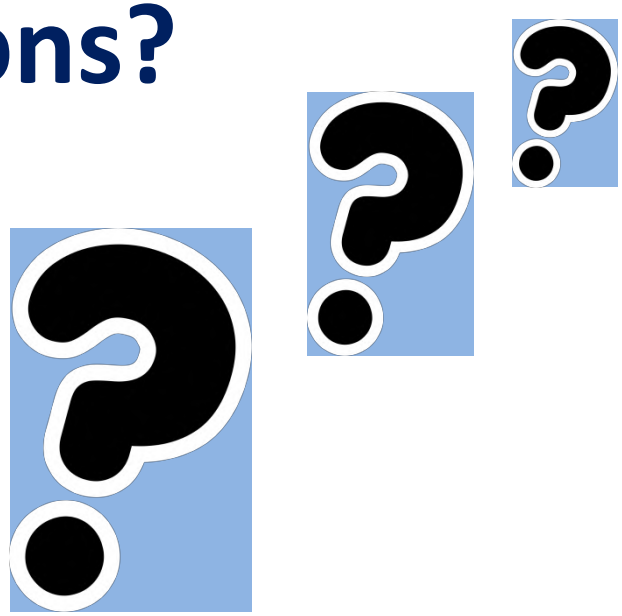
aDSM Preliminary SAE Results from Georgia: SAE Severity and Outcomes

SAE Severity	Frequency	Percent
Grade 1	2	5.40%
Grade 2	1	2.70%
Grade 3	4	10.80%
Grade 4	30	71.10%
Total	37	100%

SAE Outcome	Frequency	Percent
Fatal	26	70.30%
Not recovered/Not resolved	2	5.40%
Recovered/Resolved	8	21.60%
Recovering/Resolving	1	2.70%
Total	37	100.00%

Thank you!

Questions?



Welcome to Georgia!

Designing an ADR/SAE system: from the patient to national and global levels

Anh Innes, MD
Chief of Party, Control and Prevention of Tuberculosis Project
Clinical Assistant Professor of Medicine (Adjunct)
University of California San Francisco

USAID FROM THE AMERICAN PEOPLE

fhi360 THE SCIENCE OF IMPROVING LIVES

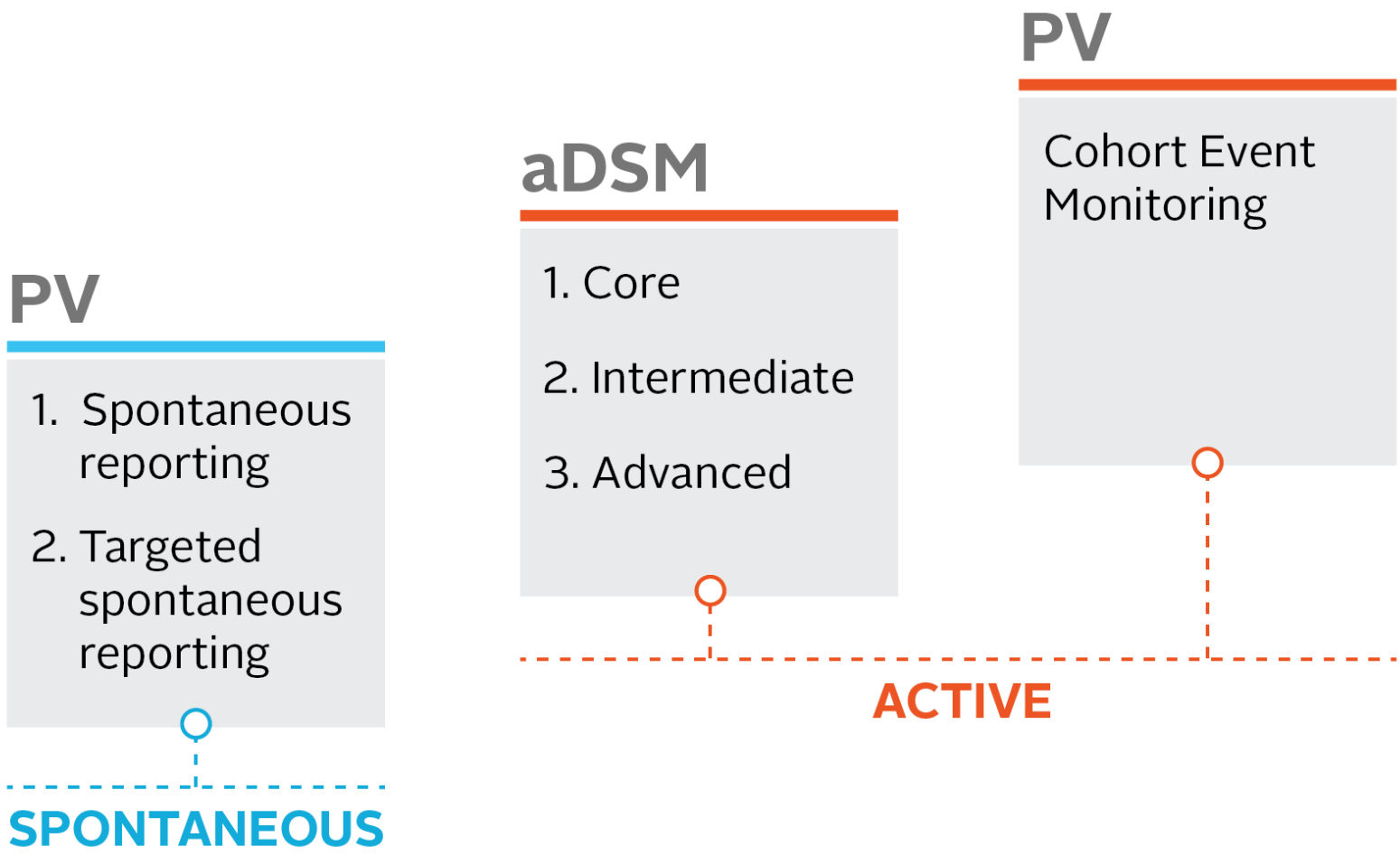
CAP-TB CONTROL AND PREVENTION OF TUBERCULOSIS

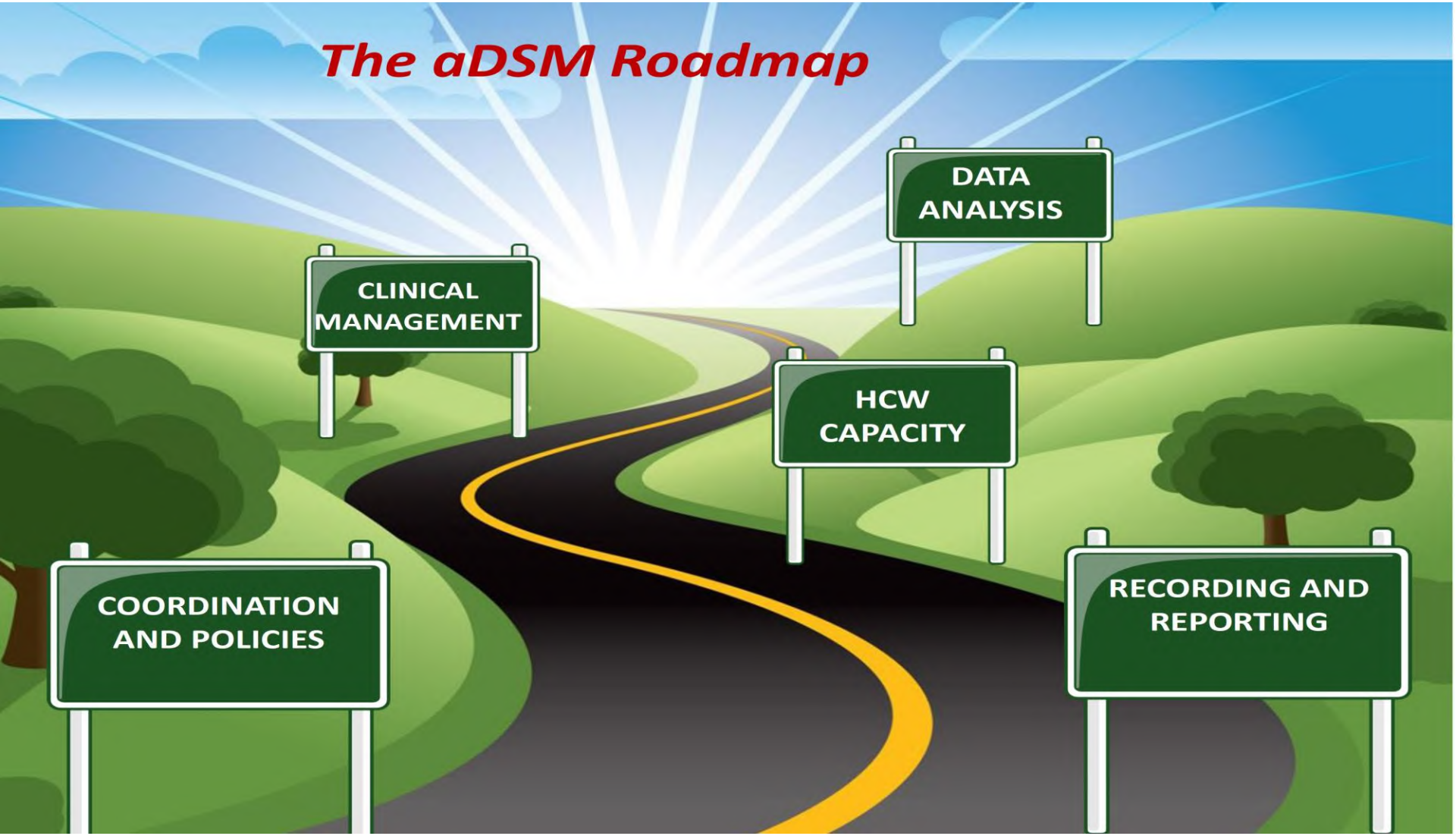
Pharmacovigilance

The science and activities relating to the **detection, assessment, understanding, and prevention** of adverse effects or any other possible drug-related problems.

The Importance of Pharmacovigilance, WHO, 2002

Spectrum of aDSM and pharmacovigilance




The aDSM Roadmap
DATA ANALYSIS
CLINICAL MANAGEMENT
HCW CAPACITY
COORDINATION AND POLICIES
RECORDING AND REPORTING

Coordination and Policies

Recording and reporting

Health care worker capacity

Which AEs are reported for aDSM?

Adverse Event	Level of aDSM
Serious	Core, Intermediate, and Advanced
Special interest	Intermediate and Advanced
Clinically significant	Advanced

AEs of Special Interest: Documented during clinical trial and of interest to report, independent of seriousness, severity, or causality.

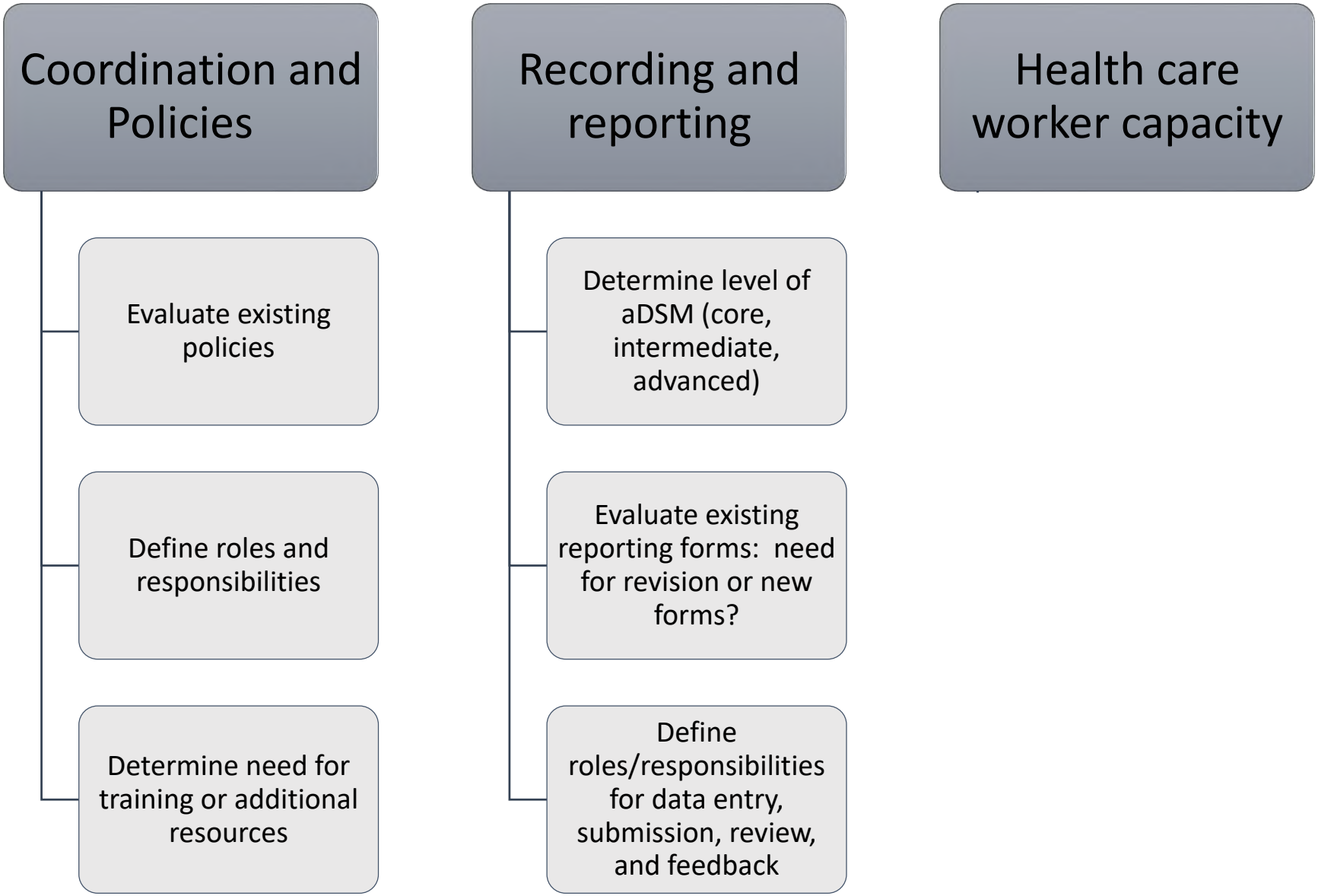
For intermediate and advanced aDSM

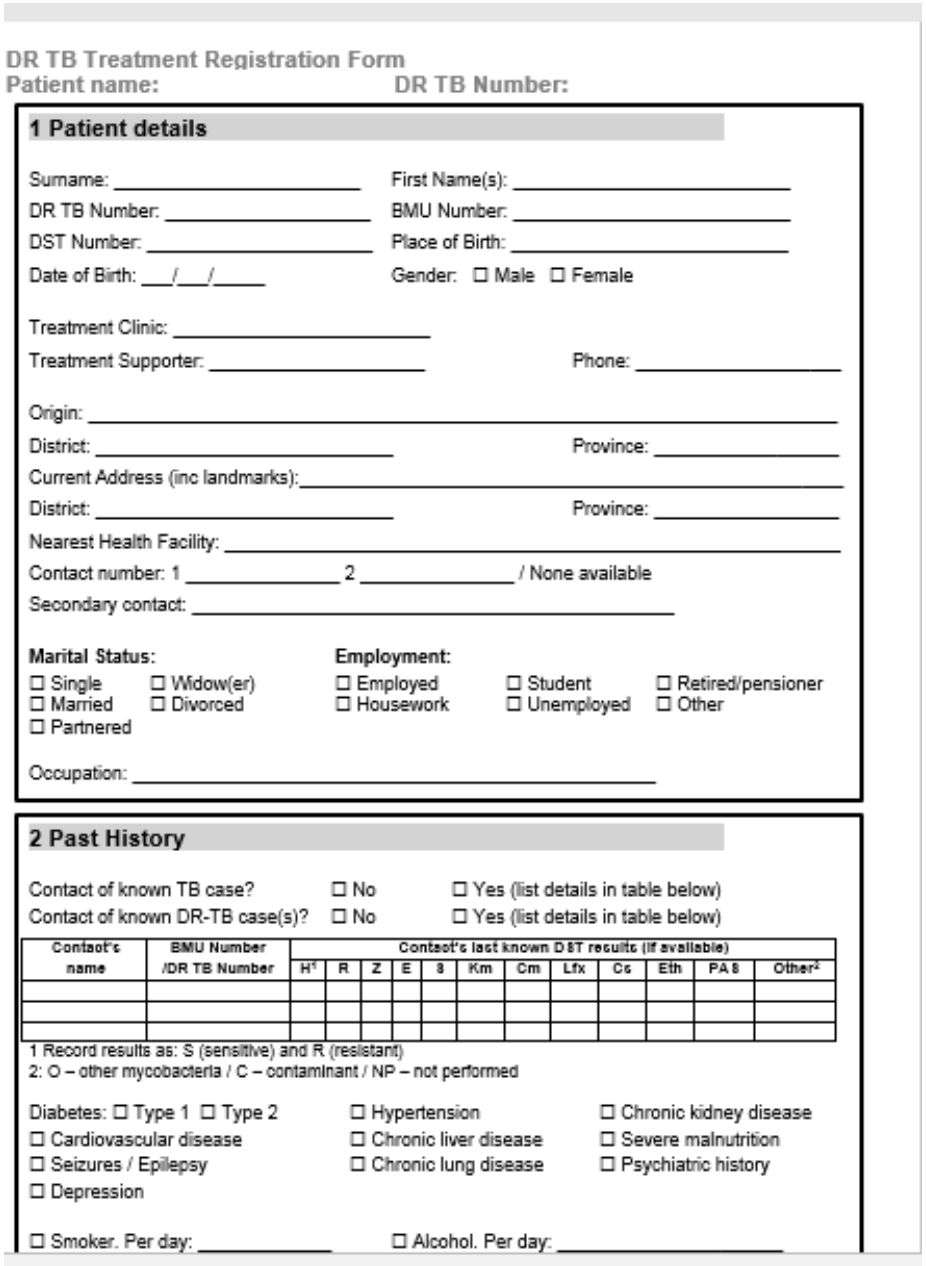
- Peripheral neuropathy (paresthesia),
- Psychiatric disorders and central nervous system toxicity
- Optic nerve disorder (optic neuritis) or retinopathy
- Ototoxicity
- Myelosuppression
- Prolonged QT interval
- Lactic acidosis
- Hepatitis
- Hypothyroidism,
- Hypokalemia,
- Pancreatitis
- Phospholipidosis
- Acute kidney injury (acute renal failure)

AEs of Clinical Significance: *Advanced aDSM*

Adverse event that meets any of the below criteria:

- Serious
- Of special interest
- Leads to discontinuation or change in drug dosage or treatment
- Is judged as otherwise clinically significant by the clinician, even if not listed as “special interest”


Coordination and Policies
Evaluate existing policies
Define roles and responsibilities
Determine need for training or additional resources
Recording and reporting
Determine level of aDSM (core, intermediate, advanced)
Evaluate existing reporting forms: need for revision or new forms?
Define roles/responsibilities for data entry, submission, review, and feedback
Health care worker capacity



DR TB Treatment Registration Form

Patient name: DR TB Number:

1 Patient details

Surname: _____ First Name(s): _____

DR TB Number: _____ BMU Number: _____

DST Number: _____ Place of Birth: _____

Date of Birth: ___/___/_____ Gender: ☐ Male ☐ Female

Treatment Clinic: _____

Treatment Supporter: _____ Phone: _____

Origin: _____

District: _____ Province: _____

Current Address (inc landmarks): _____

District: _____ Province: _____

Nearest Health Facility: _____

Contact number: 1 _____ 2 _____ / None available

Secondary contact: _____

Marital Status:

☐ Single ☐ Widow(er) ☐ Married ☐ Divorced ☐ Partnered

Employment:

☐ Employed ☐ Student ☐ Retired/pensioner ☐ Housework ☐ Unemployed ☐ Other

Occupation: _____

2 Past History

Contact of known TB case? ☐ No ☐ Yes (list details in table below)

Contact of known DR-TB case(s)? ☐ No ☐ Yes (list details in table below)

Contact's name	BMU Number /DR TB Number	Contact's last known DST results (if available)											
		H[1]	R	Z	E	S	Km	Cm	Lfx	Cs	Eth	PAS	Other[2]

1 Record results as: S (sensitive) and R (resistant)

2: O – other mycobacteria / C – contaminant / NP – not performed

Diabetes: ☐ Type 1 ☐ Type 2 ☐ Cardiovascular disease ☐ Seizures / Epilepsy ☐ Depression

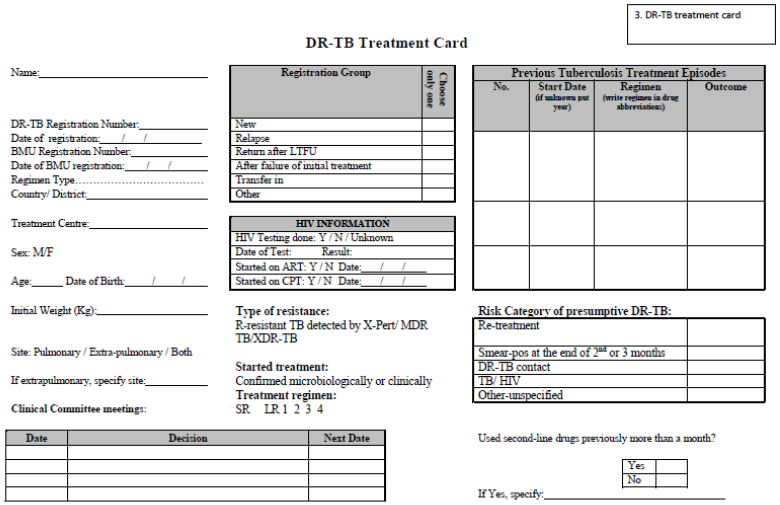
☐ Hypertension ☐ Chronic liver disease ☐ Chronic lung disease

☐ Chronic kidney disease ☐ Severe malnutrition ☐ Psychiatric history

☐ Smoker. Per day: _____ ☐ Alcohol. Per day: _____

Treatment registration: adapted Western province and ADDED as new form (in addition to clinic chart)

Monthly follow-up: REVISED existing form (DR-TB Treatment Card) to add detailed clinical monitoring table



3. DR-TB treatment card

DR-TB Treatment Card

Name: _____

DR-TB Registration Number: _____

Date of registration: ___/___/___

BMU Registration Number: _____

Date of BMU registration: ___/___/___

Regimen Type: _____

Country/ District: _____

Treatment Centre: _____

Sex: M/F

Age: _____ Date of Birth: ___/___/___

Initial Weight (Kg): _____

Site: Pulmonary / Extra-pulmonary / Both

If extrapulmonary, specify site: _____

Clinical Committee meetings:

Date	Decision	Next Date

Registration Group	Choose only one
New	
Relapse	
Return after LTFU	
After failure of initial treatment	
Transfer in	
Other	

HIV INFORMATION
HIV Testing done: Y / N / Unknown
Date of Test: Result:
Started on ART: Y / N Date: ___/___/___
Started on CPT: Y / N Date: ___/___/___

Type of resistance:
R-resistant TB detected by X-Pert/ MDR TB/XDR-TB

Started treatment:
Confirmed microbiologically or clinically

Treatment regimen:
SR LR 1 2 3 4

Previous Tuberculosis Treatment Episodes			
No.	Start Date (if unknown put year)	Regimen (write regimen in drug abbreviations)	Outcome

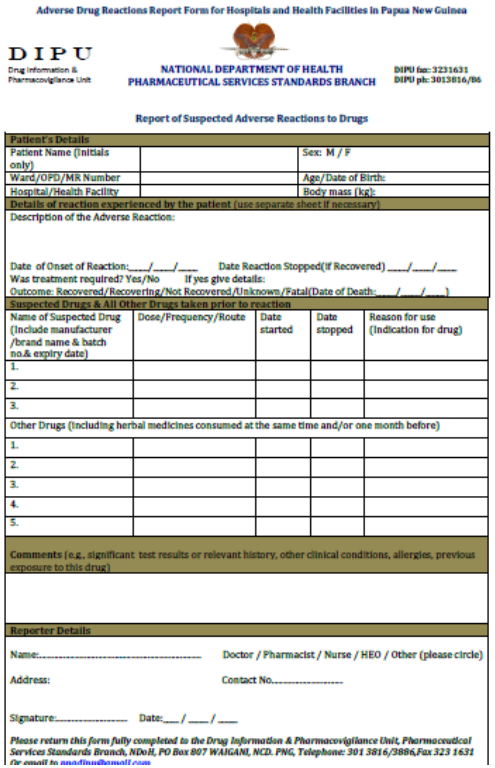
Risk Category of presumptive DR-TB:

Re-treatment	
Smear-pos at the end of 2nd or 3 months	
DR-TB contact	
TB/ HIV	
Other-unspecified	

Used second-line drugs previously more than a month?

Yes	
No	

If Yes, specify: _____



Adverse Drug Reactions Report Form for Hospitals and Health Facilities in Papua New Guinea

DIPU
Drug Information & Pharmacovigilance Unit

NATIONAL DEPARTMENT OF HEALTH
PHARMACEUTICAL SERVICES STANDARDS BRANCH

DIPU fax: 3231631
DIPU ph: 3013816/86

Report of Suspected Adverse Reactions to Drugs

Patient's Details			
Patient Name (Initials only)		Sex: M / F	
Ward/OPD/MR Number		Age/Date of Birth:	
Hospital/Health Facility		Body mass (kg):	

Details of reaction experienced by the patient (use separate sheet if necessary)

Description of the Adverse Reaction:

Date of Onset of Reaction:____/____/____ Date Reaction Stopped(if Recovered) ____/____/____
Was treatment required? Yes/No If yes give details:
Outcome: Recovered/Recovering/Not Recovered/Unknown/Fatal(Date of Death:____/____/____)

Suspected Drugs & All Other Drugs taken prior to reaction

Name of Suspected Drug (Include manufacturer /brand name & batch no.& expiry date)	Dose/Frequency/Route	Date started	Date stopped	Reason for use (Indication for drug)
1.				
2.				
3.				
Other Drugs (including herbal medicines consumed at the same time and/or one month before)				
1.				
2.				
3.				
4.				
5.				

Comments (e.g., significant test results or relevant history, other clinical conditions, allergies, previous exposure to this drug)

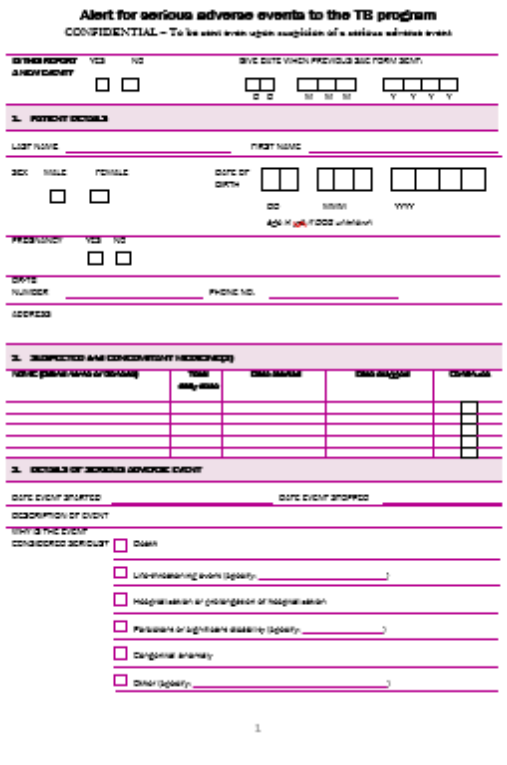
Reporter Details

Name:..... Doctor / Pharmacist / Nurse / HEO / Other (please circle)

Address: Contact No.....

Signature:..... Date:___/___/___

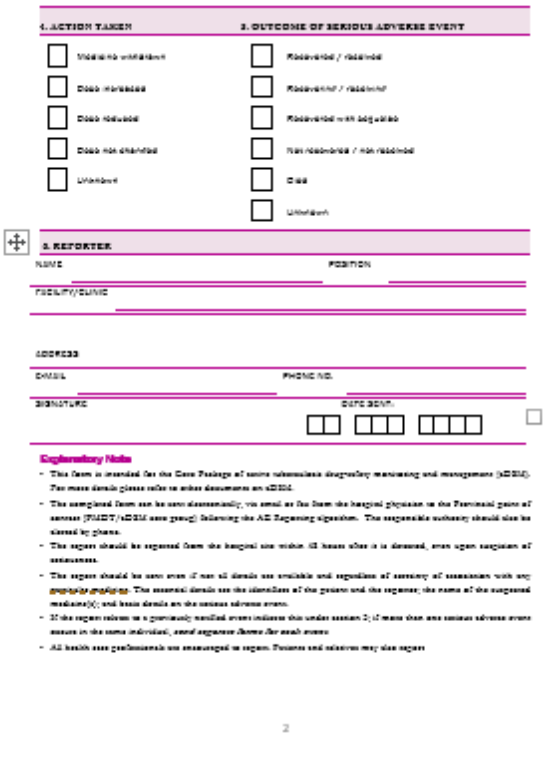
Please return this form fully completed to the Drug Information & Pharmacovigilance Unit, Pharmaceutical Services Standards Branch, NDoH, PO Box 807 WAIGANI, NCD. PNG, Telephone: 301 3816/3886,Fax 323 1631 Or email to medinedhomail.com



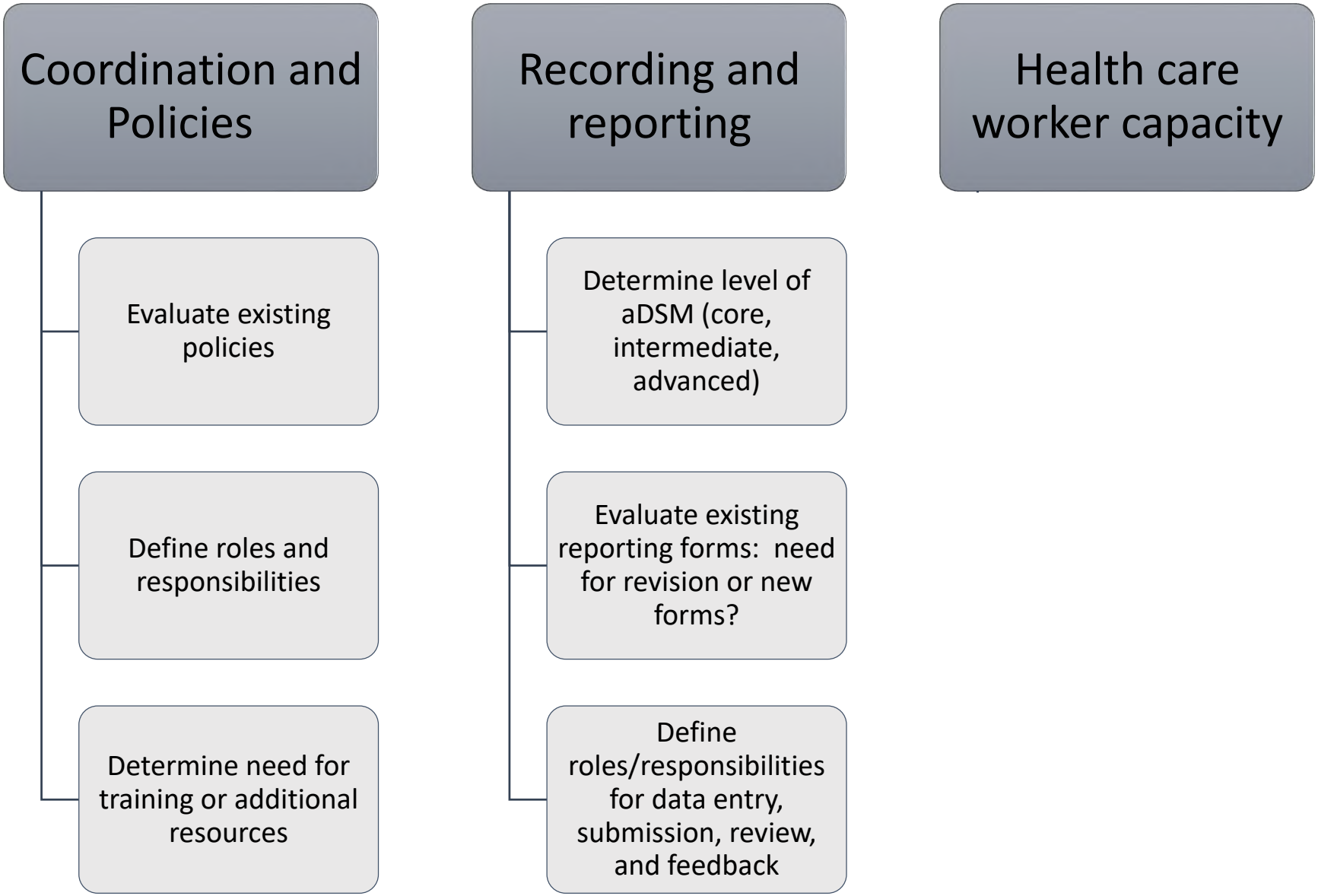
Alert for serious adverse events to the TB program

CONFIDENTIAL – To be sent even upon completion of a serious adverse event

1



2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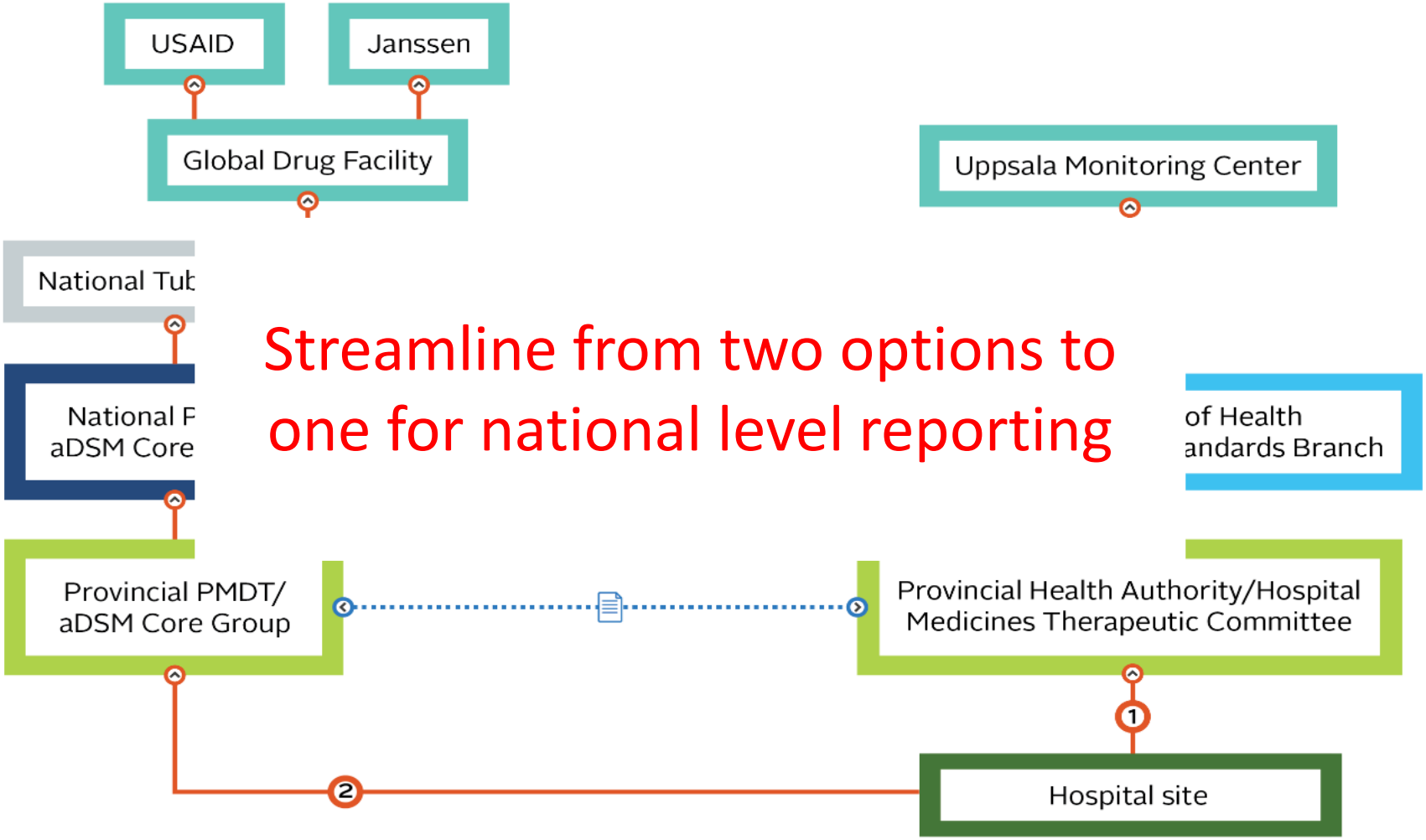
Health care worker capacity

PNG: provincial, national, and global AE/ADR reporting algorithm for bedaquiline



How can aDSM (system and data) be used?

Provincial

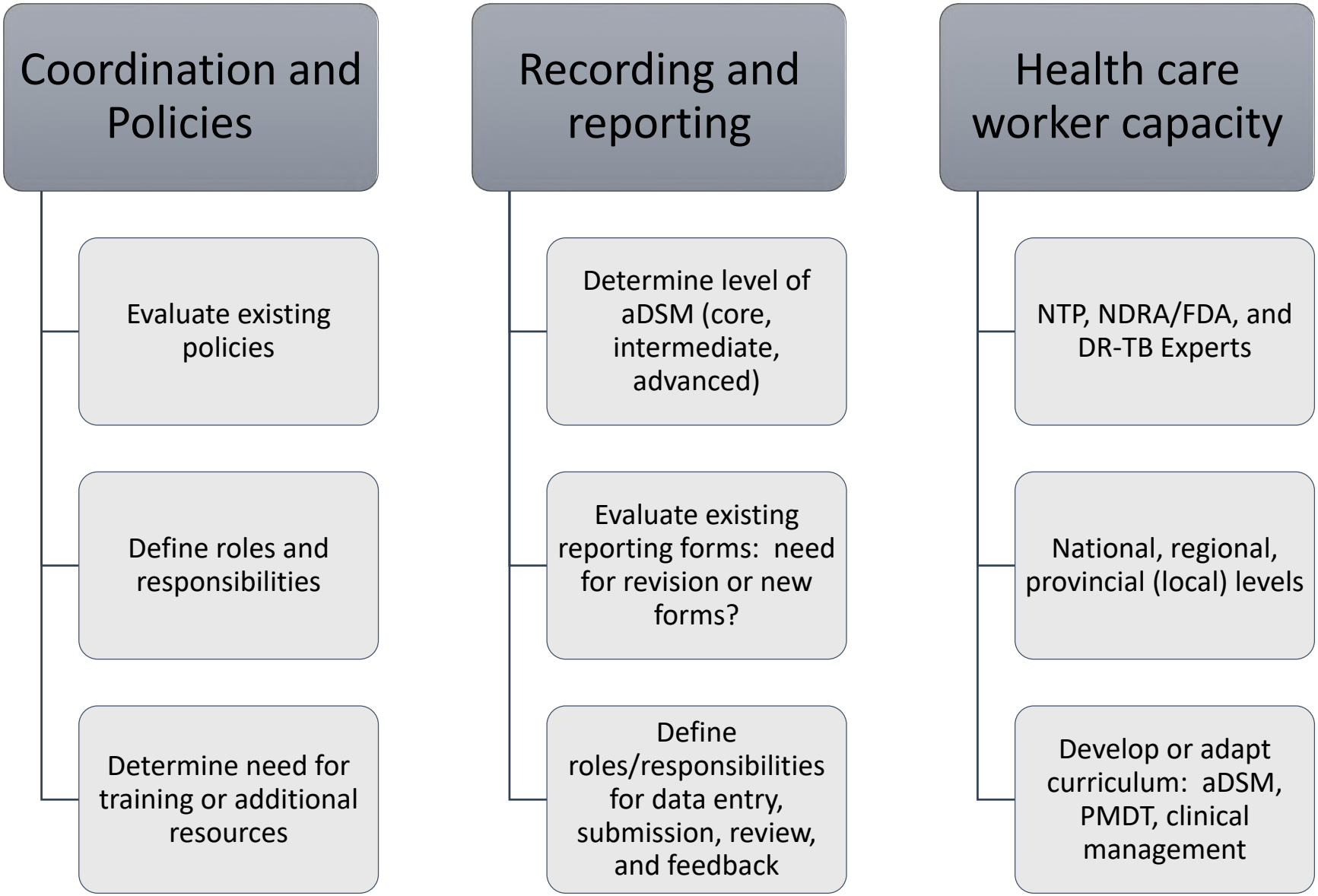
National

Global

National level cohort monitoring and case-based trainings

- Build capacity for XDR-TB, or new drug sites, through case-based trainings
  - NTP: Updates on XDR-TB, new/repurposed drug, shorter MDR-TB regimen enrollment
  - NDRA/FDA: report AEs and ADRs

- Goals:
  - Increase exposure to clinical dilemmas and decisions: sites learn from each other
  - Identify potential, addressable issues: e.g., QTcF using regimen with multiple QTcF-prolonging drugs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Define roles/responsibilities for data entry, submission, review, and feedback
Health care worker capacity
NTP, NDRA/FDA, and DR-TB Experts
National, regional, provincial (local) levels
Develop or adapt curriculum: aDSM, PMDT, clinical management

Causality Assessment: Prep for Group Work

Anh Innes, MD
Chief of Party, Control and Prevention of Tuberculosis Project
Clinical Assistant Professor of Medicine (Adjunct)
University of California San Francisco

USAID FROM THE AMERICAN PEOPLE

fhi360 THE SCIENCE OF IMPROVING LIVES

CAP-TB CONTROL AND PREVENTION OF TUBERCULOSIS

60+ woman with previous, multiple treatment for PTB now with MDR-TB. At baseline, LE edema (not diagnosed). Initiated on Km/Lfx/Eto-PAS/Cs/Z and tolerated well for 7 months. Then developed hand/feet “stiffening”, weakness, blurry vision, and mild confusion that worsened over 6 weeks.

Progressed to tetany, then found to be severely hypocalcemic (Ca2+ not routinely done thus no baseline; only one value). Patient died .

Dr. Christopher Ope, Eastern Highlands Provincial Hospital, Papua New Guinea

How do we define the event?

CHOOSE THE MAIN EVENT	
❑ Hypocalcemia	*1.19 mmol/L; severely decreased*
❑ Stiffening of hands and feet	*Muscle cramps? Potentially due to hypocalcemic tetany?*
❑ Generalized weakness	*From electrolyte disorders or something else?*
❑ Lower limb weakness and edema	*Cardiac? Would expect this to have been present at admission if CHF severe enough to cause death*
❑ Blurry vision	*Decreased level of consciousness or just blurry vision? Vertigo?*
❑ Partial deafness	*Acute onset or due to regimen?*

What is the level of severity for hypocalcemia, 1.19 mmol/L?

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.					

Is this a reportable adverse event for core level of aDSM?

A serious adverse event is one that leads to any of the following:
❑ Death
❑ Immediately life-threatening
❑ Hospitalization of prolongation of hospitalization
❑ Persistent or significant disability
❑ Congenital anomaly/birth defect
❑ Also included: AEs that do not immediately lead to above but require treatment to prevent the above

Suspected and Concomitant Medicines

Suspected	Concomitant
PZA	Pyridoxine
Kanamycin	
Levofloxacin	
Ethionamide	
PAS	
Cycloserine	

AE: Actions Taken

Action taken
❑ Medication withdrawn
❑ Dose increased
❑ Dose reduced
■ Dose not changed
❑ Unknown

AE outcome at the time of the report

Outcomes	Comments
❑ Recovered/resolved	Fully stabilized, back to baseline
❑ Recovering/resolving	Improving but still not back at baseline
❑ Recovered with sequelae	Fully stabilized but some permanent condition will remain (e.g. hearing loss after permanent stop of injectable)
❑ Not recovered/not resolved	Still ongoing
■ Died	Fatal
❑ Unknown	Outcome is unknown (e.g.., LTFU)

Alert for serious adverse events to the TB program

CONFIDENTIAL – [illegible]

IS THIS REPORT A NEW EVENT? YES ☐ NO ☐ | GIVE DATE WHEN PREVIOUS SAE FORM SENT: ☐☐ D D ☐☐☐ M M M ☐☐☐☐ Y Y Y Y

1. PATIENT DETAILS

LAST NAME ______ FIRST NAME ______

SEX MALE ☐ FEMALE ☐ | DATE OF BIRTH ☐☐ ☐☐☐ ☐☐☐☐ DD MMM YYYY

Age in yrs if DOB unknown

PREGNANCY YES ☐ NO ☐

DRTB NUMBER ______ PHONE NO. ______

ADDRESS

2. SUSPECTED AND CONCOMITANT MEDICINE(S)

NAME (generic name or brand)	Total daily dose	Date started	Date stopped	[illegible]
				☐
				☐
				☐
				☐
				☐

3. DETAILS OF SERIOUS ADVERSE EVENT

DATE EVENT STARTED ______ DATE EVENT STOPPED ______

DESCRIPTION OF EVENT

WHY IS THE EVENT CONSIDERED SERIOUS?

- ☐ Death
- ☐ Life-threatening event (specify: ______)
- ☐ Hospitalisation or prolongation of hospitalisation
- ☐ Persistent or significant disability (specify: ______)
- ☐ Congenital anomaly
- ☐ Other (specify: ______)

4. ACTION TAKEN

- ☐ Medicine withdrawn
- ☐ Dose increased
- ☐ Dose reduced
- ☐ Dose not changed
- ☐ Unknown

5. OUTCOME OF SERIOUS ADVERSE EVENT

- ☐ Recovered / resolved
- ☐ Recovering / resolving
- ☐ Recovered with sequelae
- ☐ Not recovered / not resolved
- ☐ Died
- ☐ Unknown

6. REPORTER

NAME ______ POSITION ______

FACILITY/CLINIC ______

ADDRESS

E-MAIL ______ PHONE NO. ______

SIGNATURE | DATE SENT: ☐☐ ☐☐☐ ☐☐☐☐

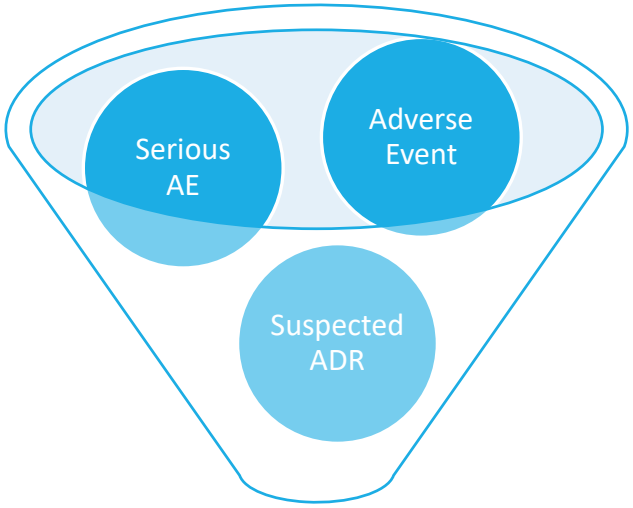
Explanatory Note

- This form is intended for the Core Package of active tuberculosis drug-safety monitoring and management (aDSM). For more details please refer to other documents on aDSM.
- The completed form can be sent electronically, via email or fax from the hospital physician to the Provincial point of contact (PMDT/aDSM core group) following the AE Reporting algorithm. The responsible authority should also be alerted by phone.
- The report should be reported from the hospital site within 24 hours after it is detected, even upon suspicion of seriousness.
- The report should be sent even if not all details are available and regardless of certainty of association with any particular medicine. The essential details are the identifiers of the patient and the reporter, the name of the suspected medicine(s) and basic details on the serious adverse event.
- If the report relates to a previously notified event indicate this under section 3; if more than one serious adverse event occurs in the same individual, send separate forms for each event.
- All health care professionals are encouraged to report. Patients and relatives may also report.

Level of relationship between event and exposure: hypocalcemic tetany and drug/regimen

Level	*Time to event plausible?*	*Other explanation excluded?*	*Recovery after dechallenge?*	*Recurrence after rechallenge?*
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No or ?
Possible	Yes	No or ?	?	No or ?
Unlikely	No	No or ?	No	No or ?
Unassessable	Yes	0	0	0

Causality assessment: distinguishes AE from ADR



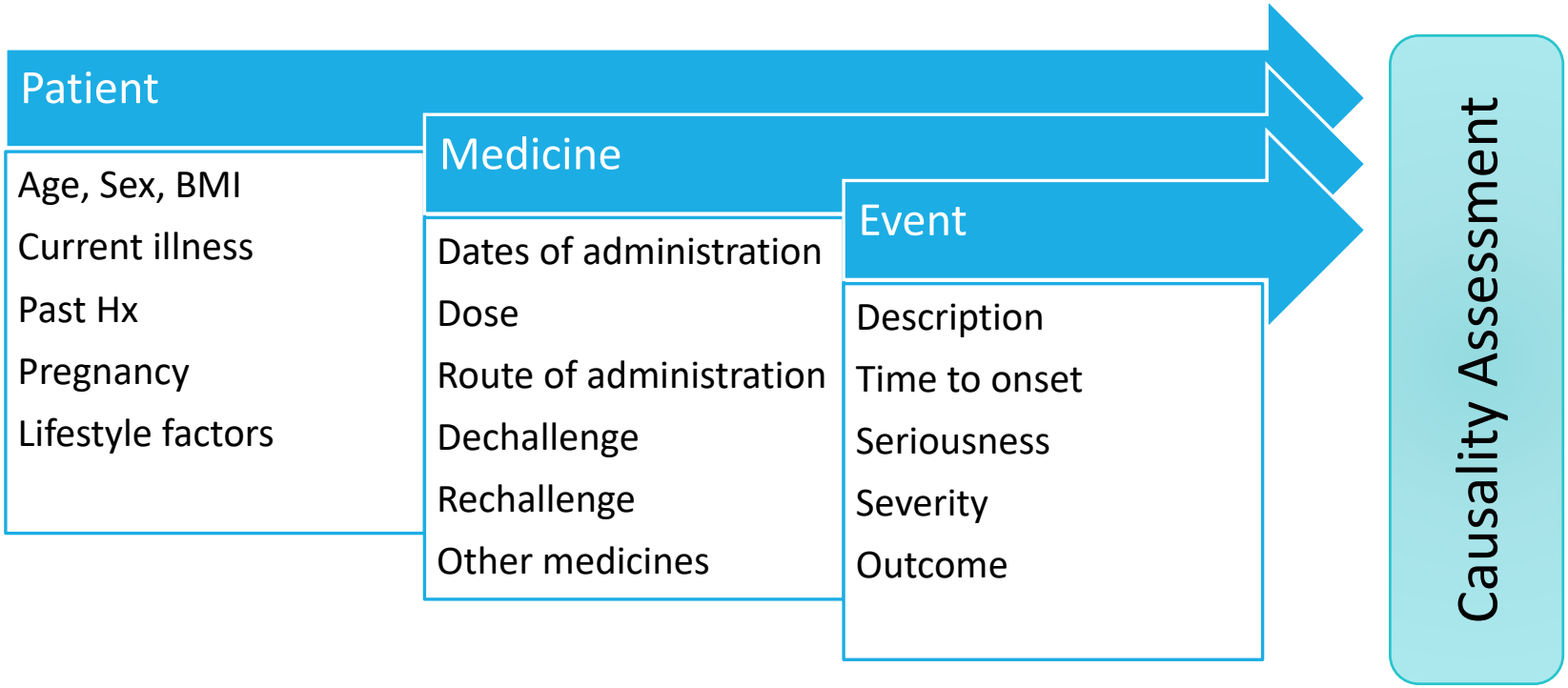
Level of aDSM will influence which cases undergo causality assessment.

Adverse Event	Level of aDSM
Serious	Core, Intermediate, and Advanced
Special interest	Intermediate and Advanced
Clinically significant	Advanced

Causality Assessment

- Who conducts the assessment? I.e., who determines whether the event was related to the drug/regimen?
  - Site level: data easily available, can be done quickly
  - National level: less subjectivity, likely delayed
- At national level, is there a "Causality Assessment Committee" that evaluates reports (quarterly, semi-annually)?
  - DR-TB expert, clinical specialists ("on call" depending on specific cases), pharmacologist, toxicologist

Multiple data variables required to accurately determine causality: the more data, the better



aDSM Serious Adverse Event Causality Assessment Check Sheet

Complete the following summary information:

TB regimen		Start date	
		Stop date (if applicable)	

SAE		Onset date	
		Time to onset (days)[i]	

Seriousness criteria	SAE Outcome
☐ Death	☐ Died
☐ Life-threatening	☐ Recovered
☐ Hospital admission or extension of hospital stay	☐ Recovering
☐ Persistent or significant disability or incapacity	☐ Recovered with sequelae
☐ Congenital abnormality	☐ Not recovered

Answer YES or NO to the following 10 questions:

SAE		
1	Is the SAE a well-defined, specific event?	
Time to onset		
2	Did the event start AFTER the TB treatment regimen was started?	
3	Is the time-to-onset consistent with the pathology of the SAE and the pharmacokinetics of the medicine(s) concerned (i.e., is there a plausible time relationship between the medicine and the SAE)?	
Other possible causes		
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Dechallenge		
5	Were any of the medicines stopped?	
6	Did the patient recover from the SAE after stopping the medicine(s)? *Yes = positive dechallenge* *No = negative dechallenge*	
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What is the causal relationship?

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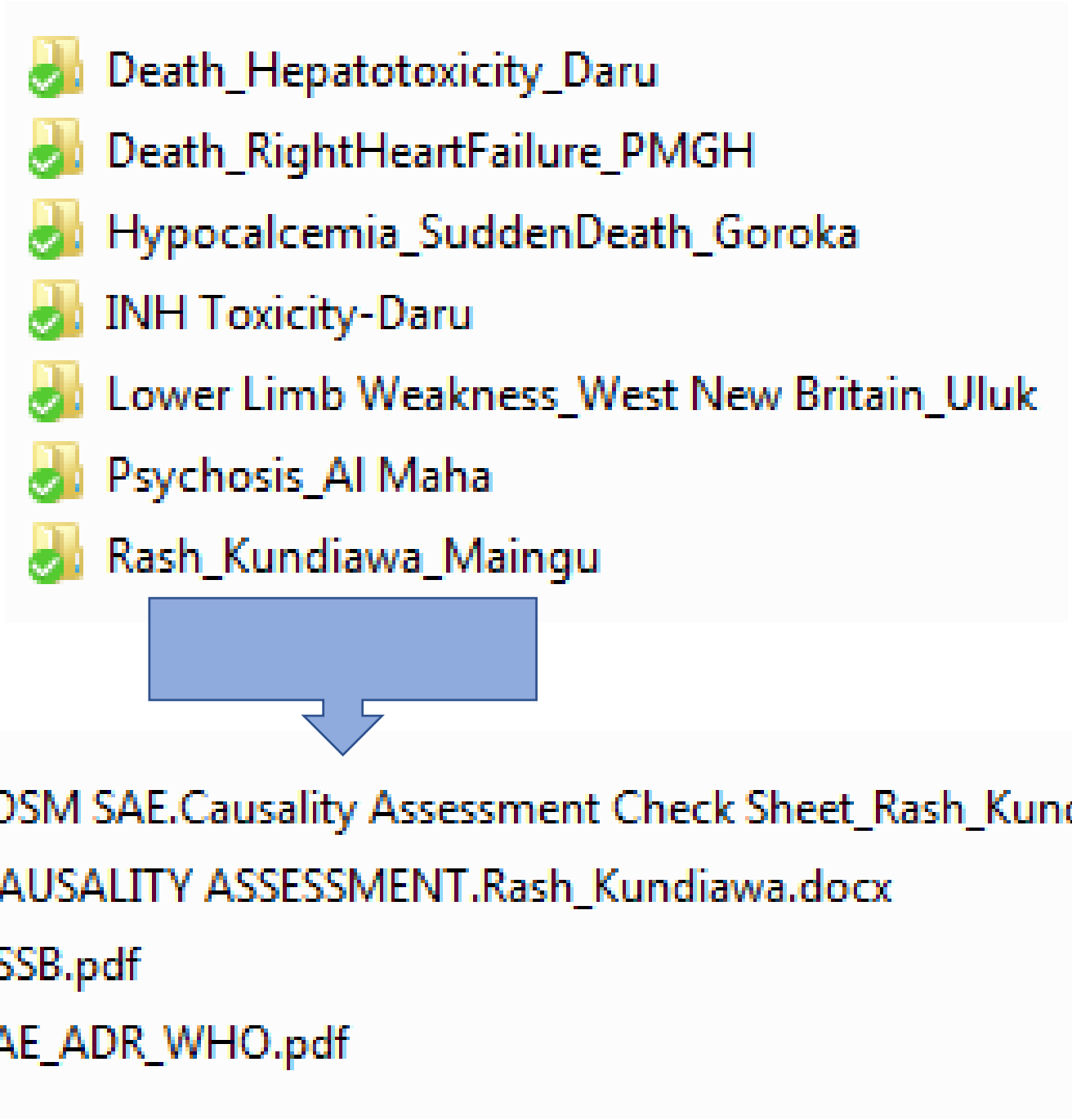
Death_Hepatotoxicity_Daru
Death_RightHeartFailure_PMGH
Hypocalcemia_SuddenDeath_Goroka
INH Toxicity-Daru
Lower Limb Weakness_West New Britain_Uluk
Psychosis_Al Maha
Rash_Kundiawa_Maingu
aDSM SAE.Causality Assessment Check Sheet_Rash_Kundi...
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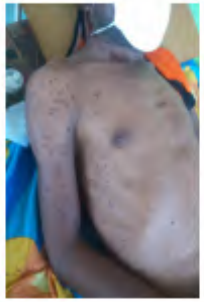

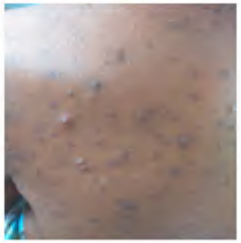

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Pre-treatment workup did not reveal any remarkable abnormalities. He had normal full blood examination, liver and renal function tests. His HIV screen test was un-reactive and was commenced on Second Line Drugs (SLD) on 12/05/16. He was noted to be generally improving on treatment in the preceding 2 and half months prior to developing the multiple vesicular skin lesions. His weight had increased to 55 kilograms from an initial 49 kilograms from the time of admission.

However, on review on 02/08/16 he was noted to have developed multiple tiny dark purple coloured lesions, over both sides of his arms, and the upper part of his body, in the front and the back (See photos for illustration). By then, he had been taking his SLD for over 2 months. His regime at the time was 8Z-km-Lfx-Cs-Et0/12Z-Lfx-Eto-Cs.

Consecutive Blood Investigations just prior to and after the skin eruptions are as listed below:

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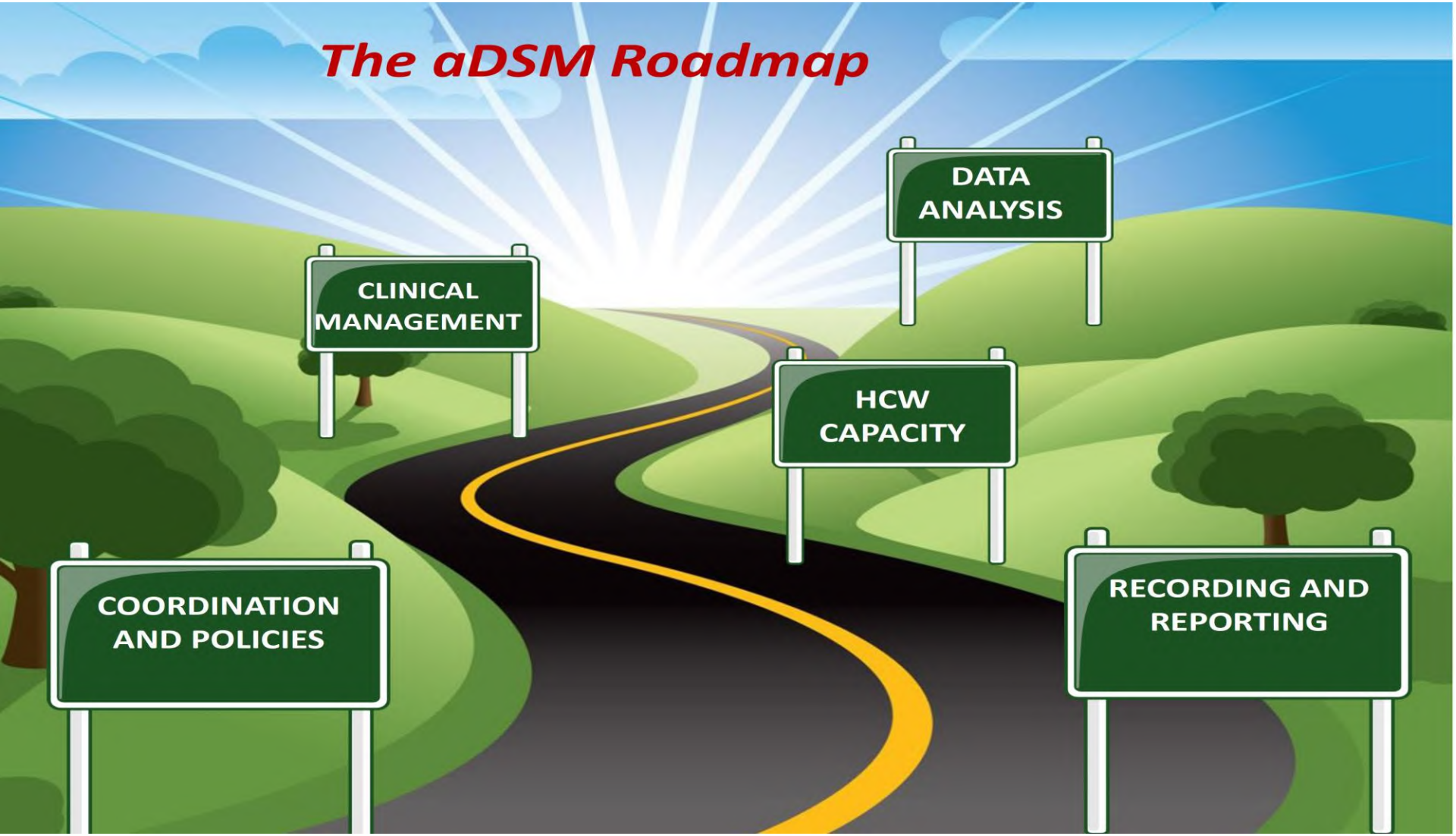
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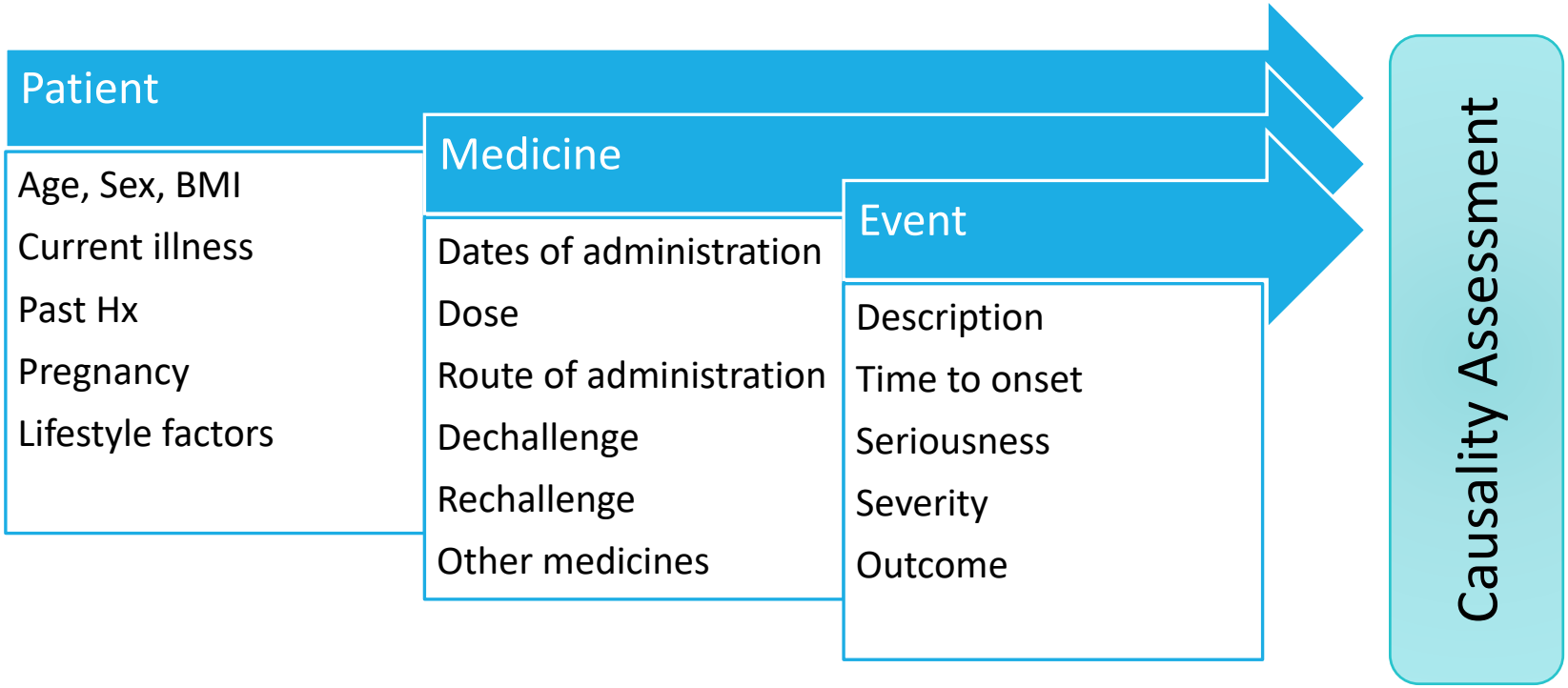
Causality Assessment

- Who conducts the assessment? I.e., who determines whether the event was related to the drug/regimen?
  - Site level: data easily available, can be done quickly
  - National level: less subjectivity, likely delayed
- At national level, is there a "Causality Assessment Committee" that evaluates reports (quarterly, semi-annually)?
  - DR-TB expert, clinical specialists ("on call" depending on specific cases), pharmacologist, toxicologist

Multiple data variables required to accurately determine causality: the more data, the better



aDSM Serious Adverse Event Causality Assessment Check Sheet

Complete the following summary information:

TB regimen		Start date	
		Stop date (if applicable)	

SAE		Onset date	
		Time to onset (days)[i]	

Seriousness criteria	SAE Outcome
☐ Death	☐ Died
☐ Life-threatening	☐ Recovered
☐ Hospital admission or extension of hospital stay	☐ Recovering
☐ Persistent or significant disability or incapacity	☐ Recovered with sequelae
☐ Congenital abnormality	☐ Not recovered

Answer YES or NO to the following 10 questions:

SAE		
1	Is the SAE a well-defined, specific event?	
Time to onset		
2	Did the event start AFTER the TB treatment regimen was started?	
3	Is the time-to-onset consistent with the pathology of the SAE and the pharmacokinetics of the medicine(s) concerned (i.e., is there a plausible time relationship between the medicine and the SAE)?	
Other possible causes		
4	Are there other factors that could account for the SAE, such as: TB infection? Concomitant disease? Another medicine (including traditional/herbal medicines)?	
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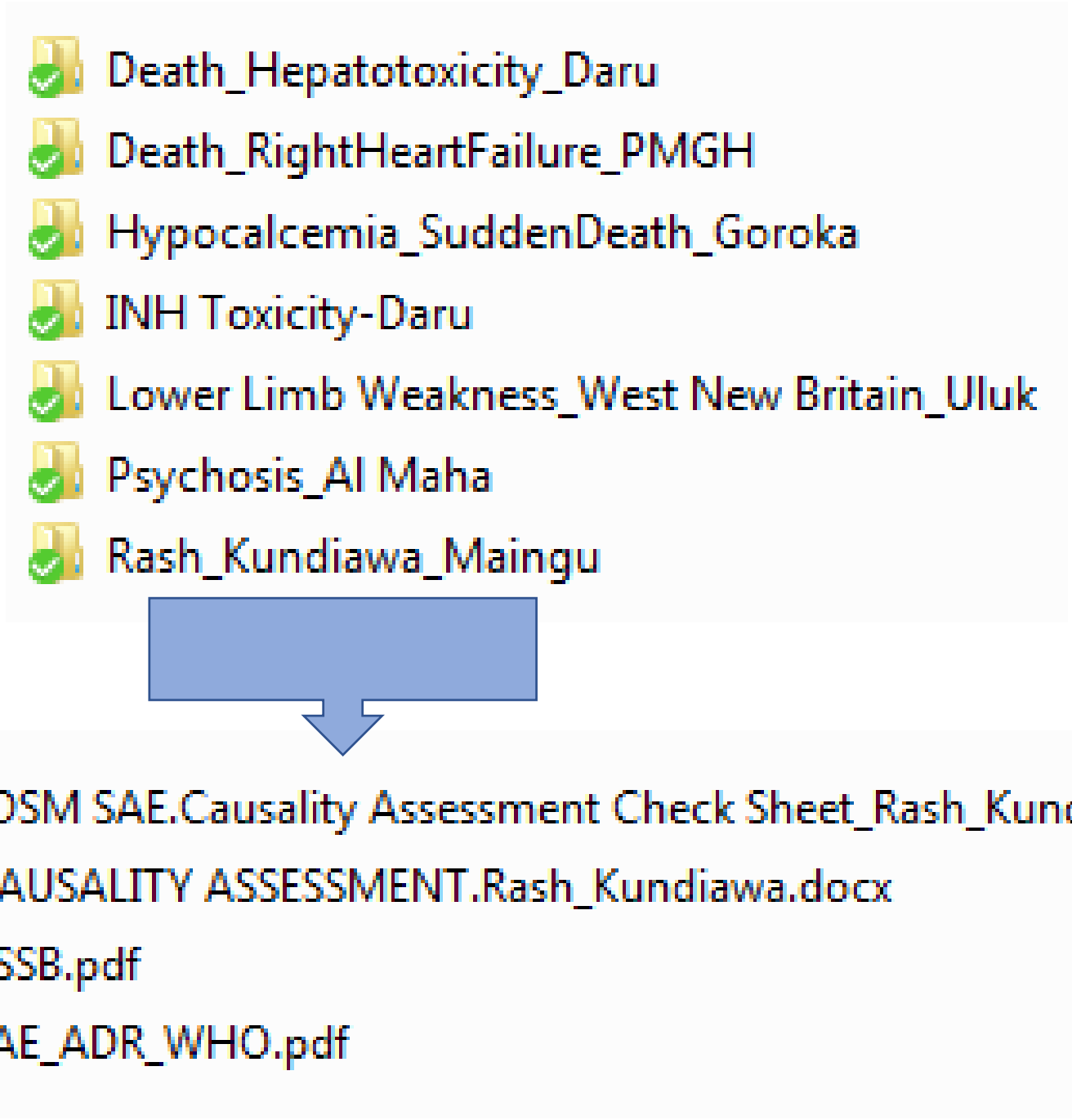
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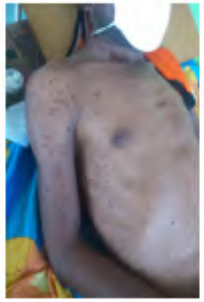

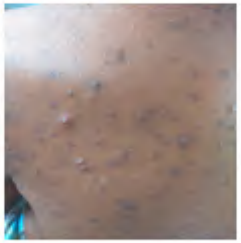

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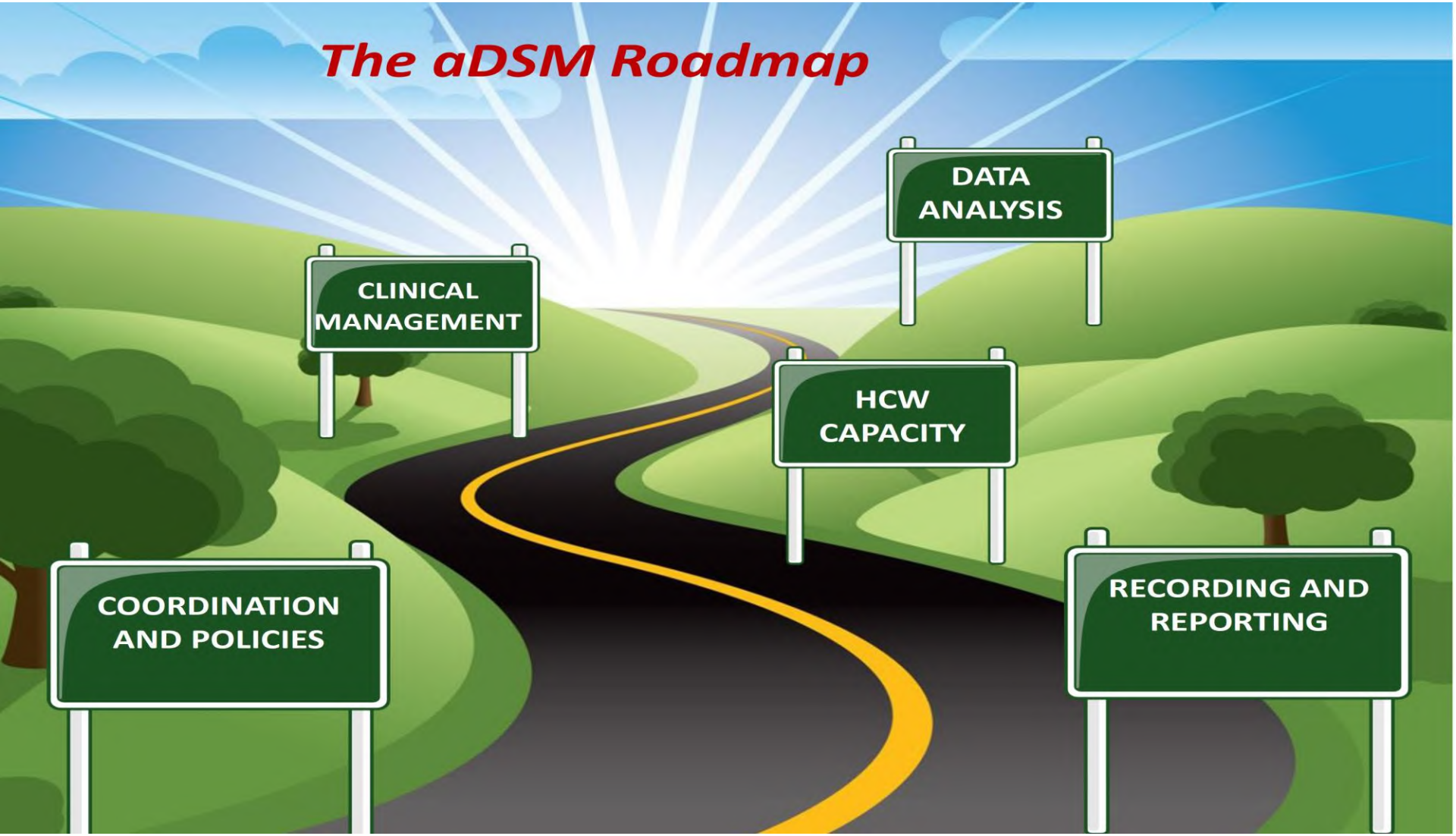
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MANAGEMENT OF NEW DRUG TOXICITIES AS A PART OF GOOD CLINICAL CARE

Dr. Vivian Cox and Dr. Sein Sein Thi

USAID/StopTB Partnership MDR TB Clinical Consultants

27 April 2017

USAID FROM THE AMERICAN PEOPLE

Stop TB Partnership hosted by UNOPS

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RESEARCH ARTICLE

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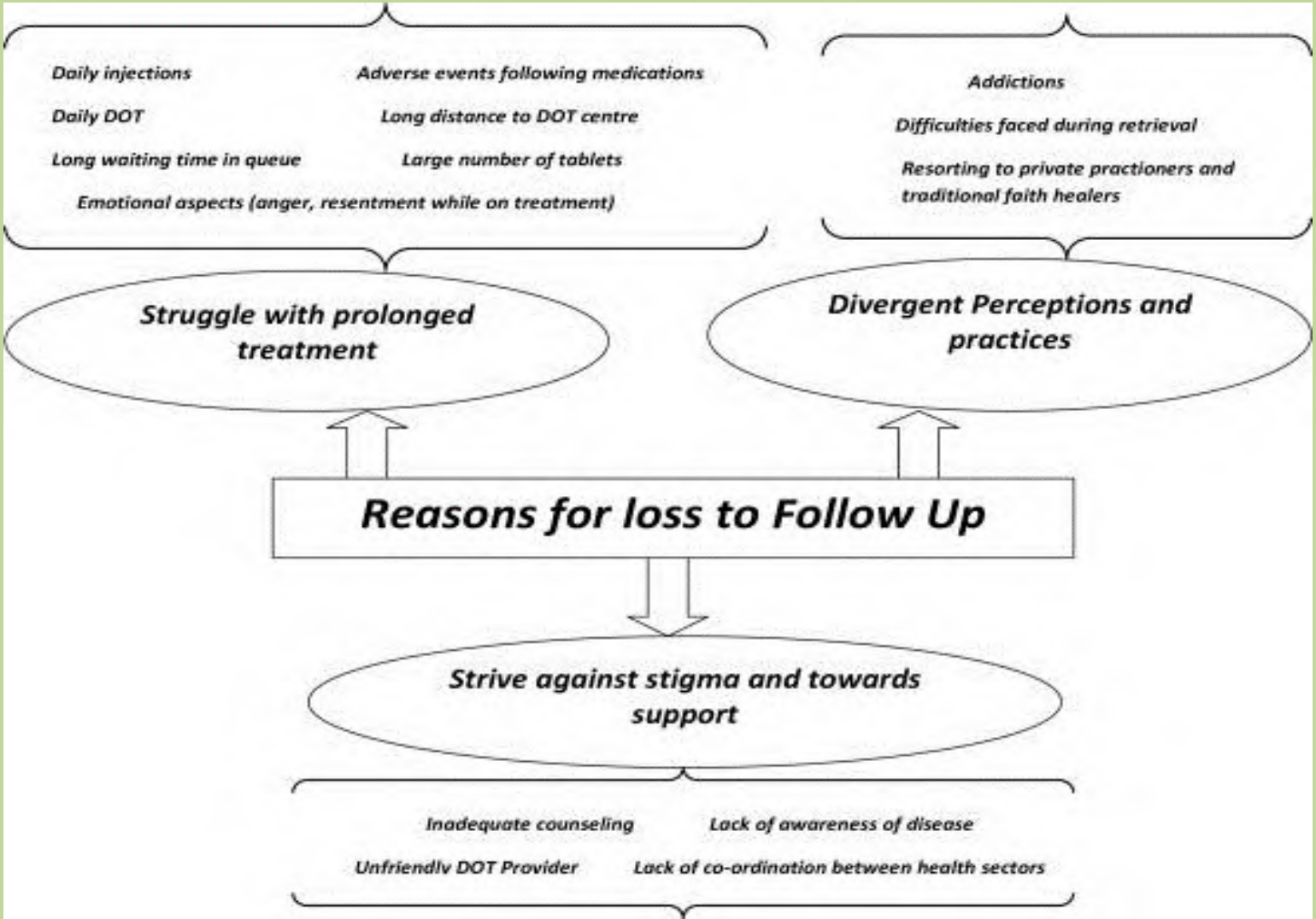
Kalpita S. Shringarpure[1]*, Petros Isaakidis[2], Karuna D. Sagili[3], R. K. Baxi[1], Mrinalini Das[4], Amrita Daftary[5,6,7]



CONTENTS

- Overview of toxicities associated with new drugs
- Role of Dx, Lab/clinical monitoring as part of routine care
- Approach to managing drug toxicities by severity grading
- Issues & recommended solutions: Discussion

Overview of toxicities associated with new drugs (common adverse/severe events)

ADVERSE EFFECT OF CONCERN WITH NEW DRUGS

Major	Minor
Cardiotoxicity (QTcF prolongation): Bdq – mean ↑ 10 ms at 8-24 wks, ↓ after 24 wk Dlm – 6-10 wks of Rx, stable afterward May be associated with low albumin level Hepatotoxicity (↑ liver enzymes) – Bdq Death -?? Bdq	**BDQ:** nausea, anorexia, arthralgia, headache, hemoptysis, chest pain, increased blood amylase, and rash **Dlm:** Nausea, vomitting, dizziness, anxiety, paraesthesia, itchiness, and tremor

WHO GDG REVIEW REPORT - JUNE 2016

Combination of 5 cohorts enrolled in investigation (multi-centric) and clinical use

Table 6. Number of patients who experienced adverse events

Country/study	At least one adverse event *n* (%)	Any severe adverse event *n* (%)	Any serious adverse event *n* (%)
France (*n* = 45)	45 (100.0)	28 (62.2)	7 (15.6)
South Africa (*n* = 195)	164 (84.1)	32 (16.4)	6 (3.1)
Drug manufacturer (*n* = 233)*	219 (93.9)	50 (21.5)	15 (6.4)
Armenia (*n* = 62)	62 (100.0)	5 (8.1)	11 (17.7)
Georgia (*n* = 30)	30 (100.0)	3 (10.0)	3 (10.0)
Total (*n* = 565)	520 (92.0)	118 (20.8)	42 (7.4)

Note—.*Includes patients (*n* = 28) who were later found to be ineligible or withdrew consent.

CONT: WHO GDG REVIEW REPORT - JUNE 2016

Table 10. Distribution of worst QTcF measurements

Worst QTcF measurement (ms)	France *n* = 45 (%)	S. Africa *n* = 141 (%)	Armenia *n* = 62 (%)	Georgia *n* = 30 (%)	Multi-centre study *n* = 233 (%)	Total *n* = 511(%)
≤450	14 (31.1)	105 (74.5)	34 (54.8)	13 (43.3)	190 (81.5)	356 (69.7)
>450-480	16 (35.6)	24 (17.0)	15 (24.2)	14 (46.7)	36 (15.5)	105 (20.5)
>480-500	7 (15.6)	6 (4.3)	6 (9.7)	2 (6.7)	5 (2.1)	26 (5.1)
>500	8 (17.8)	6 (4.3)	7 (11.3)	1 (3.3)	2 (0.9)	24 (4.7)
Total	45 (100.0)	141 (100.0)	62 (100.0)	30 (100.0)	233 (100.0)	511

QTc increase from baseline at end of follow- up (ms)	France *n* = 45 (%)	S. Africa *n* = 141 (%)	Armenia *n* = 62 (%)	Georgia *n* = 30 (%)	Multi-centre study *n* = 233 (%)	Total *n* = 511(%)
0-30	17 (37.8)	68 (48.2)	17 (27.4)	9 (30.0)	127 (54.5)	238 (46.6)
>30-60	6 (13.3)	46 (32.6)	15 (24.2)	9 (30.0)	96 (41.2)	172 (33.7)
>60	8 (17.8)	26 (18.4)	24 (38.7)	8 (26.7)	10 (4.3)	76 (14.8)
Missing	14 (31.1)	1 (0.7)	6 (9.7)	4 (13.3)	0 (0.0)	25 (4.9)
Total	45 (100.0)	141 (100.0)	62 (100.0)	30 (100.0)	233 (100.0)	511

CONT: WHO GDG REVIEW REPORT - JUNE 2016

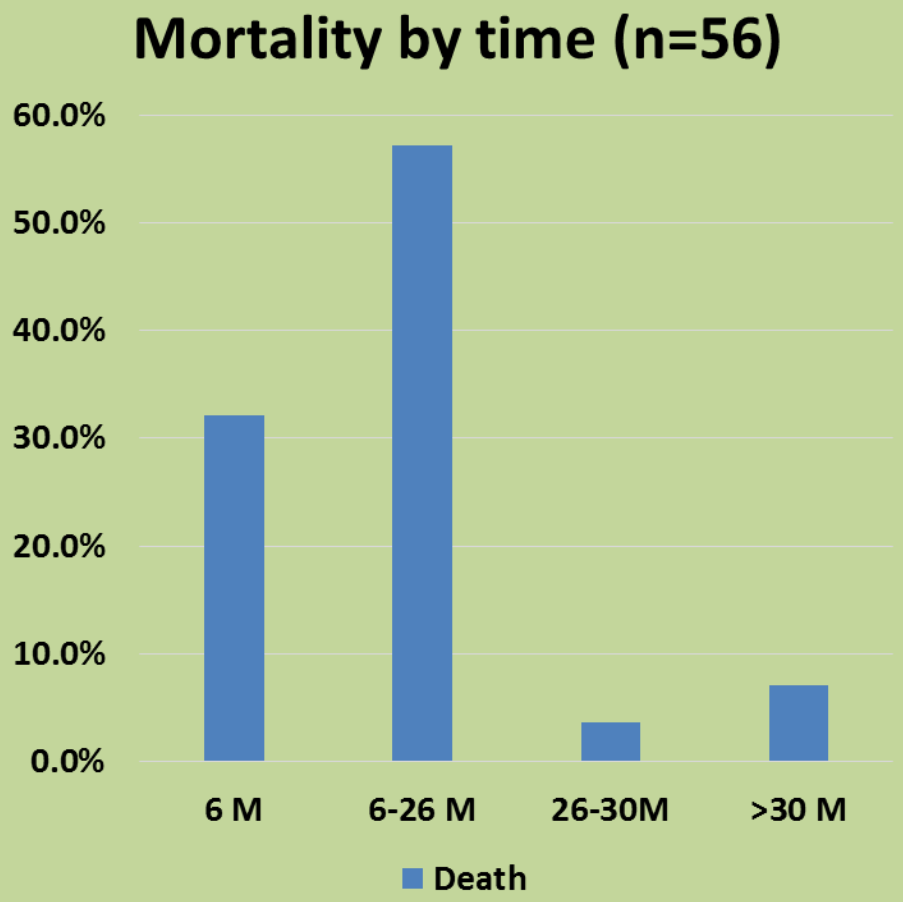
Table 9. Distribution of serious adverse events by system affected for all cohorts

System	Life-threatening	Fatal	SAE, non-categorised[†]	Total
	n (%)	*n* (%)	*n* (%)	*n* (%)
Gastrointestinal symptoms	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.1)
Metabolisms and nutrition disorders	1 (7.1)	0 (0.0)	1 (4.5)	2 (4.2)
Musculoskeletal and connective tissue disorders, arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders (dizziness, headache)	2 (14.3)	1 (8.3)	1 (4.5)	4 (8.3)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (21.4)	2 (16.7)	7 (31.8)	12 (25.0)
Ear and labyrinth disorders, Eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (7.1)	0 (0.0)	1 (4.5)	2 (4.2)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders (including ECG changes and QT prolongation)	2 (14.3)	1 (8.3)	5 (22.7)	8 (16.7)
Laboratory signs of hepatitis	1 (7.1)	0 (0.0)	6 (27.3)	7 (14.6)
Laboratory signs of pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure	1 (7.1)	1 (8.3)	0(0.0)	2 (4.2)
Other[*]	3 (21.4)	7 (58.3)	NR	10 (20.8)
Total	14 (100.0)	12 (100.0)	22 (100.0)	48 (100.0)

CONT: WHO GDG REVIEW REPORT - JUNE 2016

Mortality

- Higher in FQ resistance - 16.3%, SLI - 10.3%, XDR – 10.1 vs 2.9% MDR
- Higher in HIV coinfected (13.0% vs 8.8%)
- Comparative study from South Africa;
  - 23539 (93.8%) Std MDR Rx vs 1556 (6.2%) BDQ added Rx
  - Mortality 18.2% vs 7.6%
  - 40-60% reduction in mortality rate with BDQ added Rx [aHR 0.5 (0.41-0.61)]



INVESTIGATORS' REPORT - DLM

Table 2. Incidence of Adverse Events (Occurring in ≥10% of Patients in Either Delamanid Group and with Greater Frequency Than in the Placebo Group).*

Adverse Event	Delamanid, 100 mg Twice Daily (N=161)	Delamanid, 200 mg Twice Daily (N=160)	Placebo (N=160)
	number of patients (percent)		
Hematopoietic			
Anemia	18 (11.2)	10 (6.2)	14 (8.8)
Reticulocytosis	19 (11.8)	20 (12.5)	17 (10.6)
Gastrointestinal			
Nausea	58 (36.0)	65 (40.6)	53 (33.1)
Vomiting	48 (29.8)	58 (36.2)	44 (27.5)
Upper abdominal pain	41 (25.5)	36 (22.5)	38 (23.8)
Cardiovascular			
Palpitations	13 (8.1)	20 (12.5)	10 (6.2)
Prolonged QT interval on ECG	16 (9.9)	21 (13.1)	6 (3.8)
Respiratory: hemoptysis	19 (11.8)	15 (9.4)	17 (10.6)
Nervous system			
Headache	36 (22.4)	41 (25.6)	30 (18.8)
Paresthesias	17 (10.6)	20 (12.5)	12 (7.5)
Tremor	19 (11.8)	16 (10.0)	13 (8.1)
Insomnia	42 (26.1)	51 (31.9)	42 (26.2)
General			
Tinnitus	16 (9.9)	22 (13.8)	12 (7.5)
Asthenia	20 (12.4)	27 (16.9)	20 (12.5)
Malaise	12 (7.5)	16 (10.0)	12 (7.5)
Anorexia	23 (14.3)	34 (21.2)	24 (15.0)
Hyperhidrosis	9 (5.6)	17 (10.6)	8 (5.0)
Hyperuricemia	31 (19.3)	38 (23.8)	35 (21.9)
Hypokalemia	20 (12.4)	31 (19.4)	24 (15.0)

* With pairwise comparisons of the frequency of adverse events, only QT prolongation on electrocardiography (ECG) was significant (P=0.048 for the comparison of the 100-mg group with the placebo group and P=0.005 for the comparison of the 200-mg group with the placebo group). Furthermore, the Cochran–Armitage trend test used to evaluate for a dose–response trend in the incidence of adverse events across the three dose groups (0 mg, 100 mg, and 200 mg twice daily) yielded a P value of 0.004 for QT prolongation detected by means of ECG.

Source: Gler et al, 2012

Role of Dx, Lab/clinical capacity as part of routine care

PRINCIPLES IN MANAGEMENT OF ADVERSE EVENTS

- **Early identification (treatment monitoring) and treat immediately & adequately**
- **Rule out other cause/comorbidity, e.g electrolyte imbalance, viral hepatitis and correct underlying cause**
- **Consider additive or potentiating SE with concomitant therapy**
- **Consider drug-drug interaction (e.g. CYP3A4 inhibiter – ketoconazole, LPV/r)**
- **Some adverse effects - may disappear or diminish with time/encourage to tolerate by psychosocial support**
- **Mild to moderate - ancillary drugs**
- **Permanent dose reduction (not for Bdq/Dlm) or definitive stopping - last resort**

(Discussion point: decision to permanently stop: – to leave with reveiew team in discussion with expert or not???, mainly for the decentrailed sites)

MONITORING OF PATIENTS

	BL	W2	M1	M2	M3	M4	M5	M6	On Inj	Till end of Rx	End of Rx	Post 6 Mth rx
Clinical evaluation												
Vital signs	X	X	X	X	X	X	X	X	Monthly		X	
Functional status-Karnovsky	X			X							X	
PNP	X		X	X	X	X	X	X	Monthly		X	X
Audiometry	X		X	X	X	X	X	X	Mty		X	
Vision test	X		X	X	X	X	X	X	Monthly		X	X
Adv event	X	X	X	X	X	X	X	X	Every visit		X	X
Bacteriological												
Smear&Cul	X		X	X	X	X	X	X	Monthly		X	X
Xpert	X	If smear or culture become (+)ve										
LPA	X	If smear or culture become (+)ve										
DST	X	If smear or culture become (+)ve										

CONT: MONITORING OF PATIENTS

	BL	W2	M1	M2	M3	M4	M5	M6	On Inj	Till end	End of Rx	Post 6 M Rx
Lab tests												
ECG	X	X	X	X	X	X	X	X			X	X
CBC	X	X	X	X					Monthly		X	
Urea&Cr	X		X	X	X	X	X	X	Mtly		X	
K+,Mg+,Ca+	X		X	X	X	X	X	X	Mtly		X	
AST,ALT	X		X	X	X	X	X	X	Monthly		X	
TSH	X				X			X	Every 3 mth			
Sr Albumin	X											
HBV&HCV	X											
BS/HBA1C	X											
Pregnancy	X											
HIV	X											
CD4,VL if HIV+	X											
CXR	X							X			X	

CONT: MONITORING OF PATIENTS

- Frequency of testing and F/U will be more as indicated by clinical/lab abnormalities detected.
- Hospitalization will be required depending on clinical/lab abnormality status and to what extent the PMDT site can manage on their own.
- Recording of clinical/lab F/U info: “not primarily for data collection/research, but essential part of clinical management” , to analyze progress/response to clinical management of disease and SE
- But how to systemically record and taking action for patient management is not really easy. So how to make it happen?

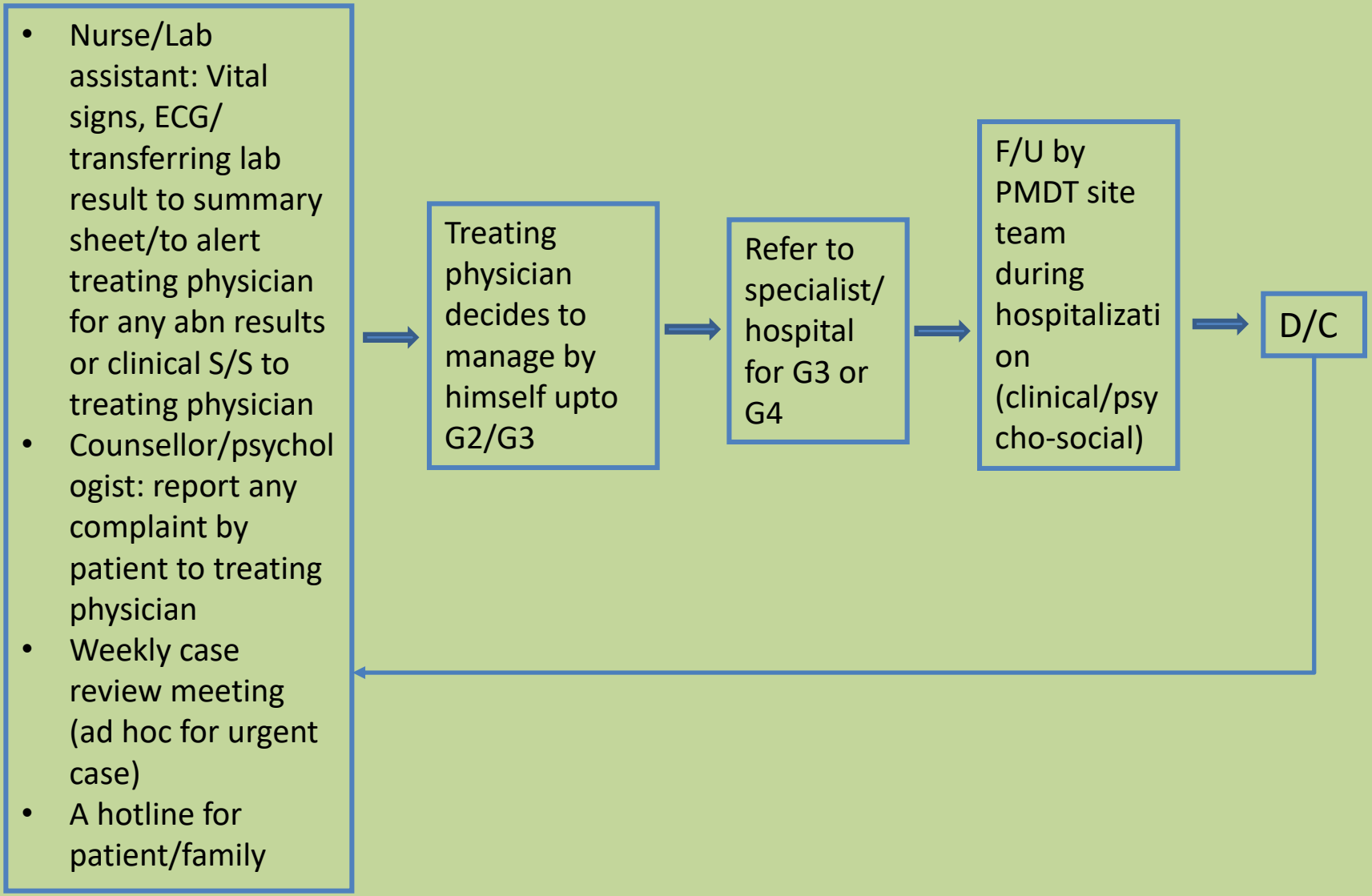
AN EXAMPLE: RECORDING OF MONITORING

Blood results																	Smear Microscopy			Culture			Weight
Date of test	date	date	date													M	Date	Sample No.	Result	Sample No.	Result	Date	Kg or BMI
Hb (g/dL)																0							
RBC (10^6/mm^3)																1							
WBC (10^3/mm^3)																2							
Plt (10^3/mm^3)																3							
Billirubin(mcmol/L)																4							
AST (U/L)																5							
ALT (U/L)																6							
Creatinine (mg/dl)																7							
Urea (mmol/L)																8							
K (mmol/L)																9							
Na (mmol/L)																10							
Mg (mmol/L)																11							
Ca (mmol/L)																12							
Albumin																14							
Gluc (mg/dl)																15							
TSH																16							
QTc																17							
Audiometry																18							
Pregnancy test																19							
HIV test																20							
CD4 count																21							
HbS – Ag																22							
HCV - AB																23							
																24							

Easier to compare with baseline, how it is going on with Rx, when is due to do next (an alert system), multi-disciplinary team work.

CASE MANAGEMENT MECHANISM

- No prefect model to apply everywhere
- One example: multi-disciplinary team approach



APPROACH TO MANAGING DRUG TOXICITIES BY SEVERITY GRADING

REFRESH ON SEVERITY GRADING

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevent normal everyday activities.

Seriousness & Severity: an overlap of definitions, but not similar or synonym (e.g. hospitalization is serious adverse event which also highlight a certain level of severity.)

In assessing severity of events, clinical judgment should be made in consideration of both the event experienced by patient and other lab parameters!

GENERAL PRINCIPLE OF MANAGEMENT OF AE/SAE BASED ON SEVERITY GRADING

Grade 1 (Mild) or 2 (Moderate): may continue intake of new drug/s.

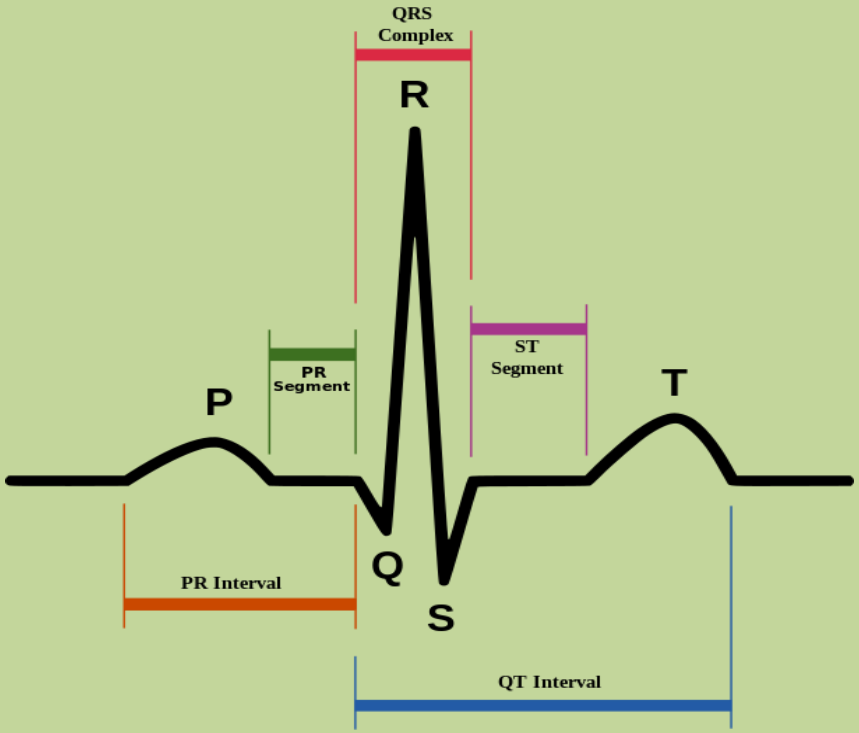
Grade 3 (Severe) or 4 (Life threatening): closely monitored and evaluated by the physician. Patient may discontinue intake of new drugs if, in the opinion of the physician, the AE or lab toxicity poses a significant risk for patient in case of continued treatment. Patient should be followed until resolution of toxicity.

This grading system is based on the standardized and commonly used toxicity table for infectious diseases, 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.

CARDIO-TOXICITY: QTc PROLONGATION

Calculation of QTc

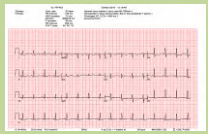
- Fredericia formula – best adjusted for heart rate



QTc = Q T/ $\sqrt[3]{RR}$
QTc = the corrected QT interval
QT = the time between the start of the QRS complex and the end of the T wave
Auto-reporting from the machine may not be programmed with Fredericia formula.

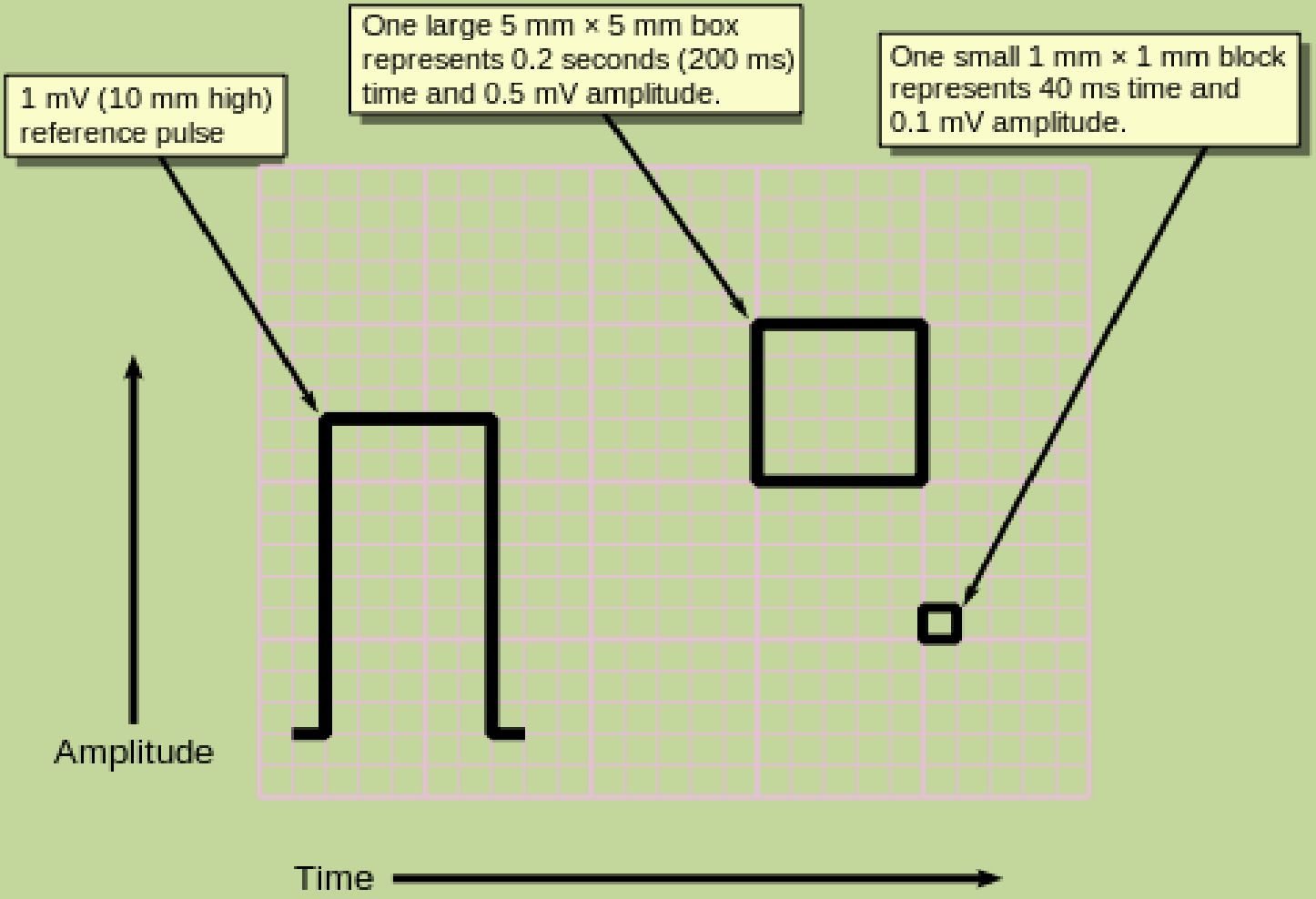
https://www.thecalculator.co/health/QTc-Calculator-385.html

http://www.qxmd.com/apps/calculate-by-qxmd



CONT: QTc CALCULATION

The ECG machine should be calibrated to ensure that the following voltage and speeds apply:



CONT: CARDIO-TOXICITY

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
QTc prolongation	450 to 480 ms	> 480 to 500 ms	>500 ms without S/s of serious arrythmia	QTcF >= 501 or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia
Action	Monitor closely, weekly ECG until QTcF <G1 or BL Correct electrolytes as necessary	Monitor closely, weekly ECG until QTcF <G1 or BL Correct electrolytes as necessary	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.
Cardiac rhythm disturbance	Asymptomatic	Asymptomatic, transient rhythm abnormality, but no treatment required	Recurrent, persistent, symptomatic arrhythmia requiring treatment	Unstable dysrythmia requiring hospitalization and treatment

REVIEW OF AE/SAES ON A SMALL COHORT ON BDQ

QTc level before, during and after Bdq

DR TB Type		QTc Baseline	Cfz exposure	Mfx Exposure	QTc w4	QTc W 24	QTc a/f M12 of Bdq	Max QTc	Max QTc from Wk of Bdq
PreXDR	Case 1	428	No	Yes	443	NA	NA	479	W7
	Case 2	474	Yes	Yes	477	472	NA	491	W5
	Case 3	474	No	No	490	360	NA	522	W1
XDR (≥2 drugs)	Case 4	421	No	No	462	451	416	476	W7
	Case 5	430	Yes	Yes	430	432	405	477	W16
	Case 6	453	No	No	487	467	454	487	W4
	Case 7	469	Yes	Yes	464	NA	NA	477	W10
	Case 8	467	Yes	Yes	495	NA	NA	525	W5
	Case 9	440	Yes	Yes	N/A	465	NA	475	W8
	Case 10	479	Yes	Yes	480	486	NA	486	W24

Major SAE:

- **QTc >500: 2 cases, 1 Death (7 M a/f Bdq), no hepatic function abn**
- **5/10 had baseline QTc > 450 ms, ?? Exposure to Mfx and Cfz long period before BDQ**

Predisposing factor of QTc prolongation

- **Congenital**
- **Acquired;**
  - **Age, female**
  - **CVS: H/T, LVH, Heart failure, MI**
  - **Endocrine: Diabetes Mellitus, Abn TSH level**
  - **Slow HR: hypothermia**
  - **Elevated serum cholesterol**
  - **High BMI**
  - **Serum electrolyte abn: Hypo - K+, Mg, Ca+**
  - **Drug induced**

(Ref: Medscape LQTS)

Drug with potential QT prolongation

- Anti-TB: Moxifloxacin, Gatifloxacin, Clofazamine
- Macrolide anti-biotics: erythromycin, clarithromycin, azithromycin
- Serotonin inhibitor: ondansetron
- Azole anti-fungal: ketoconazole, itraconazole, fluconazole
- Ant-malaria: quinine sulphate, chloroquine
- ARVs: LPV/r, ATV/r, 3TC
- Antipsychotics: chlorpromazine, haloperidol, thioridazine, resperidone, amitryptylline, escitalopram, mirtazapine
- Drugs that can lower serum electrolyte: Km,Am, Cm
- Neurontin : Gabapentin, Pregabalin

AN EXAMPLE APPROACH TO G3 QTC

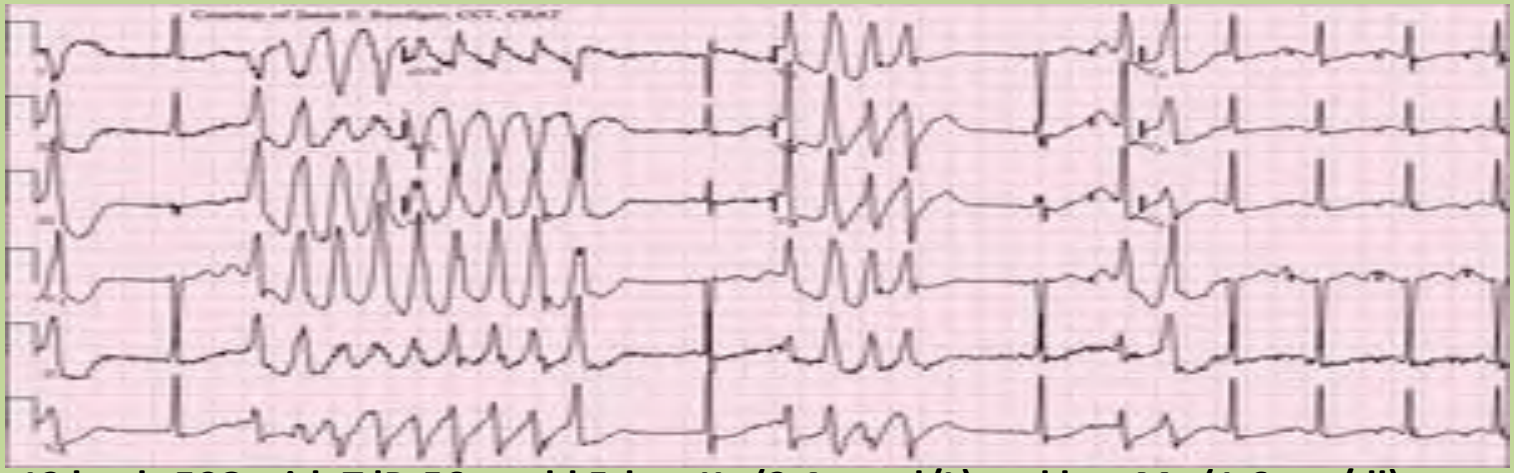
If QTc is >500 ms at two separate measurement without symptoms of cardiac dysrhythmia such as syncopal (fainting attack) attack, chest pain, sweating, light-headedness or dizziness, shortness of breath, fluttering in chest, feeling of racing or slowness heart rate.

- Hospitalize patient.
- Correct electrolyte if required. Also do TSH (esp on PAS) and blood glucose level (esp DM) , treat if found to be abnormal.
- Withhold bedaquiline and other QT prolonging drugs and injectable agent (if patient is still using) until the electrolytes have normalized.
- De-challenging (stopping) other drugs which also have potential cardio-toxicity effect such as FQ, Cfz may try first. So stop the FQ first and see what happens. Then stop Cfz and see what happens, if the QTc is still prolonged, stop BDQ. But if the patient has symptoms, such as tachycardia, syncope, palpitations, weakness or dizziness, then stop BDQ right away.

AN EXAMPLE APPROACH TO G4 QTC

If QTcF ≥ 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia;

- Hospitalize patient.
- Correct electrolyte if required. Also do TSH (esp on PAS) and blood glucose level (esp DM), treat if found to be abnormal.
- Withhold BDQ and all other QT prolonging drugs and discuss with national technical review team.



12 leads ECG with TdP, 56 ys old F, low K+ (2.4mmol/L) and low Mg (1.6 mg/dl) (Source: https://en.wikipedia.org/wiki/Torsades_de_pointes)

Re-introduction may consider simultaneously or sequentially if > 1 cardio-toxicity drugs in the regimen, e.g. Bdq/Dlm/Cfz every 2-3 days with ECG monitoring, but not > 2 wks. Mfx may be replaced with Lfx high dose.

HEPATOTOXICITY (Z, ETO, LZD, CFZ,HDH,BDQ)

	Grade 1	Grade 2	Grade 3	Grade 4
AST &/or ALT ↑	>1-<2 times UNL	>2-<3 times UNL	>3-<8 times UNL	>8 times UNL
Action	Continue treatment and follow until return to baseline or stabilization of AST/ALT elevation.	Continue treatment and follow until return to baseline or stabilization of AST/ALT elevation.	Stop all drugs, measure LFTs weekly. Reintroduced Rx after toxicity is resolved.	Stop all drugs, measure LFTs weekly. Reintroduced Rx after toxicity is resolved.

Mild baseline elevation of liver enzyme may be due to TB itself.
Cotri & NVP – to consider in HIV
Sequentially reintroduce anti-TB drugs with potential hepatotoxixity every 3-4 days with regular checking of liver enzyme.
Consider suspending the most likely offending drug permanently if it is not essential to the regimen. E.g Z

AE/SAES OF OTHER IMPORTANCE

	Grade 1	Grade 2	Grade 3	Grade 4
Acute Kidney Injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated
Hypokalaemia	3.4 - 3.0 mEq/L	2.9 - 2.5 mEq/L	2.4 - 2.0 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hypomagnecaemia (mEq/L)	1.2 to < 1.4	0.9 to < 1.2	0.6 to < 0.9	< 0.6 abnormal magnesium with life-threatening arrhythmia
Hypocalcaemia (mg/dl & mmol/l)	7.8 to < 8.4 *1.95* to < *2.10*	7.0 to < 7.8 *1.75* to < *1.95*	6.1 to < 7.0 *1.53* to < *1.75*	< 6.1 < *1.53*

CORRECTION OF HYPOKALAEMIA

level meq/L	Quantity of KCl	When to do next control - sooner if pt has vomiting or diarrhea
3.5 or more	None	Monthly while on injectable. May require
3.0 - 3.4	KCl 1 tab BD	Repeat in 1 week, if normal reduce to 1 tab daily, if not improving increase KCl to 2 BD
2.5 - 3.0	KCl 2 tabs TDS (= 16 mmol 3x / day) And add magnesium tabs	Repeat in 3 days. If not increasing, supplement magnesium, then try KCl 2 tabs Qid and consider admission for IV or KCl
< 2.5	Admit to hospital. IV potassium and magnesium After IV commence oral KCl 2 tabs QiD Withhold injectable until K+ > 2.5	Repeat potassium daily until >2.5, asymptomatic and responding to oral, then according to table above

CORRECTION OF HYPOMAGNESAEMIA

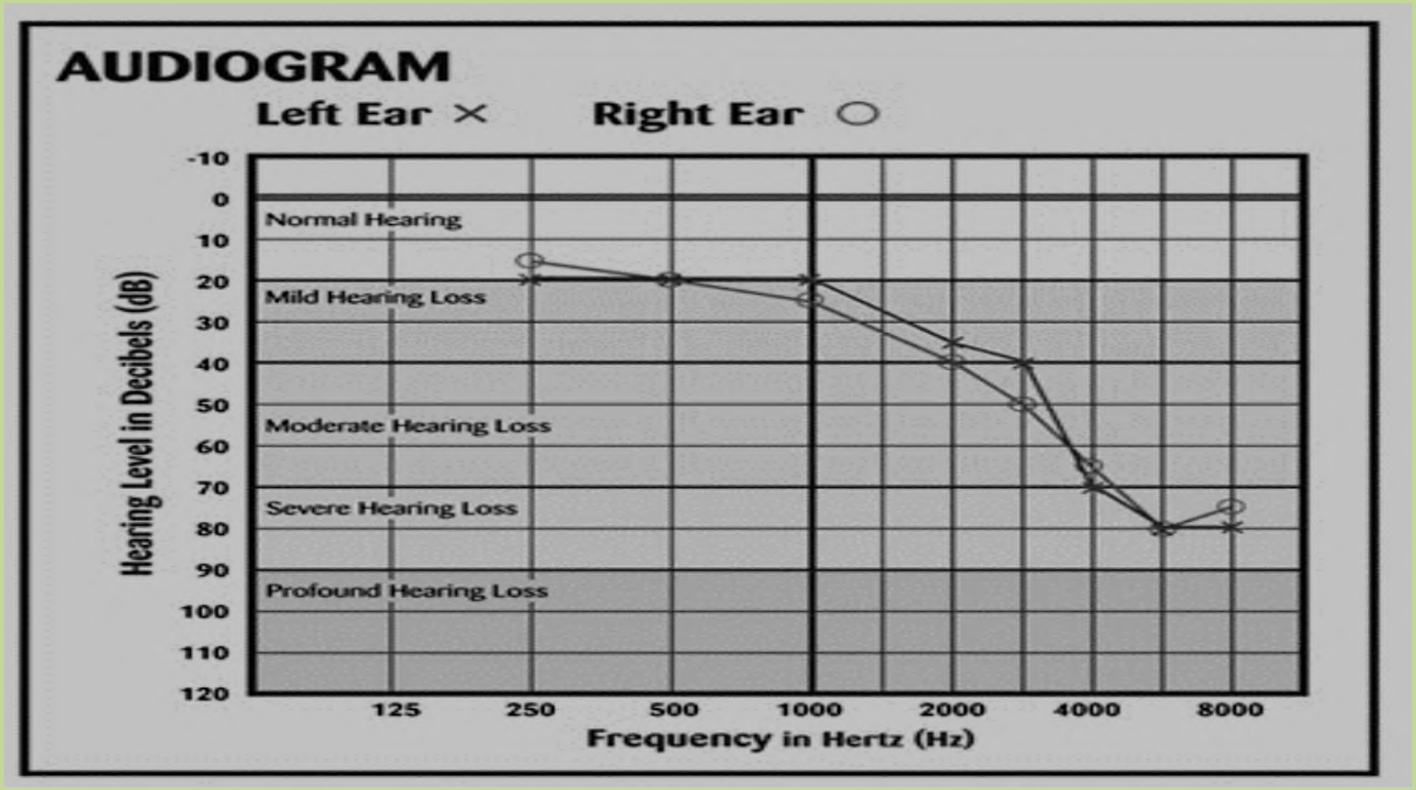
level meq/L	Quantity of Mg	When to do next control - sooner if pt has vomiting or diarrhea
>2	None	Monthly
1.5 -1.9	1000-1200 mg	Oral, Monthly
1.0-1.4	2000 mg	May consider giving IV/IM, Weekly
<1.0	3000 -6000 mg	IV, daily

Is it easy to get Mg+ (tab/liquid/suspension) that can supplement elemental form (e.g. Mg Citrate)?

HEARING IMPAIRMENT

Hearing Loss > 12 yr old	Adults: threshold shift of 15 - 25 dB averaged at 2 continuous tests (1,2,3,4,6,8 kHz audiogram) in at least one ear. Pediatric: threshold shift >20 dB at 8 kHz in at least one ear	Adult: threshold shift of >25 dB averaged at 2 continuous test in at least one ear. Pediatric: threshold shift >20 dB at 4 kHz and above in at least one ear.	Adult: threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; limiting self care ADL. Pediatric: Threshold shift >20 dB at 3 kHz and above in at least one ear ; additional speech-language related services indicated.	Adults: profound bilateral hearing loss (Threshold >80 dB HL at 2 kHz and above); nonservicable hearing Pediatric: audiologic indication for cochlear implant and additional speech-language related services indicated.
Action	**Continue injectable**	**Consider ↓ frequency of injectable or substitution.**	**Usually should stop injectbale and substitution.**	**May continue if complete loss of hearing or stop if vertigo/tinnitus (+)**

Audiogram showing hearing loss



Source: endTB guide version 3.3

Discussion: what will you do for this case?

OTHER AEs OF INTEREST

	Grade 1	Grade 2	Grade 3	Grade 4
Amylase&/or Lipase	>1-<1.5 times UNL	>1.5-<2 times UNL	>2-<5 times UNL	>5 times UNL
Musculo-skeletal (myalgia)	Mild, no limitation of activity	Muscle tenderness at the site other than injection site or moderate impairment of activity	Severe muscle tenderness and marked impairment of activity	Frank myonecrosis

CONT: OTHER AEs OF INTEREST

Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Vomiting	1 episode in 24 hours (no or minimal interference with oral intake)	2-5 episodes in 24 hours (no or mild dehydration)	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences (hypotensive shock) requiring hospitalization or requiring parenteral

CONT: OTHER AEs OF INTEREST

Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Athralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions

CONT: OTHER AEs OF INTEREST

Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

TOXICITY CONCERN WITH LZD

Dose and duration dependent

Paresthesia (Burning, Tingling, etc.) Lzd, Cs, H, S, Km, Cm, H, FQ, Pto/Eto, E	Mild discomfort (BPNS 1-3 any side) No analgesic required **BPNS – brief peripheral neurpathy score**	Moderate discomfort; (BPNS 4-6 any side) Non-narcotic analgesic required and improved	Severe discomfort; (BPNS 7-10 on any side) narcotic analgesia required and improved	Incapacitating; or not responsive to narcotic analgesia
Amitriptyliine and Lzd should not be used. Carbamazepine is strong CYP3A4 inducer, should not use with Bdq/Dlm.	May stop Cs and Lzd. If symptoms improve, consider restart: Lzd at a lower dose (300mg daily or 600 mg thrice weekly). Consider to stop Cs if not essential for Rx.	Stop Cs and Lzd. If symptoms improve, consider restart cycloserine. Do not reintroduce Lzd. Consider replacing with other drug. Provide symptomatic relief.	Same as Grade 2.	Same as Grade 2.

CONT: TOXICITY CONCERN WITH LZD

Myelosuppression (anemia, thrombocytopenia, or neutropenia) (Lzd, others AZT, Cortri) – common, 18%				
Anemia	10.5 - 9.5 g/dL	9.4 - 8.0 g/dL	7.9 - 6.5 g/dL	< 6.5 g/dL
Decreased platelets	75,000 – 99,999 /mm^3	50,000 – 74,999 /mm^3	20,000 – 49,999 /mm^3	< 20,000 /mm^3
Low absolute neutrophil count	1500 - 1000/mm3	999 - 750/mm3	749 - 500/mm3	<500/mm3
Pyridoxine 50 mg is prophylactic.	Monitor carefully, and consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly).	Monitor carefully, and consider reduction of dose of Lzd , in case of G2 neutropenia, stop Lzd ASAP, G2 anemia, consider EPO. Restart at reduced dose when subsided to G1.	Stop Lzd immediately. In case of Grade 3 anemia, consider EPO. Restart at reduced dose when subsided to G1.	Stop Lzd immediately. Consider hemotransfusion or EPO. Restart at reduced dose when subsided to G1.

CONT: TOXICITY CONCERN WITH LZD

Optic nerve disorder (optic neuritis) **Lzd, E, Eto/Pto, Cfz, rifabutin, H, S – 18 % of pts on Lzd** **More risk in DM**	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40[6/12] or better)	Limiting vision in the affected eye (worse than 20/40[6/12] but better than 20/200[6/60])	Blindness (20/200[6/60] or worse) in the affected eye
Early sign: loss of red-green color distinction, best tested by using the Ishihara test. Other symptoms include central scotomas.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.

Reference for SE management:

endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs

Version 3.3

http://endtb.org/resources/endtb-clinical-guide-v33

ISSUES AND RECOMMENDED SOLUTIONS: DISCUSSION

Gaps

No availability of LPA

No availability of 2nd line DST

LFU b/t GeneXpert and LPA

Transport

Early tracking of eligible patients

ISSUES AND RECOMMENDED SOLUTIONS: DISCUSSION

Gaps	Solutions
No availability of LPA No availability of 2nd line DST	Equip – 1st option Refer to nearest center: In-country/out-country referral to an accredited lab
LFU b/t GeneXpert and LPA	Decision by lab to forward/proceed for LPA testing from the same sample set
Transport	Motorbike/public transport/out sourcing/Courier service
Early tracking of eligible patients	Alerting system, a dedicated person to track in the team

CONT: ISSUES AND RECOMMENDED SOLUTIONS

No ECG at PMDT sites

QTc/basic ECG interpretation

Maintenance/accuracy of result

CONT: ISSUES AND RECOMMENDED SOLUTIONS

No ECG at PMDT sites	Equip – 1st option Refer to nearest center
QTc/basic ECG interpretation	Train staff Refer in case of doubt (m-health system – whatapps/e-mail) Clinically concern: timely referral to hospital with CCU/ICU for specialist care
Maintenance/accuracy of result	6 monthly calibration/service agreement with supplier

CONT: ISSUES AND RECOMMENDED SOLUTIONS

Biochemistry testing
(esp K+,Mg+,Ca+)
No machine on site

Timely availability

Accuracy of result

Abn value

No test available for Mg+
at PMDT sites

CONT: ISSUES AND RECOMMENDED SOLUTIONS

Biochemistry testing (esp K+,Mg+,Ca+) No machine on site	Equip – 1st option Refer to nearest center (reliable lab with proper QA system)
Timely availability	Ensure to get within 24 hours Alarm system in agreement with lab for abn value
Accuracy of result	Proper sample collection/transport/ time/calibration
Abn value	Train staff for mgt upto G2/?G3 and regular F/U testing IPD care for G3 patient from far distance
No test available for Mg+ at PMDT sites	Mg+ supplementation to refractory hypokalaemia cases

CONT: ISSUES AND RECOMMENDED SOLUTIONS

Audiometry

No machine on site

Testing technique/variation of results/interpretation

Maintenance

??Benefit

Vision test vs availability of opthalmologist

CONT: ISSUES AND RECOMMENDED SOLUTIONS

Audiometry No machine on site	Equip – 1st option Refer to nearest center
Testing technique/variation of results/interpretation	Proper location of machine (quiet place/sound proof booth Train staff
Maintenance	Annually/service agreement with supplier
??Benefit	Take clinical management decision
Vision test vs availability of opthalmologist	Ensure having Ishihara test/Snellen Chart, train staff

CONT: ISSUES AND RECOMMENDED SOLUTIONS

Hospitalization

Patient seeking care at other GPs/specialists for other morbidity or AEs

CONT: ISSUES AND RECOMMENDED SOLUTIONS

Hospitalization	No mandatory hospitalization for clinically stable or case with no risk of potentiated SE But need an established link with a hospital for specialist care Proper information transmission to the referral hospital
Patient seeking care at other GPs/specialists for other morbidity or AEs	Educate patient/family about AEs/SAEs and to inform to PMDT sites Patient card with info about new drug AEs/SAEs (a good example from Pakistan) 

CONT: ISSUES AND RECOMMENDED SOLUTIONS

Patient's factor

Soci-economic

Patient's factor

Distance

CONT: ISSUES AND RECOMMENDED SOLUTIONS

Patient's factor Soci-economic	Counselling and support (travel cost, stipend, food ration)
Patient's factor Distance	TB Hospital/TB village Decentralised/Peripheral linkage of care at district/township level

Thank You!

Patient [illegible] ring and [illegible]:

1. Recordin[illegible]facility level
2. Propos[illegible]s

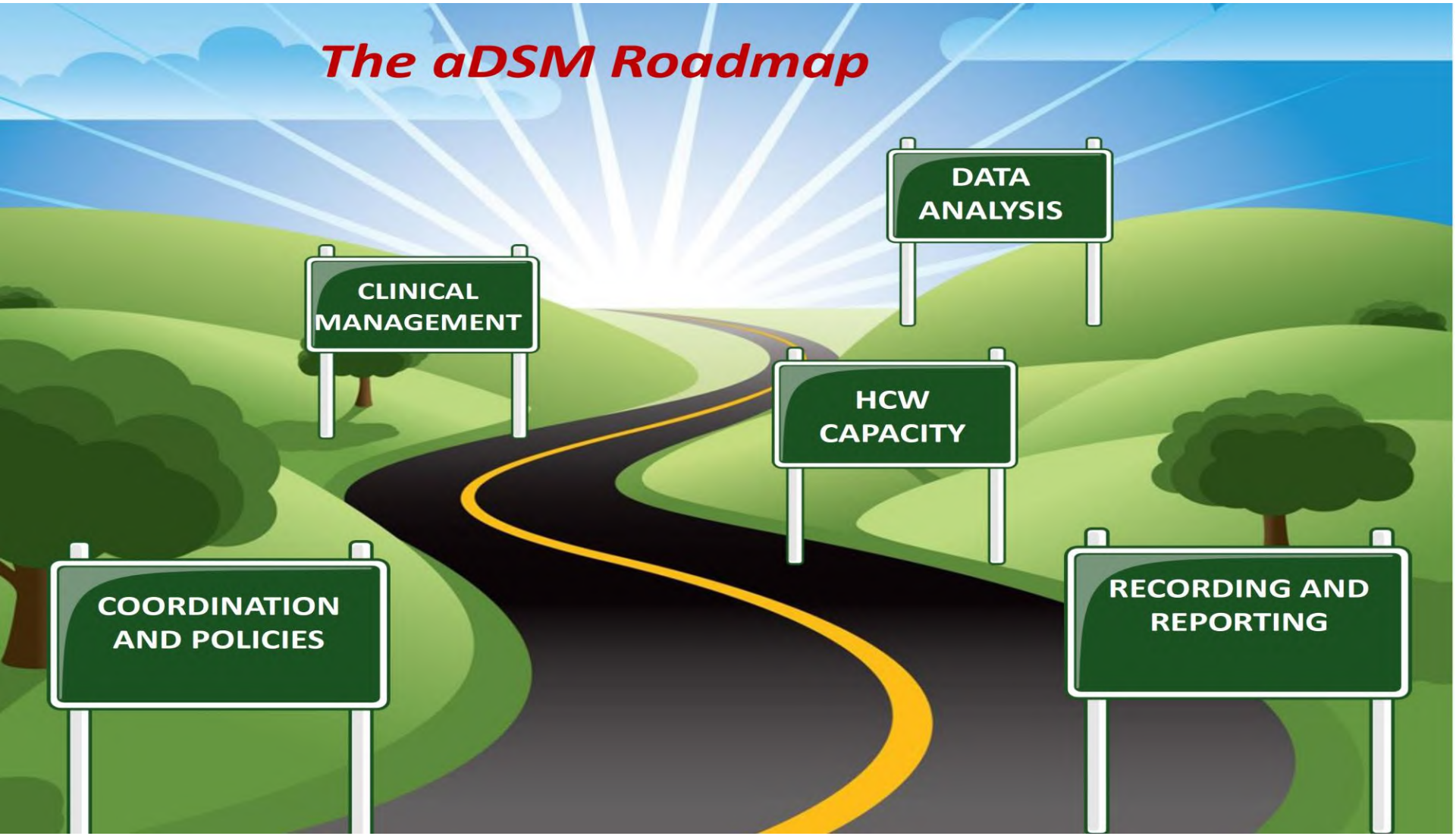
Edine Tiemersma, KNCV Tuberculosis Foundation

Bangkok; 27 April 2017

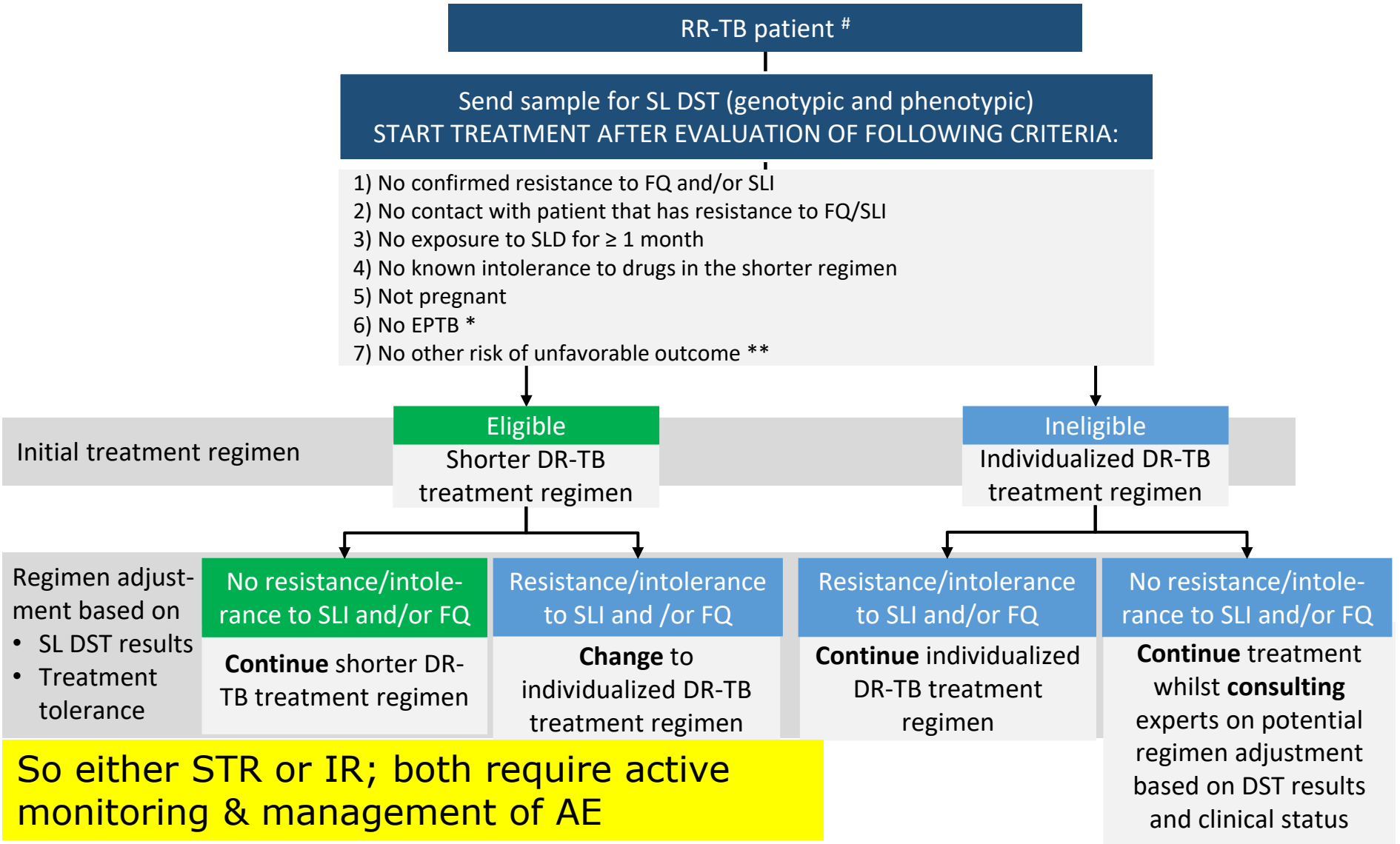
Roadmap:
from pilot project or research to country-wide implementation

Edine Tiemersma, KNCV Tuberculosis Foundation

Bangkok; 27 April 2017

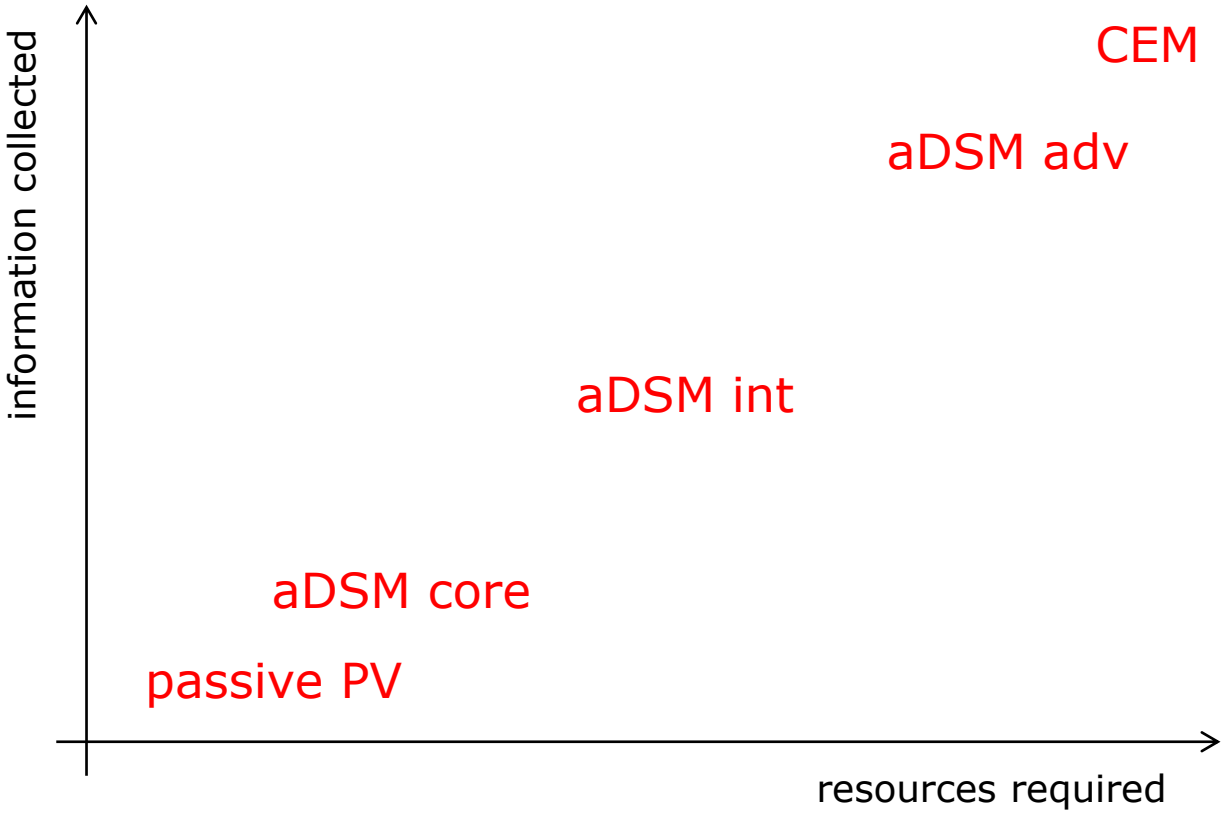


Triaging concept: Rif-R TB patient triaging

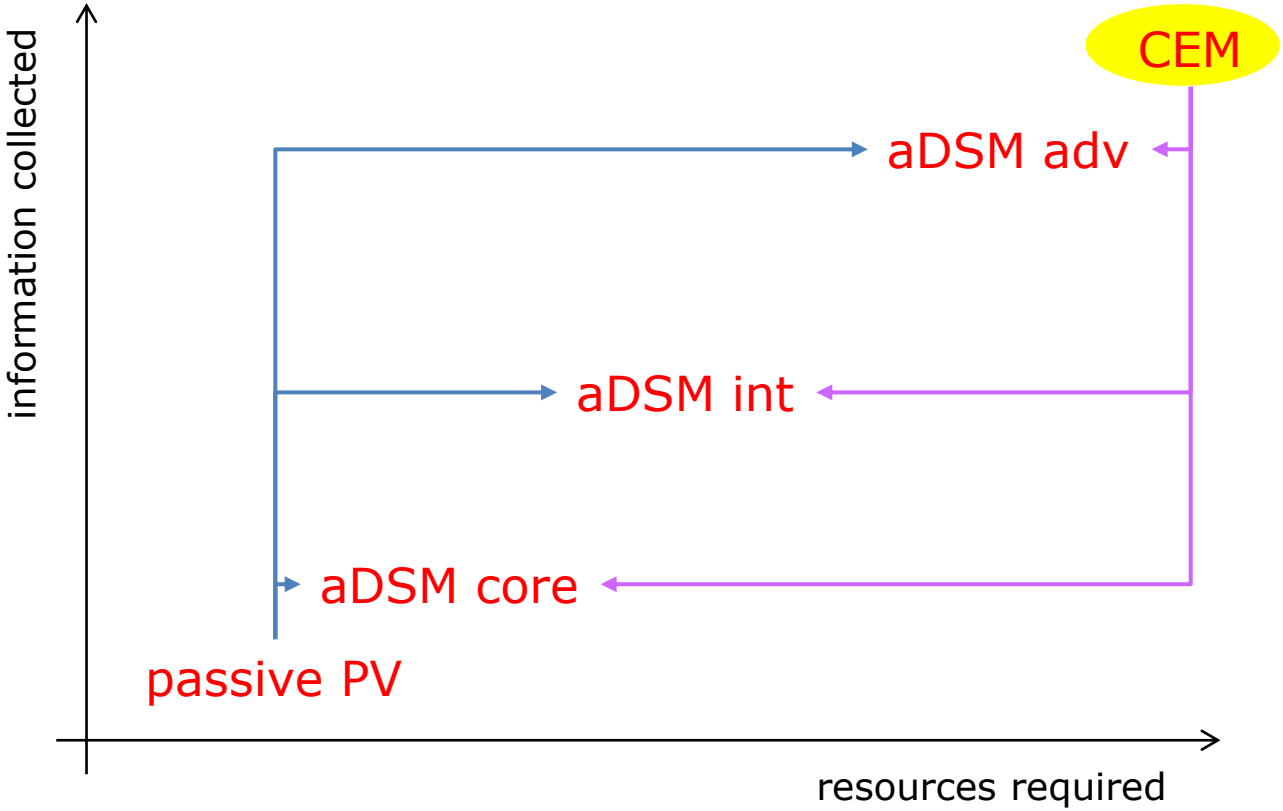


So either STR or IR; both require active monitoring & management of AE

Current situation re. active PV



From pilot/research to 'routine' aDSM



CEM vs. aDSM

	CEM	aDSM
Description	Prospective cohort study	Prospective systematic (programmatic) data collection
Main purpose	Early warning system	Strengthen management & monitoring of AEs
When used	Used in early post-marketing	Used for M/XDR-TB patients
# patients included	Limited and pre-defined	not pre-defined
Duration	Until defined #patients have complete FU	Not pre-defined
Follow-up	For a duration appropriate for drug(s) under study	At least for full duration of treatment (and if possible beyond)
Denominator	All patients enrolled in cohort	As CEM
Type of AEs collected	Any AE detected	Depends on package (but at least judged clinically significant)
Causality assessment	All AEs reported	May be on selection of AEs

Example plan Indonesia

- CEM for 100 patients on Bdq in 3 sites
  - Persahabatan hospital Jakarta
  - Hasan Sadikin hospital Bandung
  - Dr Soetomo hospital Surabaya
- Will implement patient triaging and STR nationwide → approx. 8,000 MDR-TB patients expected in 2017

Example plan Indonesia

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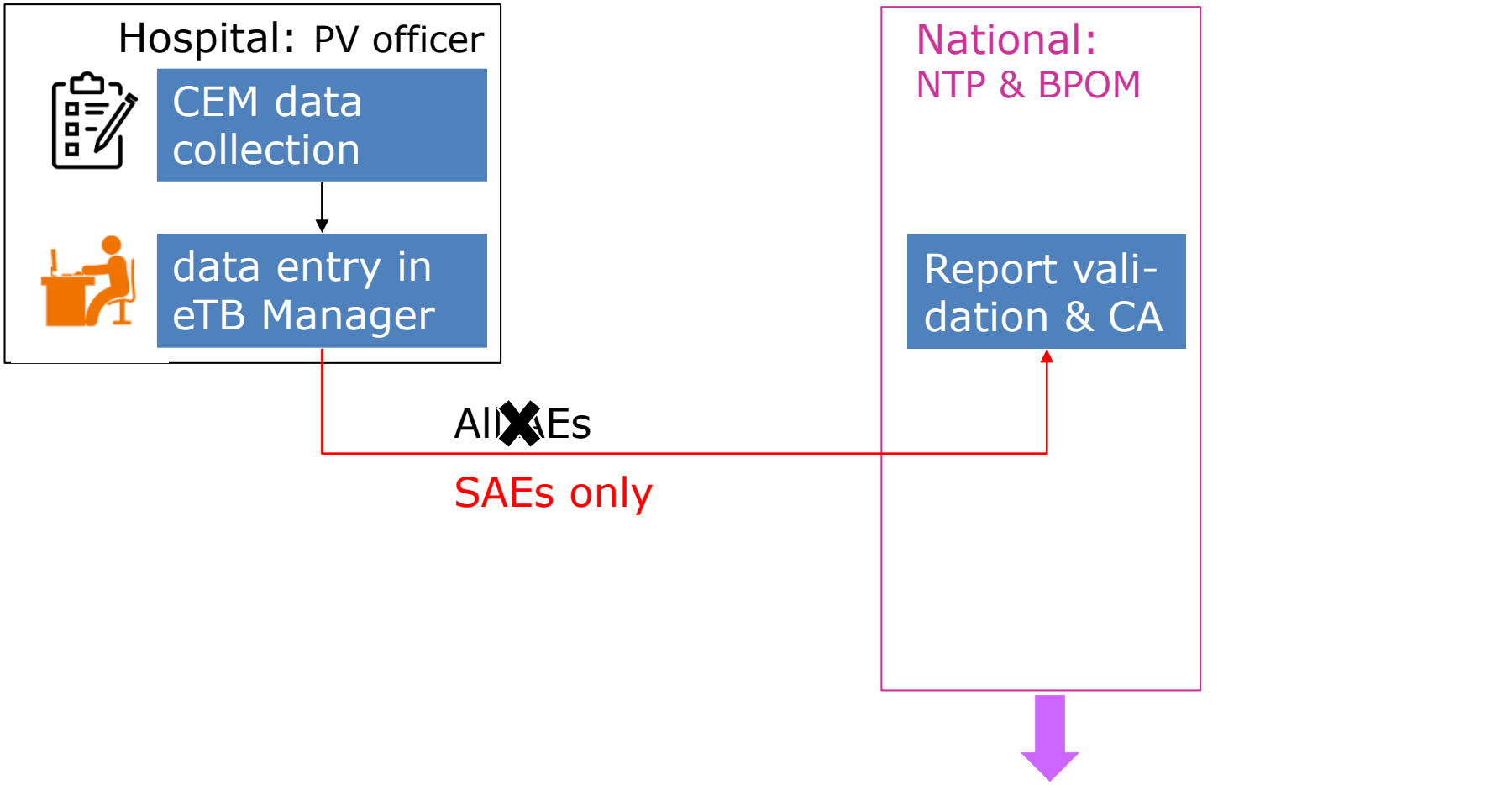
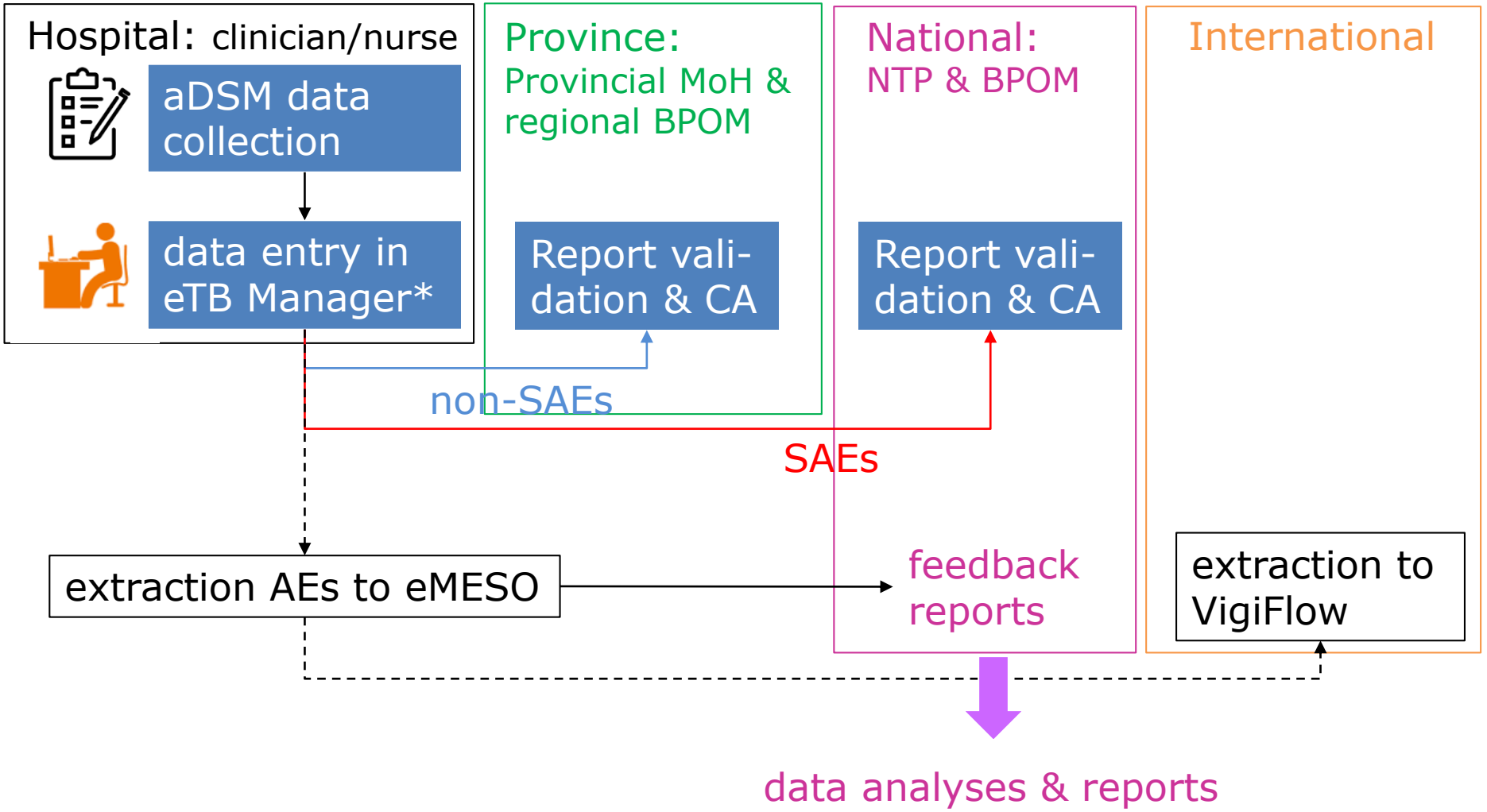
CHALLENGE TB

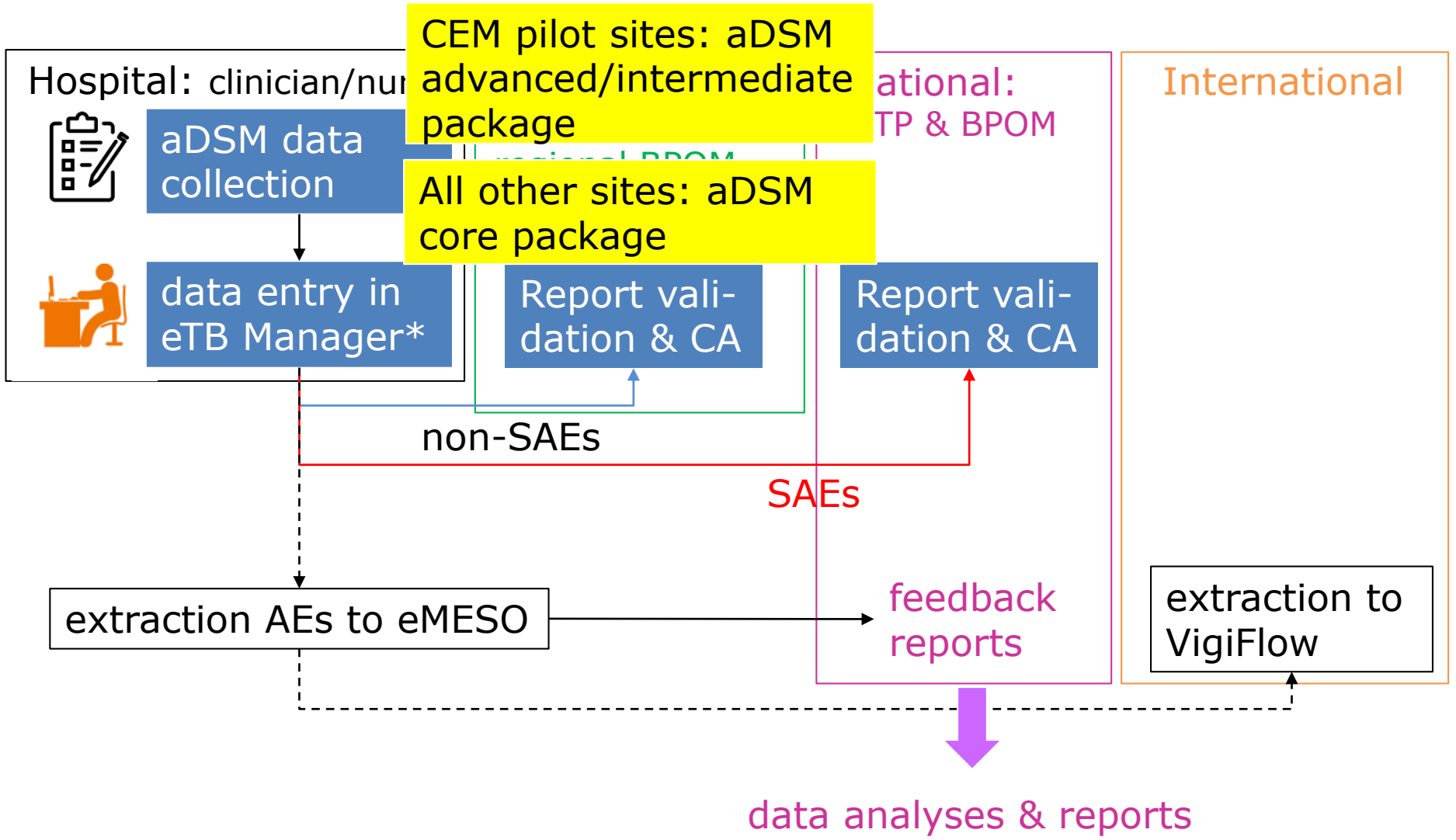
Current system Indonesia



Future system (proposed)



Future system (proposed)



R&R forms for CEM Indonesia

- Developed by PMDT group of NTP with guidance from KNCV, in collaboration with Badan POM (NPVC)
- 3 forms:
  1. Baseline (treatment initiation) form
  2. Treatment monitoring form
  3. (Laboratory) test result form
- Used in 3 pilot sites for Bdq
- Though NPVC has access to eTB-Manager it generally does not use its access rights
- Causality assessment irregular and infrequent

Treatment initiation form - Indonesia

FORM AWAL PENGOBATAN

Diisi pada kunjungan pertama pasien (Sebelum Pengobatan)

RS Rujukan : .....

Pewawancara: .....

Jabatan : .....

Administrasi

Nama Pasien : _____ Tanggal Wawancara : ☐☐ - ☐☐ - 20☐☐ (Tgl / bln / Tahun)

No NIK : _____ Tanggal Lahir : ☐☐ - ☐☐ - ☐☐☐☐

Anamnesis *(Beri tanda rumput sesuai kondisi pasien)*

Kondisi medis pasien (Yang ada sekarang dan masa lalu)	Tanggal Mulai	Tanggal Selesai	Masih berlangsung
Isi dengan data kondisi medis pasien yang terjadi satu tahun sebelumnya			
Perilaku Pasien			
Penyalahgunaan alkohol ☐			☐
Penyalahgunaan obat-obatan intravena ☐			☐
Perokok (tembakau) ☐			☐
Kondisi Medis			
Diabetes ☐			☐
Penyakit Liver, jelaskan ..... ☐			☐
Penyakit Ginjal, jelaskan ..... ☐			☐
Masalah penglihatan, jelaskan ..... ☐			☐
Masalah pendengaran, jelaskan ..... ☐			☐
Epilepsi ☐			☐
Depresi ☐			☐
Gangguan jantung, jelaskan ..... ☐			☐
Nyeri sendi, jelaskan ..... ☐			☐
Lain-lain, jelaskan			

Pengobatan lainnya yang dialami pasien dalam 30 hari sebelum dan pada saat permulaan pengobatan.

Obat	Indikasi	Dosis	Frekuensi	Tangal mulai (Tgl/Bln/Thn)	Tanggal selesai (Tgl/Bln/Thn)	Masih berlangsung
						☐
						☐

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Treatment initiation form

Kondisi Kesehatan Yang Dialami Selama 30 Hari Sebelumnya

Catatan: Laporkan semua kondisi kesehatan yg terjadi(termasuk karena TB) seperti kondisi saat ini, perubahan abnormal hasil lab, tanggal kunjungan ke RS disertai penyebab, kecelakaan, kemungkinan efek samping obat, dll.

List Pertanyaan
(Hanya sbg alat bantu)

- ❑ Hasil Lab Abnormal
- ❑ Kardiovaskuler
- ❑ Gangguan hepar
- ❑ Gangguan neurologi/psikiatri
- ❑ Muskuloskeletal/jaringan ikat
- ❑ Gastrointestinal
- ❑ Lain-lain.....

Perubahan Kondisi Kesehatan

Perubahan kondisi kesehatan atau kejadian yang tidak diinginkan	Tanggal dimulai (Tgl/Bln/Thn)	Tanggal selesai (Tgl/Bln/Thn)	Masih berlangsung	Keparahan (Severity) Detail informasi lihat lampiran 6	Tingkat Keseriusan (Seriousness)	Langkah/Solusi yang diambil (Jelaskan secara rinci:, nama obat, tanggal,frekuensi,dll)	Hasil
			❑	❑ Ringan ❑ Sedang ❑ Parah ❑ Mengancam Jiwa	❑ Tidak Serius ❑ Rawat inap yg lama ❑ Cacat Permanen ❑ Kelainan Bawaan ❑ Mengancam Jiwa ❑ Kematian	❑ Pengoban dilanjutkan, tidak ada perubahan ❑ Obat dihentikan seterusnya (withdrawn): ..... ❑ Obat dihentikan sementara lalu dilanjutkan kembali (interrupted): ..... ❑ Pengurangan dosis atau frekuensi obat (reduce) : ..... ❑ Lainnya,jelaskan	❑ Sembuh/ Selesai ❑ Belum Sembuh ❑ Sembuh dgn gejala sisa ❑ Tidak sembuh/ selsai ❑ Meninggal ❑ Tidak Diketahui
			❑	❑ Ringan ❑ Sedang ❑ Parah ❑ Mengancam Jiwa	❑ Tidak Serius ❑ Rawat inap yg lama ❑ Cacat Permanen ❑ Kelainan Bawaan ❑ Mengancam Jiwa ❑ Kematian	❑ Pengoban dilanjutkan, tidak ada perubahan ❑ Obat dihentikan seterusnya (withdrawn): ..... ❑ Obat dihentikan sementara lalu dilanjutkan kembali (interrupted): ..... ❑ Pengurangan dosis atau frekuensi obat (reduce) : ..... ❑ Lainnya,jelaskan	❑ Sembuh/ Selesai ❑ Belum Sembuh ❑ Sembuh dgn gejala sisa ❑ Tidak sembuh/ selsai ❑ Meninggal ❑ Tidak Diketahui

Treatment monitoring form - Indonesia

FORM MONITORING PENGOBATAN
Di isi pada saat setiap kunjungan pasien

RS Rujukan :.....
Pewawancara:.....
Jabatan: .....

Nama Pasien : _____ Tanggal Wawancara ☐☐ - ☐☐ - 20☐☐
(Lihat TB 01 atau data dasar pasien) *Tgl bln Tahun*

Tipe kunjungan: ❑ Follow-up Rutin
❑ Diluar jadwal rutin (alasan): _____

Apakah ada perubahan pengobatan lainnya (selain TB) sejak kunjungan terakhir atau pada saat kunjungan dilakukan?
❑ Tidak ❑ Ya Isi tabel dibawah apabila ada perubahan

Obat	Indikasi	Dosis	Frekuensi	Tangal mulai (Tgl/Bln/Thn)	Tanggal selesai (Tgl/Bln/Thn)	Masih berlangsung
						❑
						❑
						❑

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Treatment monitoring form: AE data

Adverse Events (Kejadian yang Tidak Diharapkan)

Catatan: Laporkan semua kondisi kesehatan yg terjadi sejak kunjungan terakhir seperti kondisi saat ini, perubahan abnormal hasil lab, tanggal kunjungan ke RS disertai penyebab, kecelakaan, kemungkinan efek samping obat,kehamilan, kematian dan penyebabnya, kemungkinan interaksi obat, dll.

List Pertanyaan
Hanya sebagai alat bantu

- ❑ Hasil lab abnormal
- ❑ Kardiovaskuler
- ❑ Keadaan hepar
- ❑ Renal
- ❑ System saraf / psikiatrik
- ❑ Musculoskeletal/jaringan ikat
- ❑ Gastrointestinal
- ❑ Anemia/ gangguan darah lainnya
- ❑ Penglihatan
- ❑ Pendengaran
- ❑ Perubahan status HIV/AIDS
- ❑ Perubahan kadar alkohol/penyalahgunaan obat
- ❑ Perubahan status merokok
- ❑ Kejadian lain/perubahan kondisi yang sebelumnya ada

Pencatatan kejadian BARU dan Perubahan Kondisi

Perubahan Kesehatan (Jelaskan secara detail)	Tanggal dimulai Tgl/Bln/Thn	Tanggal selesai Tgl/Bln/Thn	Keparahan (Severity)	Tingkat Keseriusan (Seriousness)	Langkah atau solusi yang diambil	Perkiraaan Causality Assessment	Rechallenge	Hasil Akhir [1]
			❑ Ringan ❑ Sedang ❑ Berat ❑ Mengancam Jiwa	❑ Tidak Serius ❑ Rawat inap yg lama ❑ Cacat Permanen ❑ Kelainan Bawaan ❑ Mengancam Jiwa ❑ Kematian	❑ Pengoban dilanjutkan, tidak ada perubahan ❑ Obat dihentikan seterusnya (withdrawn): ..... ❑ Obat dihentikan sementara lalu dilanjutkan kembali (interrupted): ..... ❑ Pengurangan dosis atau frekuensi obat (reduce) : ..... ❑ Lainnya,jelaskan	❑ Certain ❑ Probable ❑ Possible ❑ Unlikely ❑ Unclassified ❑ Unassessable	❑ Tidak dilakukan ❑ KTD terjadi kembali ❑ KTD tidak terjadi ❑ Hasil tidak diketahui	❑ Sembuh/ Selesai ❑ Belum Sembuh ❑ Sembuh dgn gejala sisa ❑ Tidak sembuh/ selsai ❑ Meninggal ❑ Tidak Diketahui
			❑ Ringan ❑ Sedang ❑ Berat ❑ Mengancam Jiwa	❑ Tidak Serius ❑ Rawat inap yg lama ❑ Cacat Permanen ❑ Kelainan Bawaan ❑ Mengancam Jiwa ❑ Kematian	❑ Pengoban dilanjutkan, tidak ada perubahan ❑ Obat dihentikan seterusnya (withdrawn): ..... ❑ Obat dihentikan sementara lalu dilanjutkan kembali (interrupted): ..... ❑ Pengurangan dosis atau frekuensi obat (reduce) : ..... ❑ Lainnya,jelaskan	❑ Certain ❑ Probable ❑ Possible ❑ Unlikely ❑ Unclassified ❑ Unassessable	❑ Tidak dilakukan ❑ KTD terjadi kembali ❑ KTD tidak terjadi ❑ Hasil tidak diketahui	❑ Sembuh/ Selesai ❑ Belum Sembuh ❑ Sembuh dgn gejala sisa ❑ Tidak sembuh/ selsai ❑ Meninggal ❑ Tidak Diketahui

(Lab) test results form

Pengukuran/Penilaian Laboratory	Nilai / Hasil	Tidak Diukur[1]	Tanggal Pemeriksaan
Berat	.....Kg	❑	
Tinggi	.....Cm	❑	
Test HIV	❑ positif ❑ negatif	❑	
Test Kehamilan[2]	❑ Hamil ❑ Tidak Diketahui ❑ Tidak Hamil Haid Terakhir: ..... (tgl/bln/thn) Menyusui : ❑Ya ❑Tidak	❑	
Kimia Darah dan elektrolit	Hb : ..... g/dL Leukosit : ..... $10^3/\mu$ Kreatinin : ..... mg/dL Kalium : ..... mEq/L Magnesium : ..... mEq/L Kalsium : ..... mg/dL Asam laktat: : ..... mg/dL Lipase : ..... U/L Glukosa puasa : ..... mmol/L	❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑	
Test Fungsi Liver	Albumin : .....g/dL SGOT/AST : .....IU/L SGPT/ALT : ..... IU/L Bilirubin Total : ..... mg/dL	❑ ❑ ❑ ❑	
Thyroid Stimulating Hormon	.....		
Electrocardiogram	QTcF interval [ ][ ][ ] ms [3]	❑	
Lainnya, Jelaskan:.....			

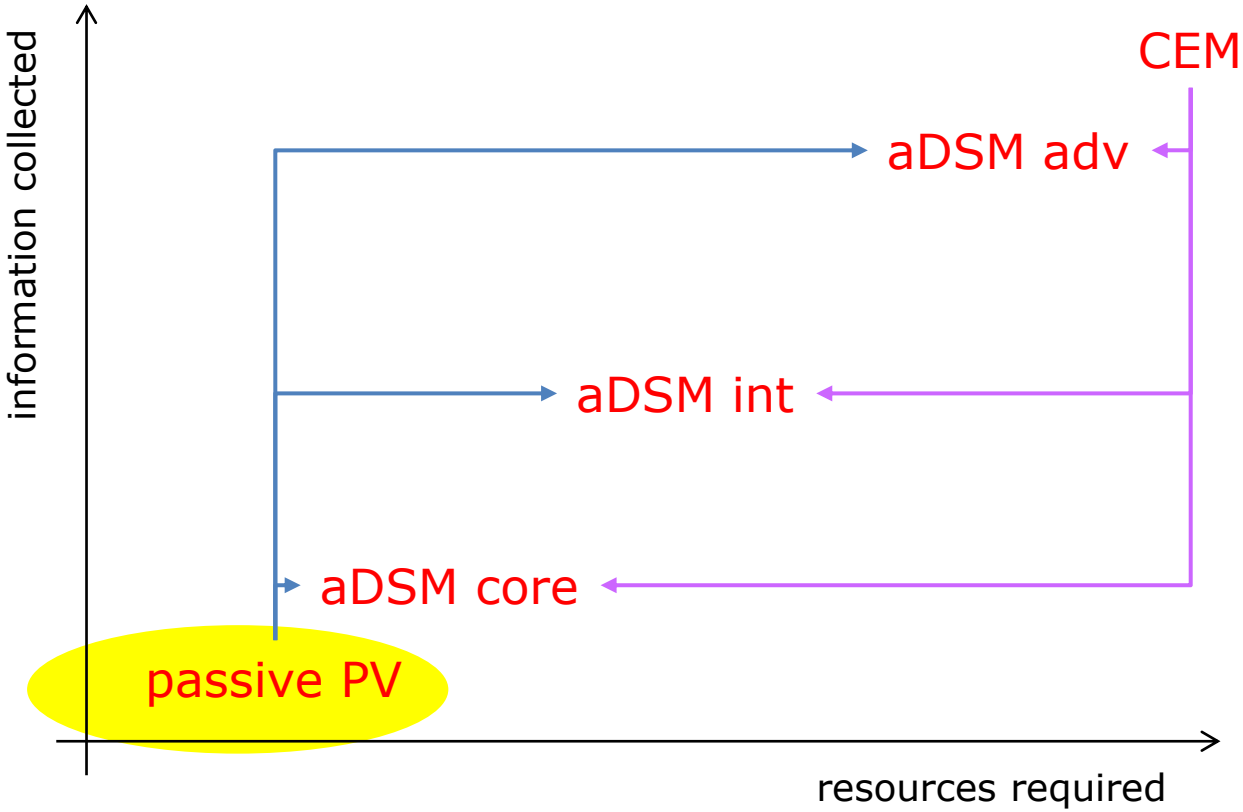
Test Lainnya/ Konsultasi:	Hasil	Tidak dilakukan
Konsultasi Psikiatri		❑
Audiometri		❑
Test Penglihatan		❑
Lainnya, Jelaskan:.....		

CHALLENGE TB

R&R plan for Indonesia

- Collect the data in routine PMDT forms and registers
  → *see where these need adaptation*
- Register all clinically relevant AE in patient file: good clinical practice
- Avoid duplicate data collection and entry at any level
  → *automated linkage between TB and PV systems*

From pilot/research to 'routine' aDSM



Example Tajikistan

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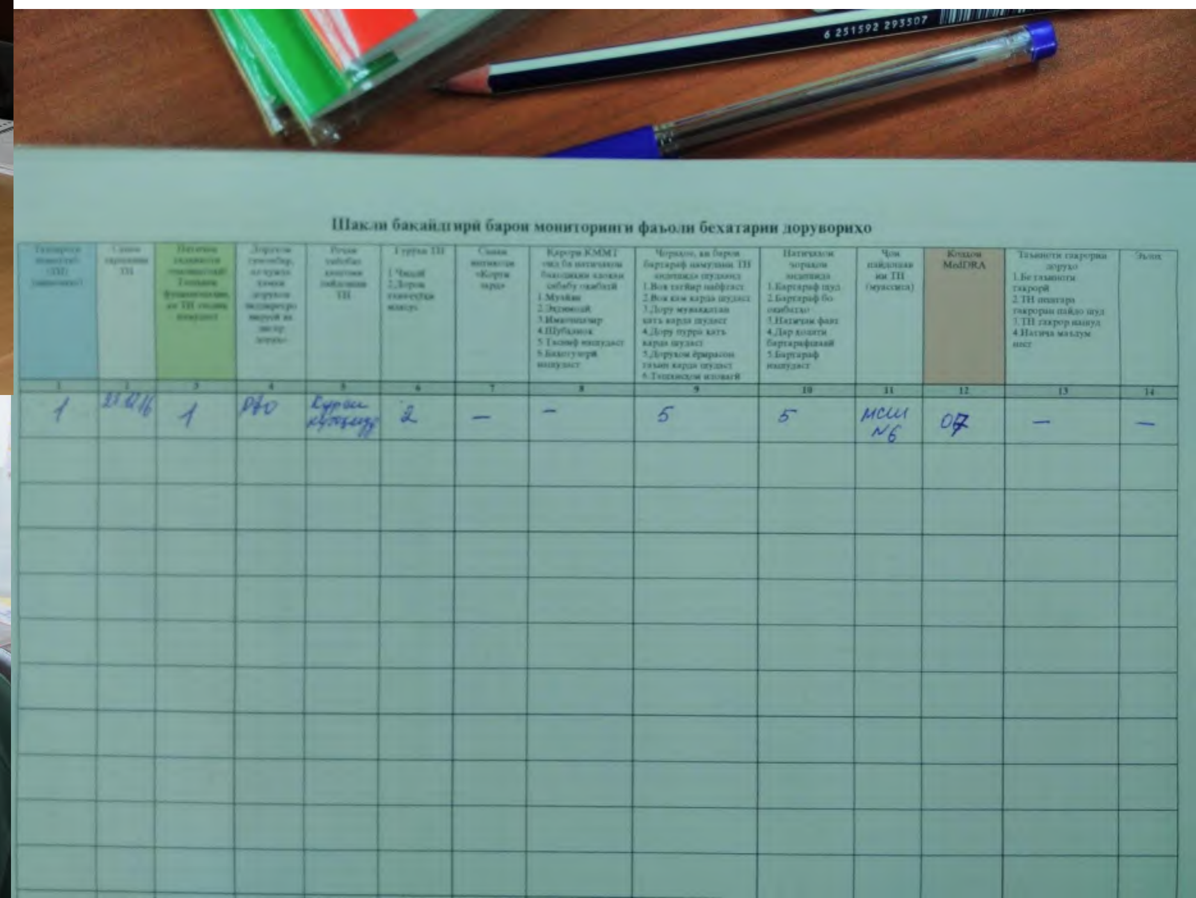
CHALLENGE TB

Tadjikistan

- aDSM intermediate package for all M/XDR-TB patients on ND&R in 3 pilot sites
- R&R integrated in routine recording and reporting system:
  - AE data registered on paper forms being part of patient file
  - In principle **all** AEs of clinical relevance recorded in patient file
  - Data entry in Patient Triage Application (PTA) for SAEs and AEs of special interest

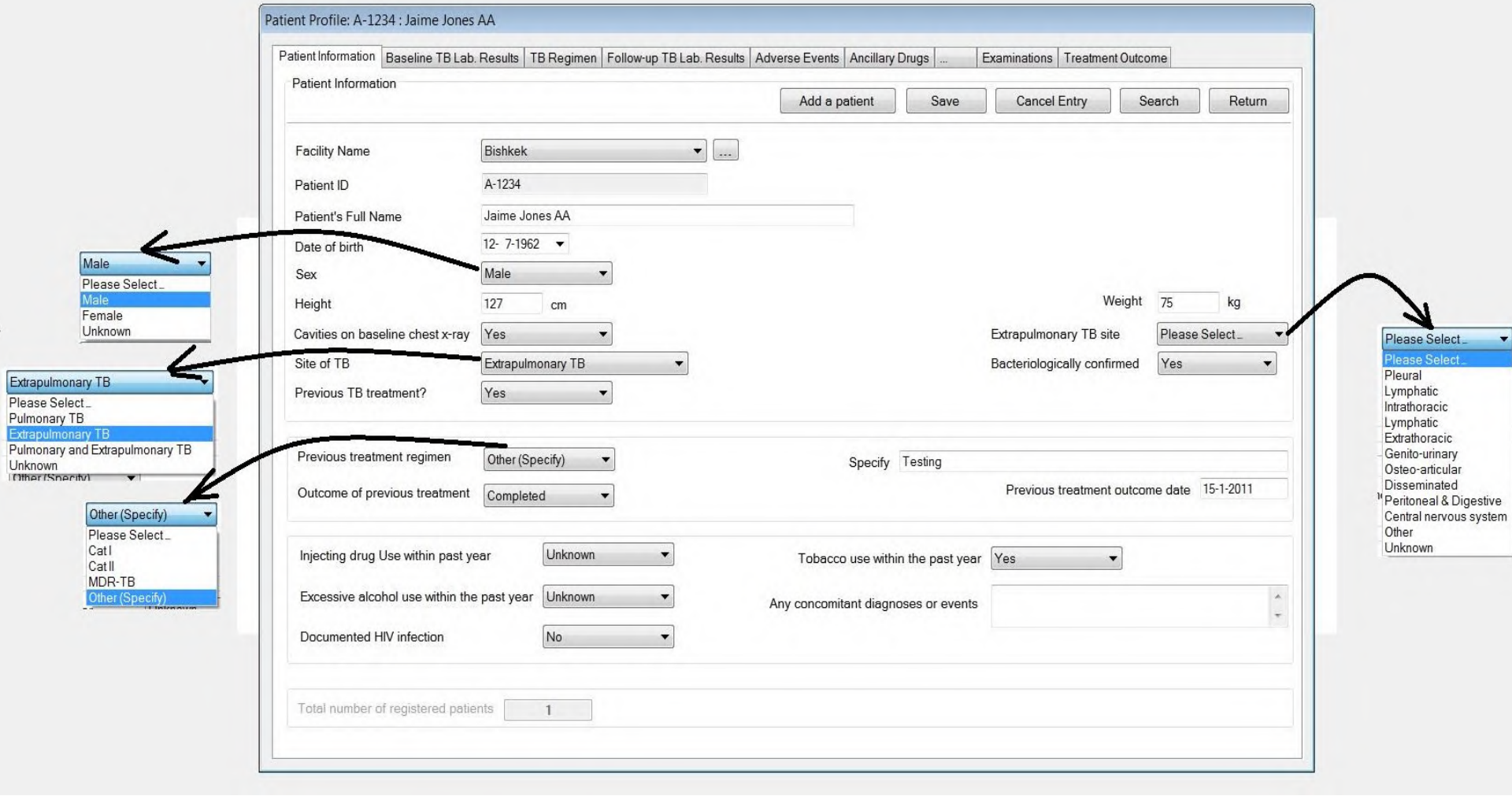
R&R form for AE Tadjikistan is part of the patient file



Patient triage application

- Interim solution – no electronic data collection so far
- Desktop application on personal computers running MS Windows – not internet-based
- Data collection of adverse events
- Validation rules for good data quality
- User friendly, minimum data entry, use of pre-defined values
- Automation of data exportation to Excel and PDF
- System reports can be generated
- Open for customization and integration of database into national surveillance systems
- Easy look and feel

Patient registration



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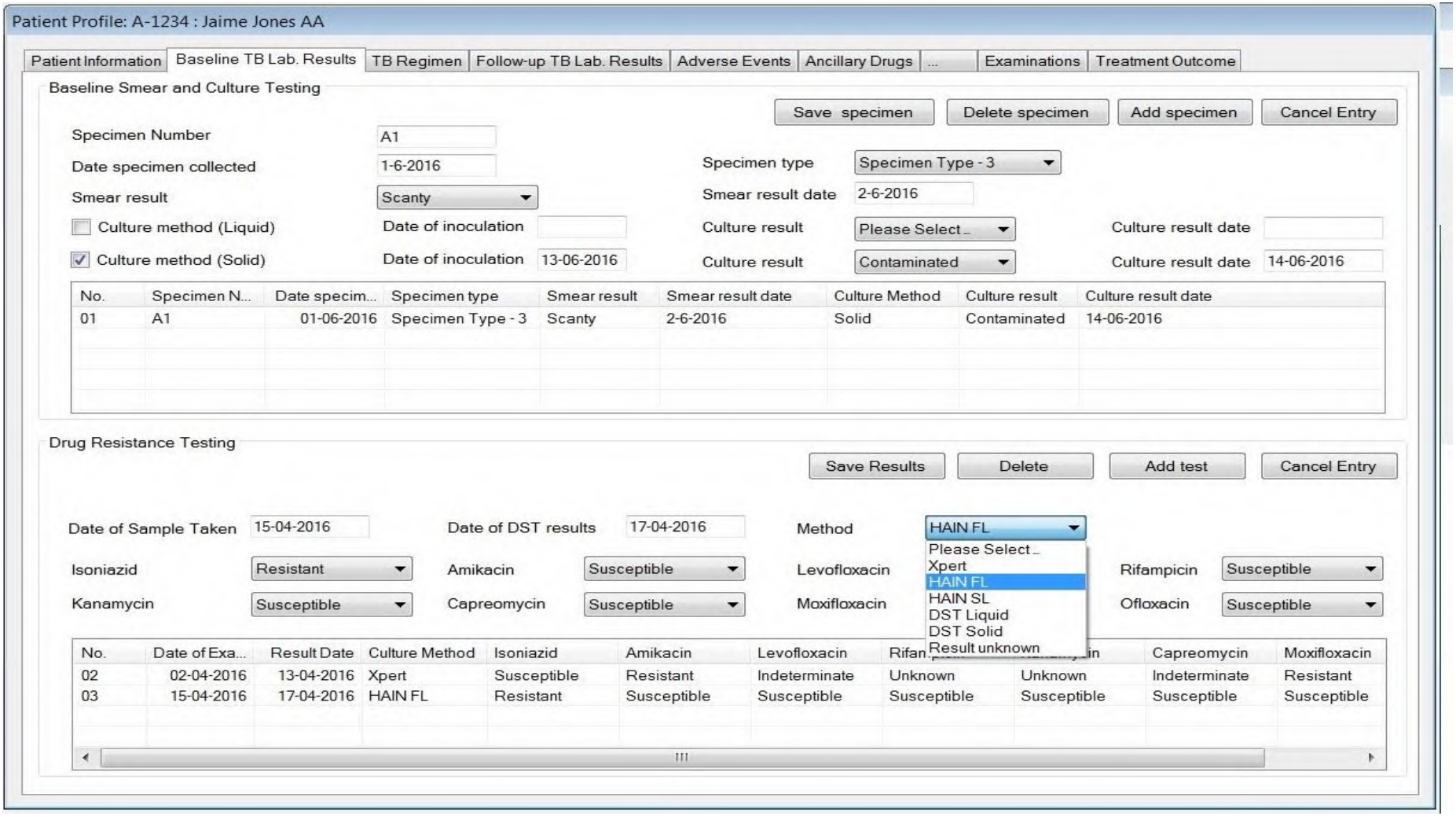
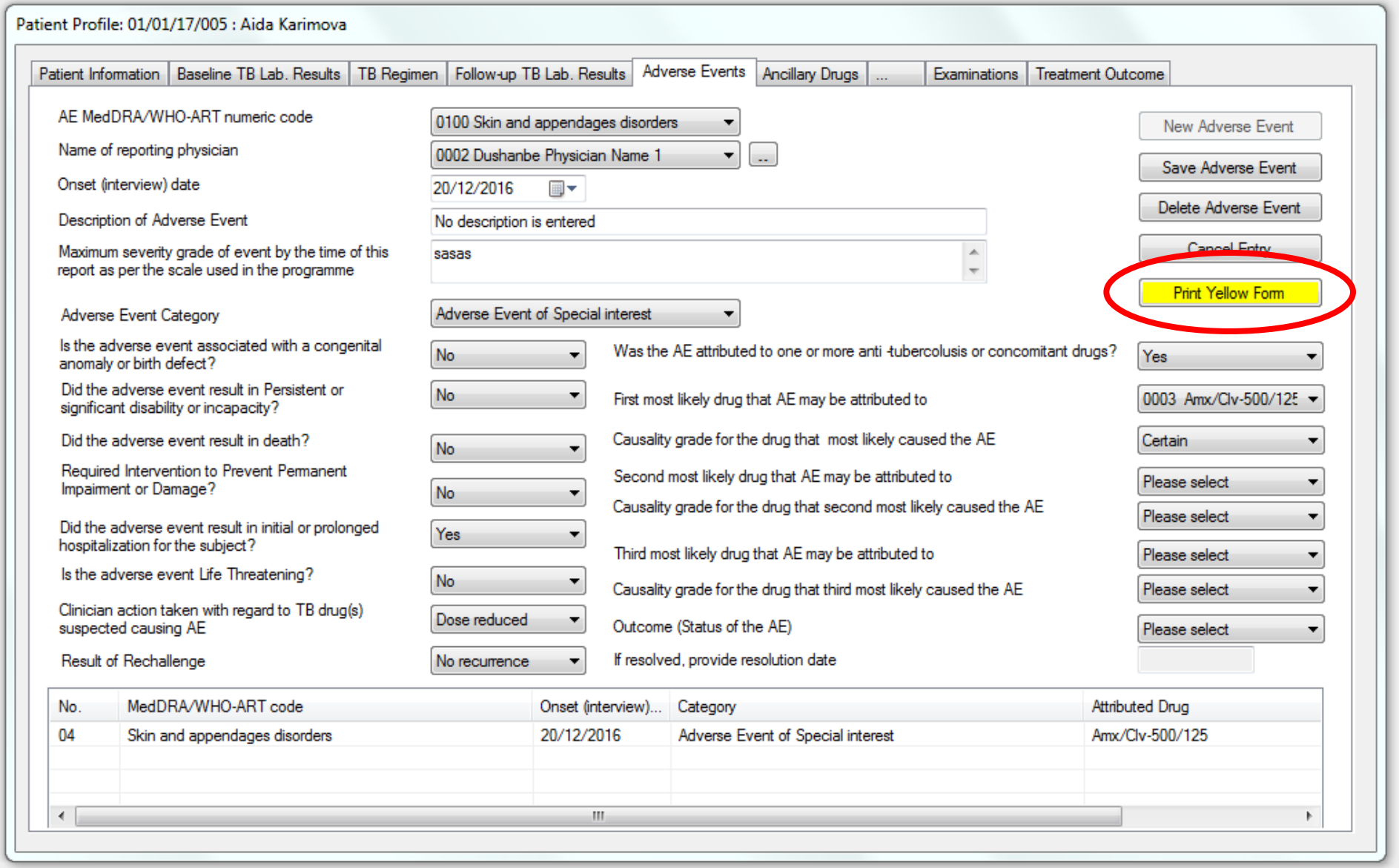
CHALLENGE TB

Baseline lab results



Adverse events



MINISTRY OF HEALTH AND SOCIAL PROTECTION OF POPULATION
OF THE REPUBLIC OF TAJIKISTAN
STATE AGENCY ON CONTROL OF PHARMACEUTICAL ACTIVITY
IN THE REPUBLIC OF TAJIKISTAN
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ADVERSE EVENT OR DRUG INEFFICACY REPORT

(to be filled out by health or pharmaceutical staff)

AE – Adverse Event
DI – Drug inefficacy
D – Drug
PWID – People who use injection drugs

INN - International Non
SD – Suspected drug
ICD-10 – International (

Is this AE report the first one? Yes ☐ No ☐

If "No", please specify the date of previous report: ___ ___ .
DD / MM /

1. Patient's information

1. Patient's name and surname	2. Patient's address	3. № Medical
Aida Karimova		**01/01/17/005**

6. Clinical diagnosis (with indication of code accordingly ICD -10)
Main diagnosis: _____
Secondary diagnosis: _____

7. Pregnancy Yes ☐ No ☐ 11. Passport № ___
8. Alcohol abuse Yes ☒ No ☐ 12. Telephone № _
9. Smoking Yes ☒ No ☐ 13. Height of patient
10. PWID Yes ☒ No ☐ 14. Weight of patient

15. Consequences of AE		16. Other important information (anamnesi
☒ recovery without consequences **Please select**	☐ recovery with consequences	condition and others) *Please indicate the treatment regimen:* ☐ Short-term treatment regimen for MDR- ☐ Treatment regiment, including Bedaquili ☐ Treatment regiment, including Delaman ☐ Treatment regimen for XDR-TB patients with

2. Information about suspected drug

17. Brand name **Amx/Clv-500/125**		24. Drug and dose
18. INN (generic)		25. Daily dose in n
19. Drug manufacturer		26. Single dose in
20. Drug serial number		27. Frequency of u (intake/injection)
21. Drug expiration date		28. Ways of use/ad
22. Indication to suspected drug		29. Date of drug ca
23. Date of drug prescription		

3. Information about Adverse Event/ Lack of Efficacy

30. Date of AE/DI appearance	31. Date of AE/ID stopping	33. Category of AE seriousness:
20/12/2016		**Adverse Event of Special interest**

32. Describe AE: / Indicate DI:
No description is entered

☐ death of patient
☐ threat for life
☐ hospitalization
☒ prolongation of hospitalization period
☐ temporary or serious disability / invalidity
☐ congenital abnormalities of development
☐ other (Please indicate)

34. Did the patient had earlier AE for this drug: ☐ Yes ☐ No

4. Information about drugs for treatment of main and noncurrent diseases

(excluding drugs, which were used for AE management)

	35. Brand name or INN of drug	36. Dosage form and dose strength	37. Single dose in mg (g)	38. Frequency of use	39. Ways of use	40. Date of prescription	41. Date of cancellation
Drugs for treatment of main disease							
Drugs for treatment of concomitant disease							

5. Management of adverse event

42. Did AE disappear after cancellation of suspected drug: ☐ Yes ☐ No	45. Did AE management was not done ☐ Yes ☐ No
43. Did AE appear again after repeated prescription of suspected drug: ☐ Yes ☐ No	46. In case of drug therapy, please indicate name of drugs, doze regimens and duration of the prescription:
44. Did AE appear again after reducing the doze of the suspected drug: ☐ Yes ☐ No	

6. Causality assessment of clinical implications of adverse reactions with suspected drug

☐ Certain	☐ Probable	☐ Possible	☐ Doubtful	☐ Non-classifiable	☐ Non-assessable

7. Information about person, provided this information / notifier

Other solutions are possible

- Depends on country's current situation and preferences

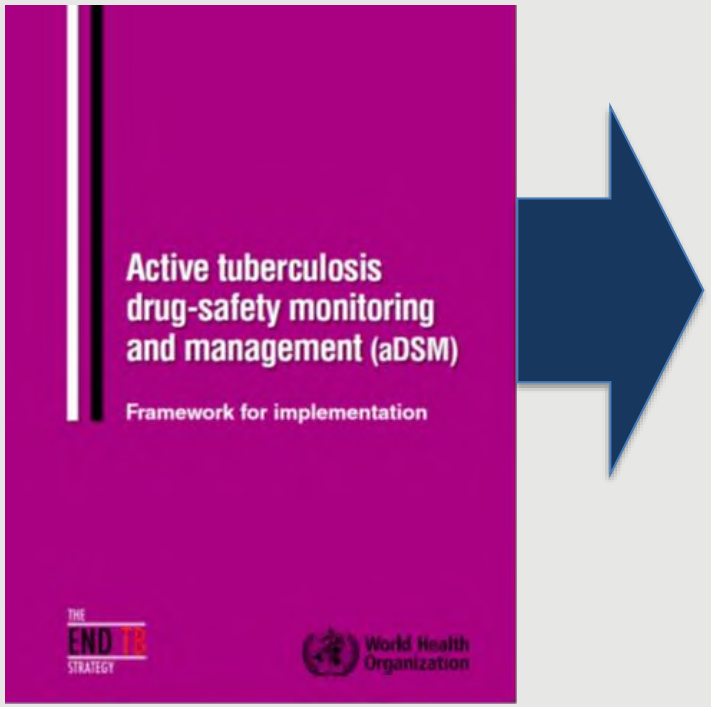
Guidance for introduction of new drugs and regimens

- Available at http://www.challengetb.org/publications/tools/pmdt/Generic_programmatic_and_clinical_guide_for_the_introduction_of_new_drugs_and_shorter_regimens.pdf
- Includes guidance on aDSM with examples:
  - laboratory testing schedule
  - data to be recorded
  - reporting forms

V
ON

CHALLENGE TB

Components of aDSM Roadmap
(adapted from WHO aDSM framework)



- National coordination, policy, guidelines and implementation plan development
- Recording and reporting
- Health care workers capacity development
- Clinical management
- Data management and analysis

Steps in chronological order

Develop aDSM coordination structure at national level

Develop national guidance document with (aDSM) activities and SOPs

PV data elements* added to routine data collection forms

Electronic database that captures collected data developed/adapted

Training for all staff involved in PV

Data collection during the full period of patient monitoring

Implementation, management and supervision of aDSM

Data analysis with causality assessment and identification of signals

** See aDSM framework document*

Analyses and reporting:
some indicators

Class	Indicator name	Calculation
Coverage	DR-TB patients started on DR-TB treatment	Numerator: #TB cases started on DR-TB treatment incl. in aDSM Denominator: #TB cases started on DR-TB treatment
SAEs	DR-TB patients included in aDSM with any SAE	Numerator: #TB cases included in aDSM with one or more SAE Denominator: #TB cases included in aDSM
adverse drug reactions	Frequency of drug-associated ADRs	Numerator: #ADRs attributed to drug in regimen (per drug, per ADR) Denominator: #TB cases included in aDSM
	Time to development of ADRs	Difference in days between the date of starting drug of interest and the date of first detected onset of ADR (per drug, per ADR)

Challenges & potential solutions

- Recording and reporting time consuming
  - Solution: Indonesia has PV officers who report and record
  - However for ideally it should be the treating clinical recording and reporting

→ Keep recording and reporting to a minimum, while ensuring that enough data is collected for proper causality assessment!

→ Only enter data on aDSM in the package chosen

→ Avoid duplicate recording and reporting

Challenges and potential solutions (2)

- Digital data collection/data entry
  - Away from source → ideally entry of the data should be at the site
  - Internet-based systems → offline mode should be available for quick and safe entry of data

Challenges and potential solutions (3)

- Capacity of national PV centers still weak
  - Understaffing/staff turnover
  - No causality assessment for all reported AE
  - Irregular causality assessment, no checks of data entry
  - No feedback reports

→ Further international awareness raising and advocacy needed to increase funding for PV centers

Thank you!

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CHALLENGE TB