



Priorities and Lessons Learned in the endTB Multi-Country Observational Study: Future Analysis Plans

Uzma Khan
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Lessons Learned





Lessons Learned 1

Barriers to Access: Drug Procurement



Drug importation

- Procure Bdq, Dlm, Lzd, Cfz
 - Support documentation and importation process
 - Establish communication b/w implementing projects and procurement agent

Issues faced

- Lengthy and different process across countries



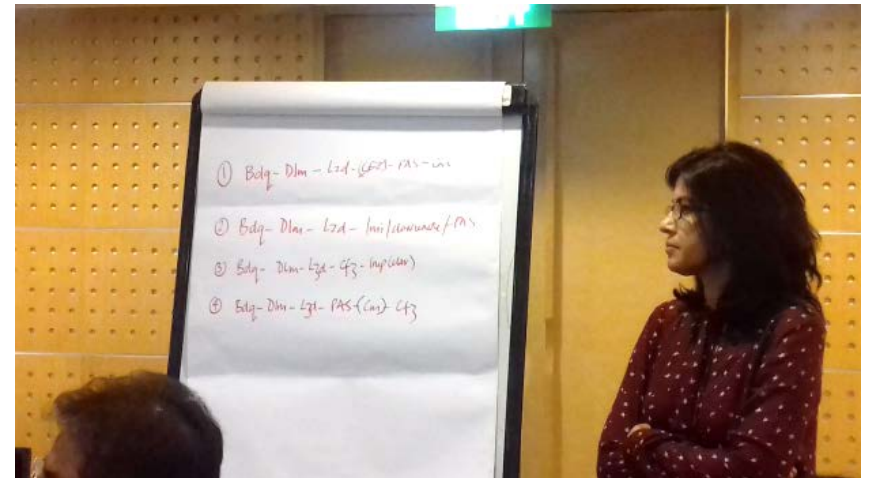
Lessons Learned 1 Barriers to Access: Approvals from Ethical Review Boards



- Ethical approvals were required, not just for the observational study but also for introducing Bdq and Dlm in some countries for routine clinical care
 - Central and site specific approval obtained
 - Time consuming process, caused additional delays in access
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Lessons Learned 2 Capacity Building: Trainings







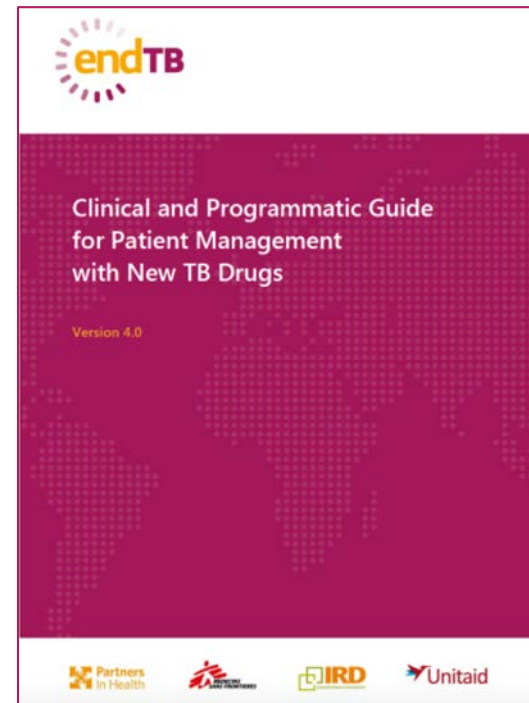


Lessons Learned 3

Strengthening Capacity: Resources – clinical guidance

The endTB Clinical Guide

- Guidance on regimen design, drug interactions, safety monitoring and management
- Used by clinicians and programs
- Dynamic document, incorporates learnings from the field, last version 4.0
- Available in different languages – English, Russian and Spanish





Lessons Learned 3

Strengthening Capacity: Resources - PV Unit



Safety reporting



Access to new
information



Access to resources



Interactions between sites
to improve knowledge
and experience



Advise on PV issues
and dissemination of
information



Lessons Learned 3 Strengthening Capacity: Resources - endTB Medical Committee



- Includes internal and external experts on weekly roster
 - Direct access to country teams to share cases and seek advise
 - So far >550 cases reviewed from 20 countries
 - 57% from non-endTB countries
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Lessons Learned 3

Strengthening Capacity: Resources-endTB Website



endTB clinical
guide



PV
Forms



E-learning
modules



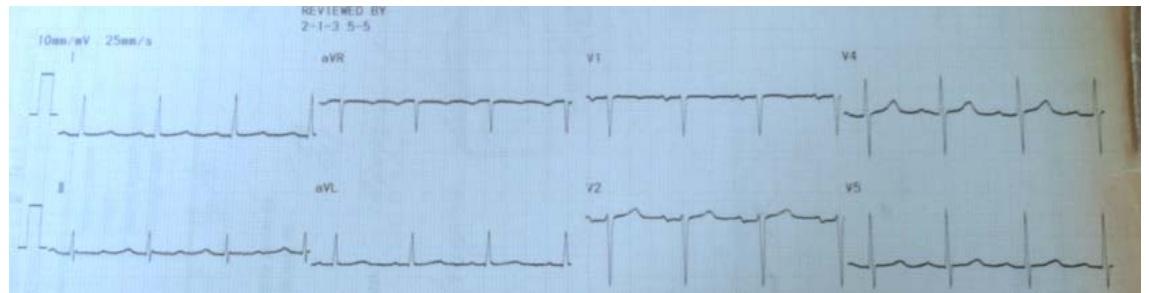
Report - endTB
interim analysis



Lessons Learned 3

Strengthening Capacity: Clinical Evaluation and Monitoring

- Brief Peripheral Neuropathy screen
- Visual acuity screen
- Color Blindness screen
- ECG
- Audiometry (hearscreen app)
- Lab capacity: routine SL DST not available in some countries. Introduced Second-line LPA, additional tests not routinely done





Lessons Learned 3

Strengthening Capacity: Development of the endTB EMR

EndTB Patient Dashboard
Patient Summary

Nida Yaqoob (PAK-001-00018-01) | Female | 20 Years 7 months 22 days

TREATMENT INFORMATION
Treatment start date: 15 Aug 16
Current month of treatment: 6.4

CASE DEFINITION
WHO registration group: Treatment After Failure
Disease site: Pulmonary
Drug resistance profile: Confirmed drug resistant TB
Sub-class of drug resistance profile: Confirmed MDR

SEROLOGY STATUS
HIV: Negative
Hep B ag: Non-reactive
Hep C ab: Non-reactive
Baseline HIV: Negative
Hepatitis B: No
Hepatitis C: No

CO-MORBIDITIES
No Co-morbidities for this patient

IMPORTANT DATES
Treatment start date: 15 Aug 16

PAST TB TREATMENT INFORMATION
Year first TB treatment: 2016
Drug-Susceptible TB Treatment in the Past: No
Drug-Resistant TB Treatment in the Past: Yes
How Many Drug-Resistant TB Treatments: 1
Past TB drugs > 1 month: Cycloserine (Cs), Pyrazinamide (Z), Amikacin (Am), Levofloxacin (Lfx), Ethionamide (Eto)

PREVIOUS TB TREATMENT TABLE

Start date of past TB treatment	End date of past TB treatment	Type of treatment	Regimen type	Past TB outcome
03 Feb 15	05 Aug 16	DR-TB	Cat 4	Failed

DST RESULTS

No	Date	H	H	R	E	S	Z	Of	M	M	A	K	C	E	Et	PA	Bd	Di	Lx	Clz	
nth		0.2	1.0					x	x	0.2	2.0	m	m	o	Cs	S	q	m	d	Clz	
-3	06 Dec 15			Re	Re	Re	Re	Su	Su			Su	Su	Su							
-1	05 Aug 16			Re	Re	Re	Re	Su	Su			Su	Su	Su							
3				S	S	S	S	S	S			S	S	S							

- Developed customized EMR
- Standardized data collected at all sites
- Can be used for clinical monitoring
- Generate customized reports
- Global resource and “endTB legacy”

Rule Name	Treatment Reg No	Name	Treatment Facility	EMR ID	Notes	Endtb Exports		
						Date	Job Status	Download
Baseline Firstline DST missing					DST more than a n			
Baseline Firstline DST missing					No results by the e treatment.	05-Sep-2017 23:30	COMPLETED	
Baseline Firstline DST missing					No results by the e treatment.	05-Sep-2017 16:20	COMPLETED	
Baseline Firstline DST missing					No results by the e treatment.	04-Sep-2017 23:30	COMPLETED	
Baseline Firstline DST missing					No results by the e treatment.	03-Sep-2017 23:30	COMPLETED	
Baseline Firstline DST missing					No results by the e treatment.	02-Sep-2017 23:30	COMPLETED	
Baseline Firstline DST missing					No results by the e treatment.	01-Sep-2017 23:30	COMPLETED	
Baseline Firstline DST missing					No results by the e treatment.	31-Aug-2017 23:30	COMPLETED	
Baseline Firstline DST missing					No results by the e treatment.	30-Aug-2017 23:30	COMPLETED	
Baseline Firstline DST missing					No results by the e treatment.	29-Aug-2017 23:30	COMPLETED	
Baseline Firstline DST missing					No results by the e treatment.	28-Aug-2017 23:30	COMPLETED	

Lessons Learned 4 Data Management



Trainings

Importance of data collection and using it for programmatic decision making



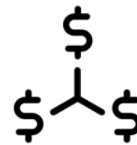
Central Data Quality Check

Queries sent back to sites, sites then make changes as needed



On-Site Data Quality Checks

Improving data completeness, and communication between data and clinical teams



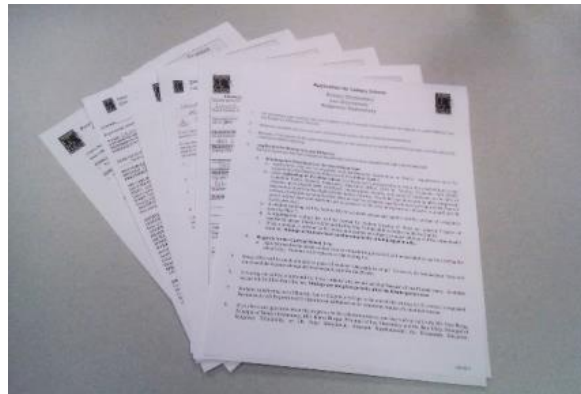
Funding

Huge amount of effort – even with single EMR takes a long time – cleaning, verifying, resolve outstanding queries, analysis. Time and labor intensive and costs!! Requires \$\$\$



Lessons Learned 5 Informed Consent

- Time consuming process
 - Additional consent forms signed for treatment with Bdq or Dlm
- Risk of patient refusals
- Should be universal for all regimens, not specific to a drug





Lessons Learned 6 Patient-Centered Care



- Individualized regimen design
 - Empowering clinicians & patients in clinical decision making
 - Treating patients with co-existing conditions (HIV, hep C), children and pregnant women
 - Experience in prolonged use of Bdq, Dlm and concomitant use
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Lessons Learned 7

Diverse Implementation strategies

- Heterogenous care models
- Private sector engagement
- HIV or hep C co-infected populations
- Urban and rural; developing or integrating existing strategies to link patients to healthcare centers





Lessons Learned 8 Working in a Consortium





Lessons Learned 9 - endTB Interim Analysis

<http://www.endtb.org/resources/endtb-interim-analysis-july2018>



Delamanid analysis

- \geq Grade 3 QTc interval prolongation infrequent:
- Culture conversion occurs in ~ **80%**, including among XDR and patients with comorbidities
- Balance of efficacy and safety supports delamanid use

Injectable analysis

- Important toxicity common among patients receiving SL injectable
 - 20% of patients had hearing loss
 - 36% had injectable-related AE (hearing loss, acute renal failure, electrolyte imbalance)
- Balance of evidence does not support universal use of SL injectable
- Monitoring of injectable-related toxicity key

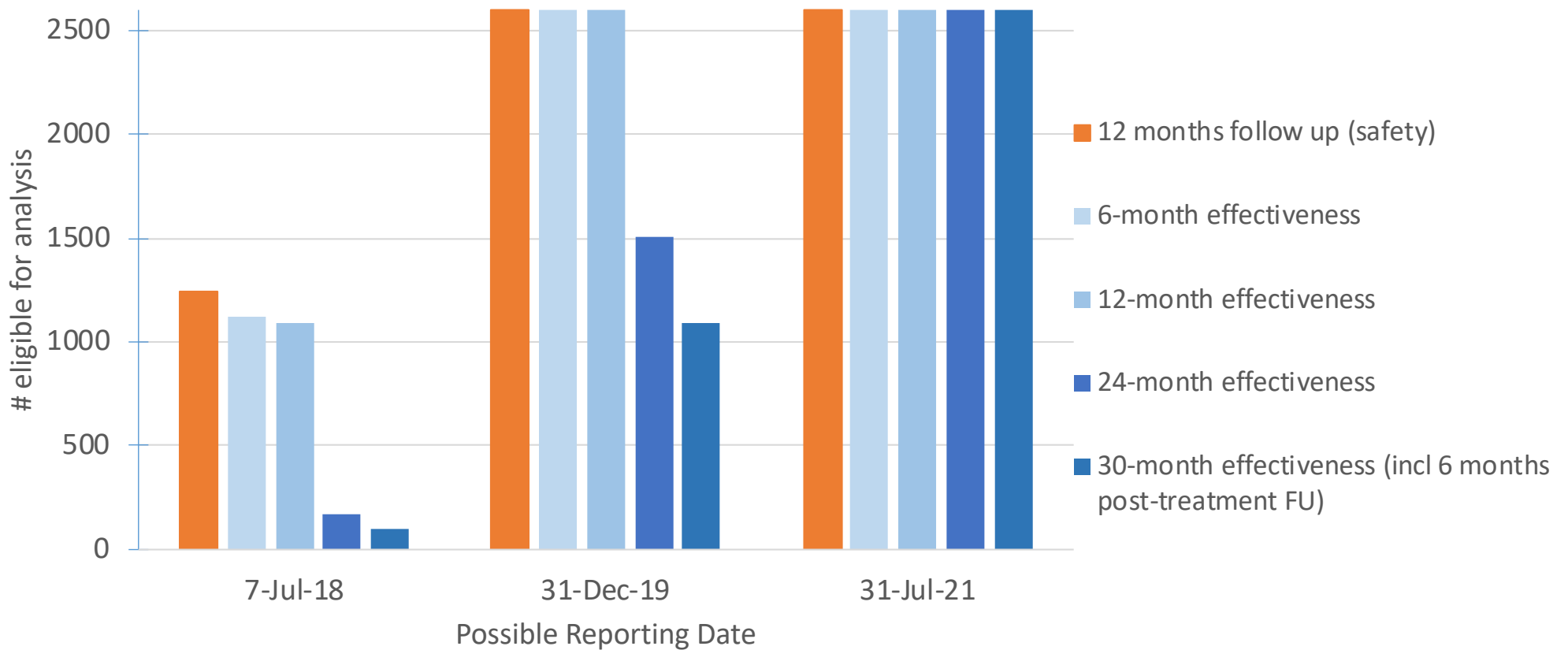


Lessons Learned-Summary



- PV as done for endTB observational study impractical for routine care
 - Good clinical monitoring for toxicity essential for all drugs and regimens.
 - Important to empower clinicians to make decisions with good supervision
 - Some of the resources from endTB should have been routinely available, however that was not always the case (e.g. audiometry, second-line DST)
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Possible Ns for reporting on endTB outcomes, by date and endpoint





Priorities for Future Analysis - 1



- Culture Conversion at six months, reversion
- Safety analysis (AEIs and SAEs)
- Safety & effectiveness of prolonged and concomitant use
- At least 50% of the endTB cohort on prolonged use
- Safety & effectiveness of companion drugs
 - Linezolid (by duration, baseline anemia)
 - Injectables (by SLI)



Priorities for Future Analysis - 2



- Special population subgroup analyses
 - Children
 - Pregnant women
 - Hep C, HIV co-infected patients
 - Less “chronic” MDR-TB patients
- Optimal monitoring schedule for toxicity
- endTB experience of setting up, implementing PV and lessons learnt
- Other Sub-studies
 - Amplification of resistance
 - Specific AEs related to drugs – e.g. linezolid