

Tuberculosis in 2017: Searching for new solutions in the face of new challenges

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Short MDR-TB Regimen, Uzbekistan

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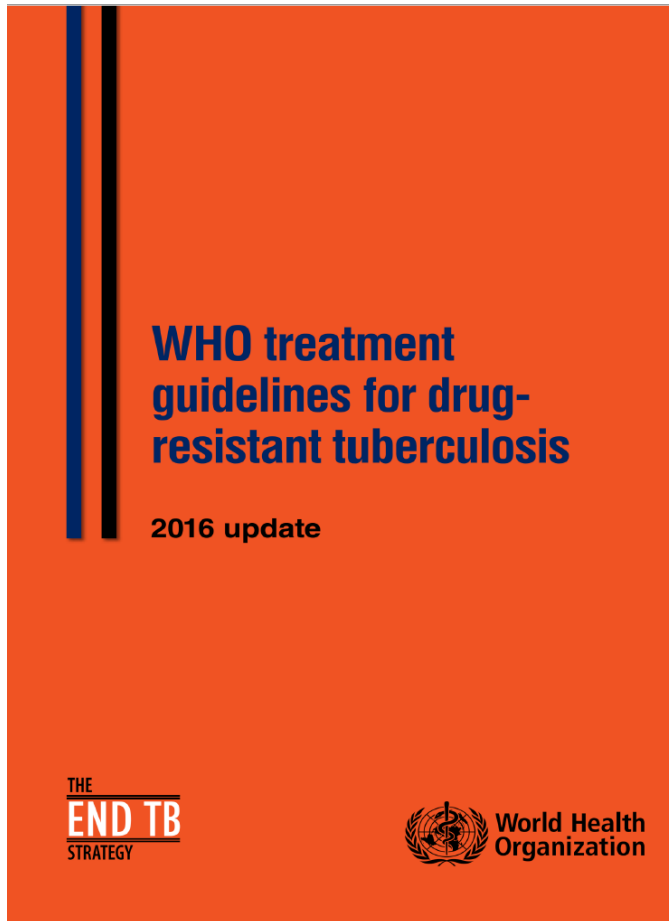
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Problem Statement



- WHO recommends the shorter MDR-TB treatment regimen (SCR) under specific conditions
- But is this feasible in Europe?

Overview

- Study Design
- Overall Cohort Results
- Comparison SCR vs standard of care
 - Sputum Culture conversion at 2 months
 - Outcomes 20+ months

- Implications



Background

- Karakalpakstan Population 1.7 million
- TB prevalence: 100.3/100, 000
- MDR: New = 23 % Retreatment cases = 62%
- MDR-TB success rate = 57%
- Amongst MDR-TB patients
 - Ethambutol resistance = 77.1%
 - Pyrazinamide resistance = 73.6%

Short Course Study

- Single-arm prospective observational
- Standardised assessment
 - ECG, Audiometry, Visual assessment
 - GeneXpert, Hain First & Second line, smear, culture
- Ethics approval from National and MSF ERBs





Intensive Phase

4-6 Cm/Km – Mfx – Pto – Cfz – Z – H_{HD} – E

Continuation Phase

5 Mfx – Pto – Cfz – Z – E

Moxifloxacin dose = 400 mg

Eligibility

Inclusion Criteria

- RR TB patients (GeneXpert, Hain MTBDR and/or DST)
- If <14yo, confirmed close contact with RDR TB case
- Informed consent

Exclusion Criteria

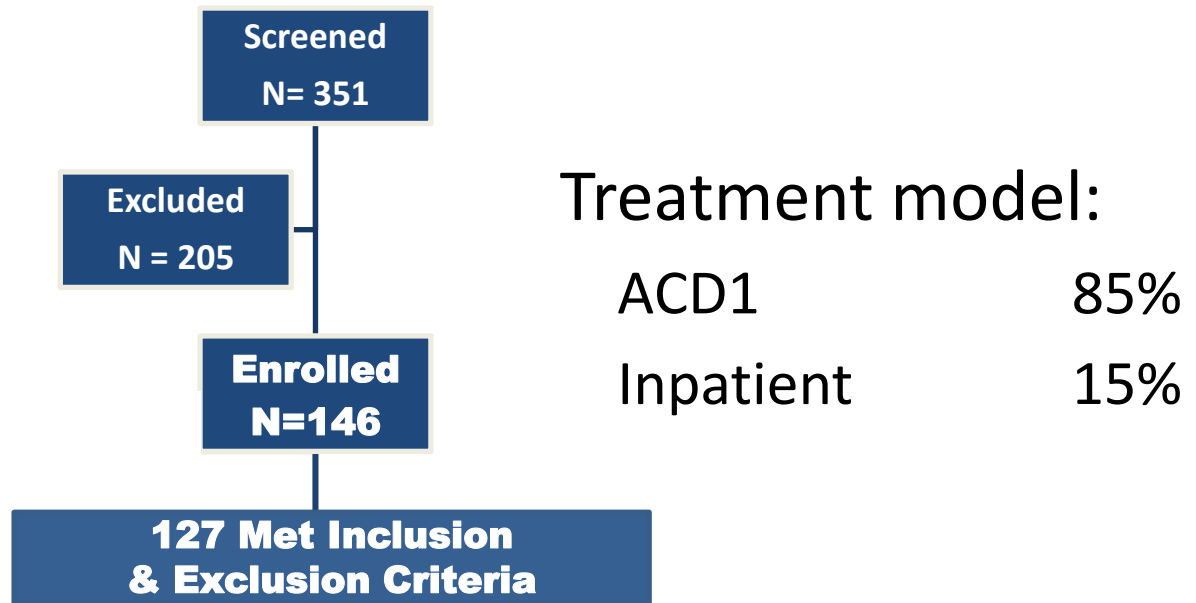
- Taken Second line drugs > 1 month
- Critically ill
- Meningeal/Osteoarticular disease
- Resistance to Ofx or dual-injectables (Km/Cm) or XDR TB
- CrCl <30ml/min
- QTc >500ms
- Pregnancy

Treatment model

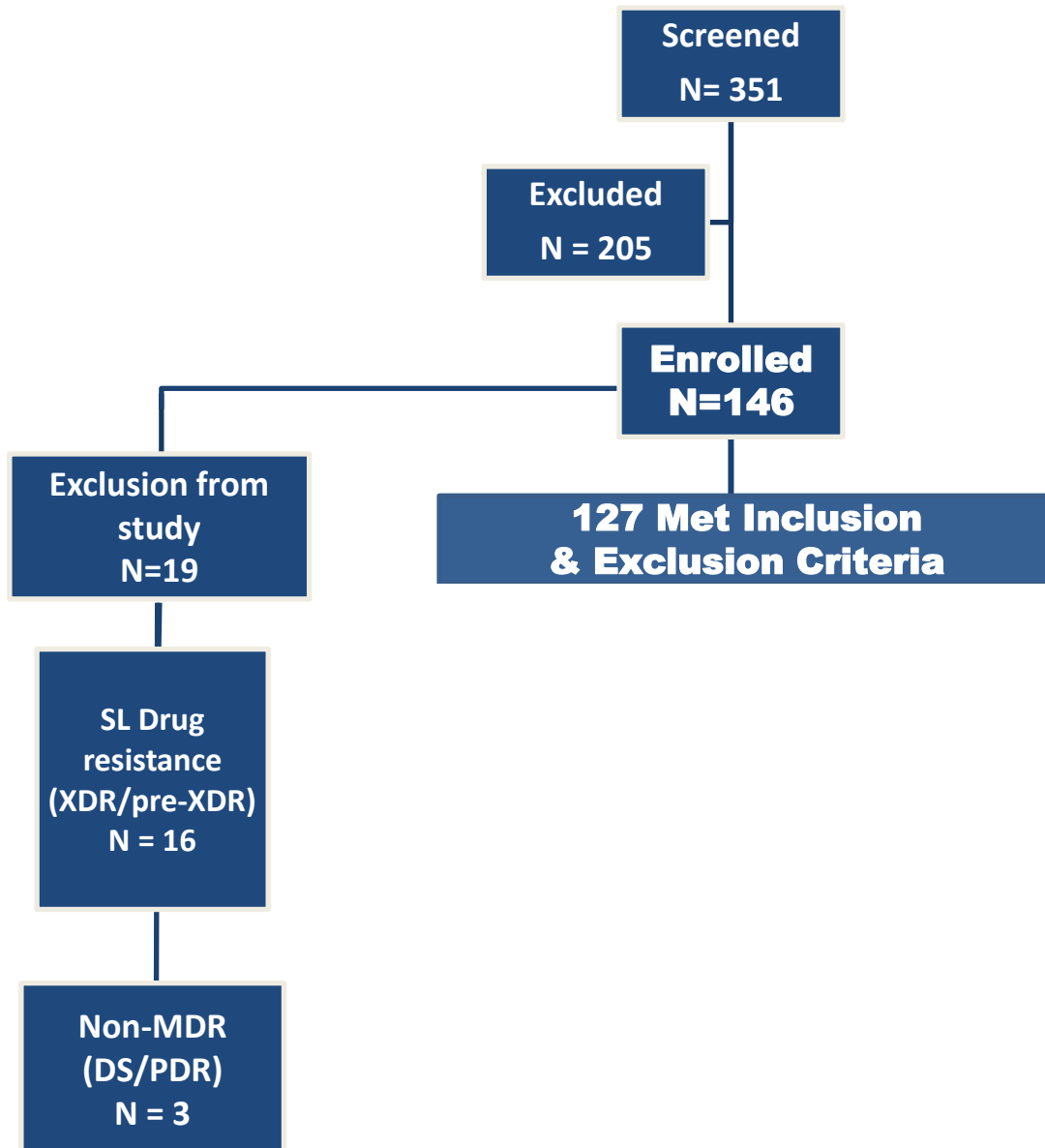
- Ambulatory care from diagnosis
- Social, psychological and adherence support
- Early identification and management of side-effects
- Direct observed therapy 7 days per week
- Additional ECG monitoring (baseline, 2w, 4w) for SCR
- Follow-up at 2 weeks, then monthly & 6 & 12 months post-treatment

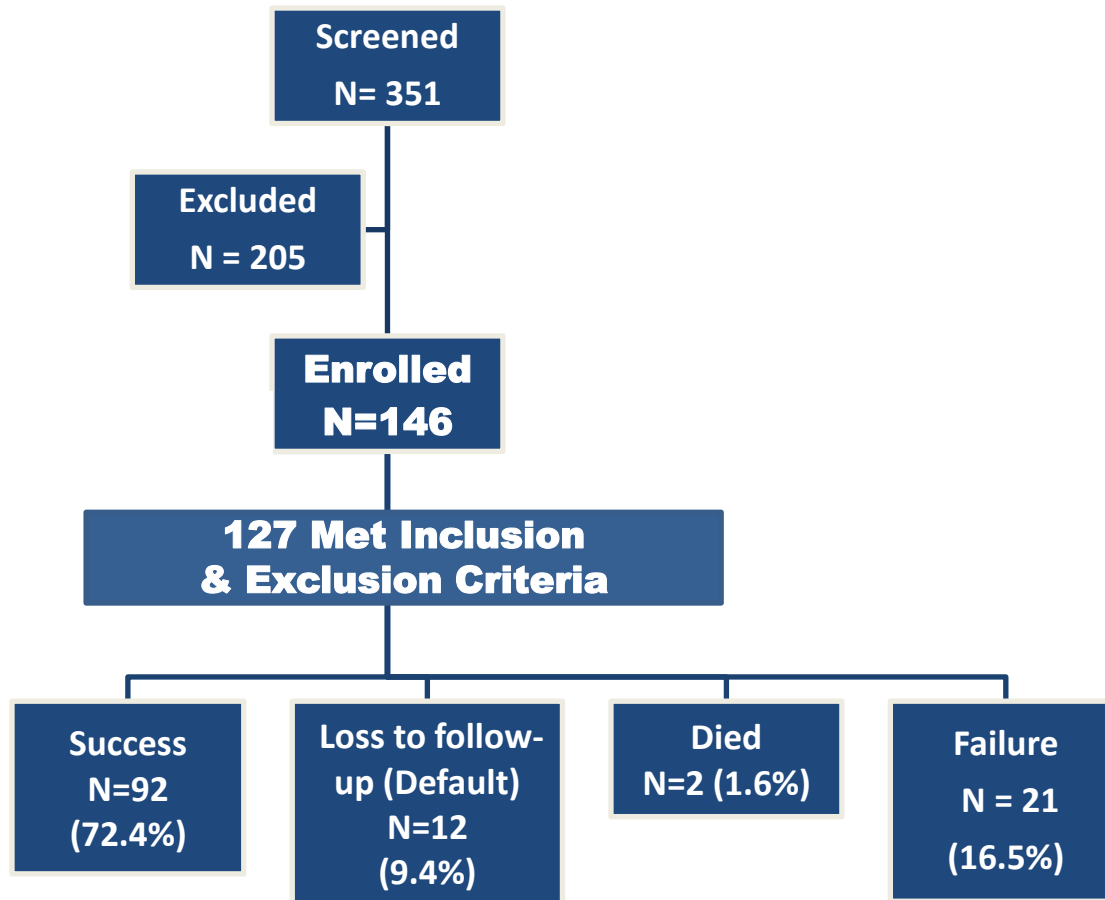
Snapshot

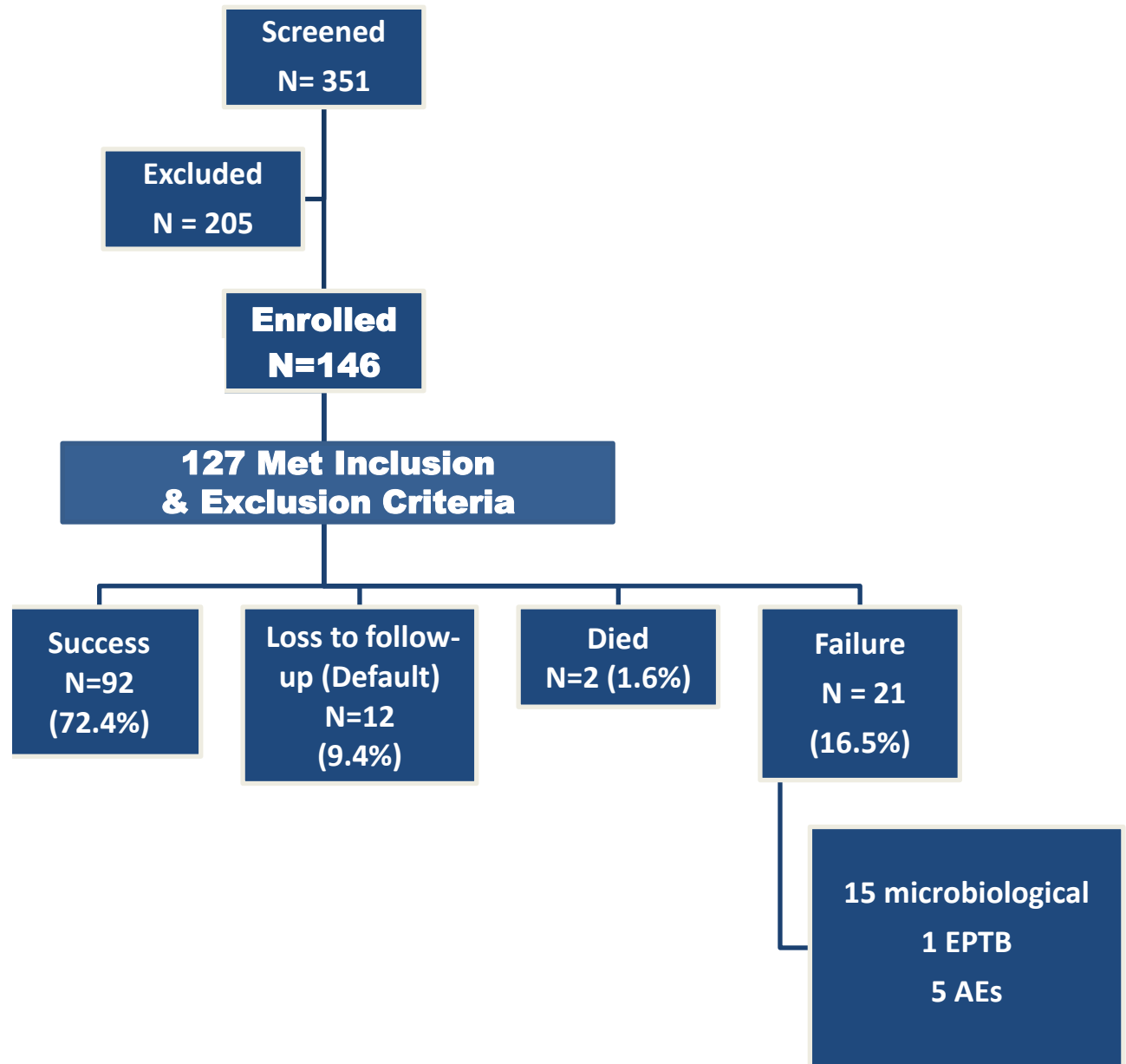
- Recruited September 2013 - May 2015 in 3 Rayons
- 127 patients met inclusion and exclusion criteria
- Additional 19 patients commenced SCR but met exclusion criteria → withdrawn
- Last patients completed treatment Feb 2016
- Final follow up visits and cultures still in progress



Main Reasons Exclusion	%
History of 2 nd Line drug use > 1 month	25%
Additional resistance (Ofx, dual-injectables)	19%
Lost to follow up	11%
Lack of consent	17%







Adverse Events

- Any adverse event 78% pts
- 1 grade 4 adverse event
- >75% adverse events grade 1 and 2
- Major adverse events: gastrointestinal, headache, arthralgia, anorexia, elevated creatinine, tinnitus/hearing loss
- Serious adverse events:
 - 15 SAEs;
 - 2 deaths

Interim follow-up outcomes

Follow up point	No. of patients	Completed Clinical Ax	Sputum not collected	Relapse	Confirmed Relapse Free
12 months	90	82	6	1*	66 culture neg (cultures results still awaited)

- Patient was out of country at 12 months – on return at 17 months had positive sputum culture – currently being considered as relapse.

Comparison of SCR versus Standard of Care in Uzbekistan

- Comparison of SCR with the Standard of Care
- Analysis 1 – 2 month culture conversion comparison
- Analysis 2 – SCR with 1 year follow-up and Standard of Care after 20+ months treatment
- Exclusions: 2nd line drug exposure, Km/Cm or ofloxacin resistance, EPTB

Analysis 1:

2-month culture conversion

- Short course regimen associated with higher proportion of 2-month culture conversion
 - SCR: adjusted odds ratio of 2.28 (95% CI 1.24-4.18; p=0.08)
 - Adjusted for age, gender, baseline smear
 - Baseline DST to pyrazinamide, ethambutol and kanamycin had not significant effect

Preliminary analysis 2:

End of treatment outcomes

- SCR 1 year post treatment follow up (21-23 months) versus standard of care (20-24 months)
- No statistical evidence of difference between short course regimen and standard of care at 20+ months
 - aOR 1.19 (95% CI 0.71 – 2.00; p=0.498)
 - Adjusting for age, gender, baseline kanamycin resistance
 - Further analyses still in progress

In summary...

- The 2 analyses show faster culture conversion, and similar final treatment outcomes
 - For appropriately selected patients
 - Region with high rates of second-line drug resistance

Implications for scale up of the regimen

Patient selection in contexts with high second line drug resistance

- Not suitable for all patients
 - 35-50% patients eligible in this context
- Importance of adherence support for commencing ambulatory treatment from day 1

Patient selection in contexts with high second line drug resistance

- What to do with Z or Km resistance?
 - Preliminary analysis suggests could still use, but may be prudent to await more data on Km resistance
 - An option – wait for full DST results and then switch patients to SCR

Management of patients failing the regimen

- If failing regimen
 - 4-6 Cm/Km – Mfx – Pto – Cfz – Z – H_{HD} – E
- Likely effective drugs
 - (Injectable), Cs, Lzd, Bdq, Dld, Imp/Clv, PAS

Conclusions

- Good end-of-treatment and interim follow-up outcomes in selected group of patients
- Adverse events and LTFU in this study highlight importance of adherence support management

Conclusions

- SCR achieves faster sputum culture conversion
- SCR has low relapse rate
- Roll out SCR in high SLD resistance context requires molecular test lab capacity and roll out of Group C and D drugs

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