SHINE Trial

Shorter Treatment for Minimal Tuberculosis (TB) in Children

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Trial Design

- Multicenter, open-label, parallel-group, non-inferiority, randomized controlled, two-arm trial
- Comparing a 4-month vs the standard 6-month regimen
- Used fixed-dose, combination dispersible tablets
  - mg/kg: INH 10 (7-15), rifampin 15 (10-20), EMB 20 (15-25), PZA 35 (30-40)
- Endpoint: favorable outcome; TB-free survival at 72 weeks
- Margin of Inferiority set at 6%

Inclusion Criterion

- Age 0-16 years
- Weight ≥ 3kg.
- Clinician has decided to treat with standard first-line regimen
- Symptomatic but non-severe TB including:
  - extrathoracic lymph node TB; intra-thoracic uncomplicated (hilar) lymph node TB
  - minimal or no parenchymal abnormality on CXR
  - smear negative on gastric aspirate/other respiratory sample

Note: GeneXpert may be positive or negative and a negative GeneXpert can be used as a substitute for a negative smear;

culture of respiratory sample may be positive or negative;

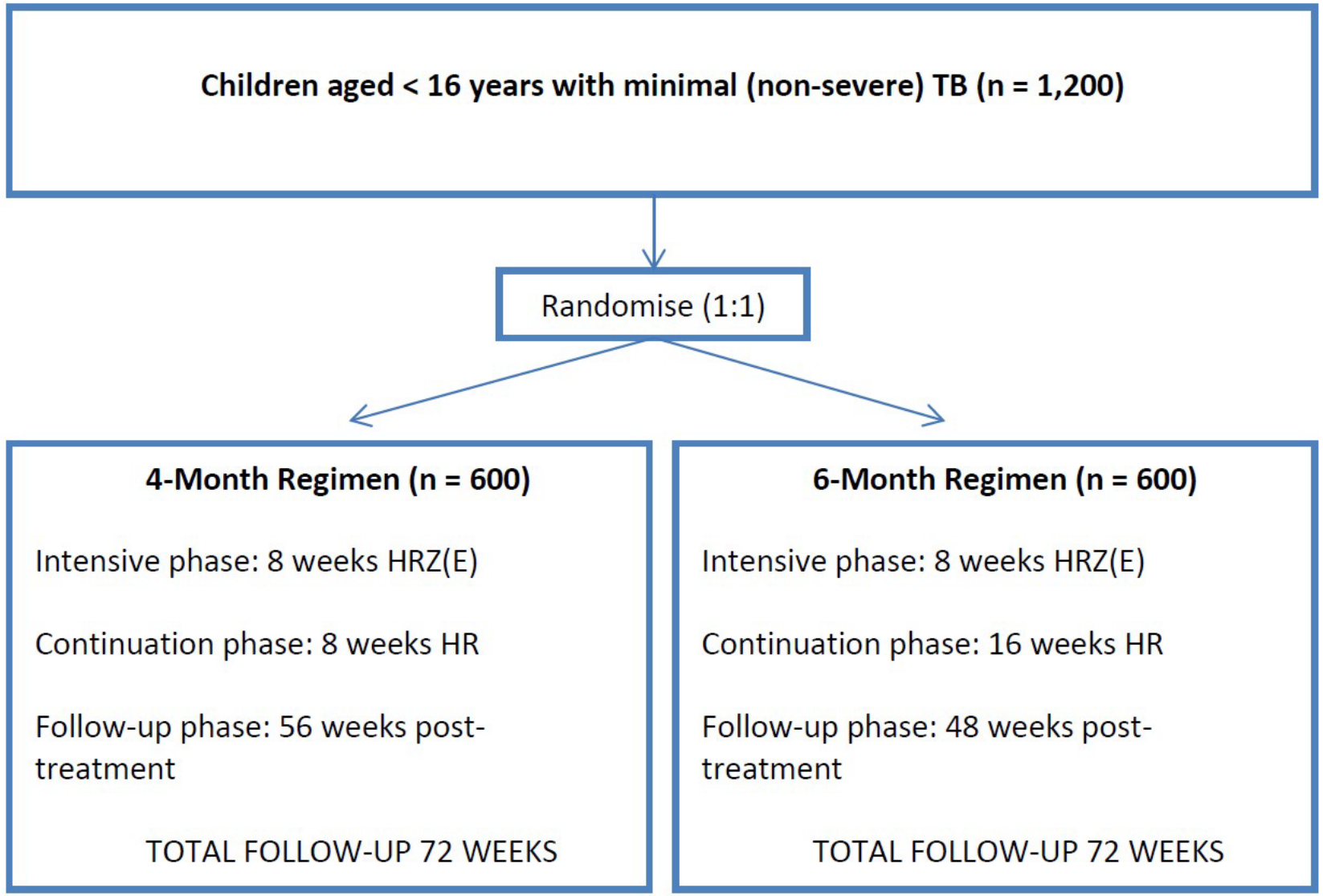
lymph node aspirate may be smear/culture/GeneXpert positive or negative)

- Not treated for previous TB unless successfully treated > 2 years since last completed treatment
- Known (or pending confirmation of) HIV status; HIV-infected or HIV-uninfected
- Willing and likely to adhere to 72 weeks follow up
- Informed written consent from the parent/legal caregiver(s) and assent in children
- Home address accessible for visiting and intending to remain within the recruitment area

Exclusion Criterion

1. Smear-positive respiratory sample TB
   (note: smear-positive peripheral lymph node sample is allowed)
2. Premature (<37 weeks) **and** aged under 3 months
3. Miliary TB, spinal TB, TB meningitis, osteoarticular TB, abdominal TB, congenital TB
4. Pre-existing non-tuberculous disease likely to prejudice the response to, or assessment of, treatment e.g. liver or kidney disease, peripheral neuropathy, cavitation
5. Any known contraindication to taking anti-TB drugs
6. Known contact with drug resistant adult source case (including mono-resistant TB)
7. Known drug resistance in the child
8. Severely sick
9. Pregnancy

Methods


Children aged < 16 years with minimal (non-severe) TB (n = 1,200)
Randomise (1:1)
4-Month Regimen (n = 600)
Intensive phase: 8 weeks HRZ(E)
Continuation phase: 8 weeks HR
Follow-up phase: 56 weeks post-treatment
TOTAL FOLLOW-UP 72 WEEKS
6-Month Regimen (n = 600)
Intensive phase: 8 weeks HRZ(E)
Continuation phase: 16 weeks HR
Follow-up phase: 48 weeks post-treatment
TOTAL FOLLOW-UP 72 WEEKS

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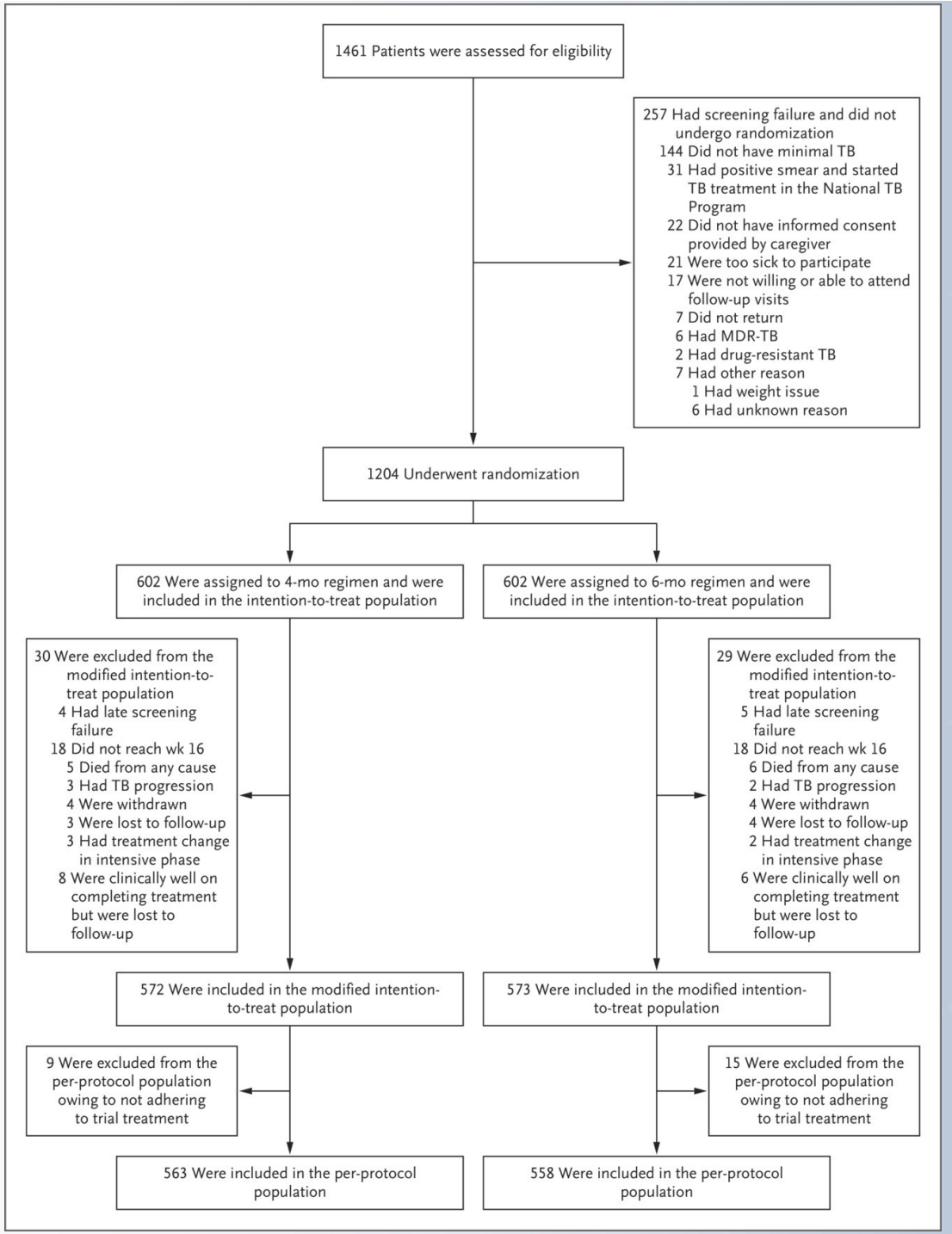
Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

Randomization and Treatment of the Patients.



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Demographic and Clinical Characteristics of the Participants at Baseline.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	4-Month Treatment (N = 602)	6-Month Treatment (N = 602)	Total (N = 1204)
Age			
Median (interquartile range) — yr	3.4 (1.5 to 6.9)	3.5 (1.5 to 7.1)	3.5 (1.5 to 7.0)
Range	2 mo to 15 yr	2 mo to 15 yr	2 mo to 15 yr
Female sex — no. (%)	297 (49)	286 (48)	583 (48)
Site country — no. (%)			
Uganda	188 (31)	188 (31)	376 (31)
Zambia	183 (30)	181 (30)	364 (30)
South Africa	156 (26)	159 (26)	315 (26)
India	75 (12)	74 (12)	149 (12)
HIV-positive status — no. (%)	65 (11)	62 (10)	127 (11)
WHO weight band — no. (%)			
3–3.9 kg	0	3 (<1)	3 (<1)
4–7.9 kg	86 (14)	92 (15)	178 (15)
8–11.9 kg	162 (27)	152 (25)	314 (26)
12–15.9 kg	126 (21)	116 (19)	242 (20)
16–24.9 kg	142 (24)	153 (25)	295 (25)
≥25 kg	86 (14)	86 (14)	172 (14)
Clinical presentation — no. (%)			
Respiratory tuberculosis	398 (66)	406 (67)	804 (67)
Mixed respiratory and peripheral lymph-node tuberculosis	182 (30)	171 (28)	353 (29)
Peripheral lymph-node tuberculosis	19 (3)	21 (3)	40 (3)
Other†	3 (<1)	4 (1)	7 (1)
M. tuberculosis culture and Xpert MTB/RIF testing results — no. (%)‡			
All positive results	85 (14)	80 (13)	165 (14)
Tuberculosis culture–positive only	40 (7)	40 (7)	80 (7)
Xpert MTB/RIF–positive only	14 (2)	5 (1)	19 (2)
Tuberculosis culture–positive and Xpert MTB/RIF–positive	31 (5)	35 (6)	66 (5)

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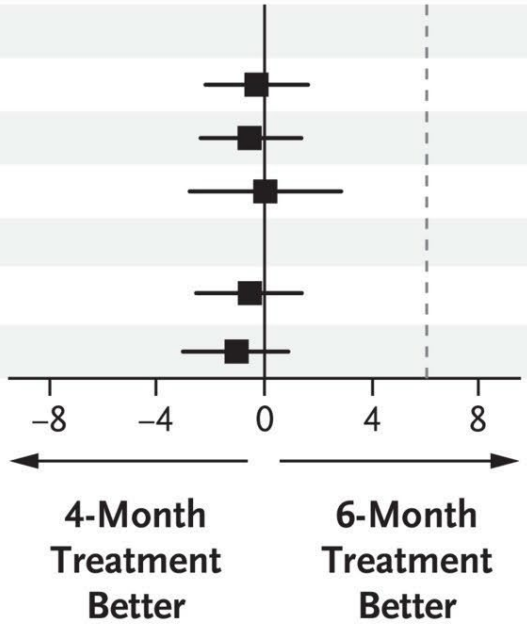
Unadjusted Analysis of the Primary Efficacy and Key Secondary Outcomes in the Trial Populations.

	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		*percentage points*
Primary outcome				
Modified intention-to-treat population	1145	16/572 (3)	18/573 (3)	–0.3 (–2.3 to 1.6)
Per-protocol population	1121	14/563 (2)	17/558 (3)	–0.6 (–2.5 to 1.4)
Intention-to-treat population	1204	44/602 (7)	44/602 (7)	0 (–2.9 to 2.9)
Key secondary outcome				
Modified intention-to-treat population	910	10/450 (2)	13/460 (3)	–0.6 (–2.6 to 1.4)
Per-protocol population	895	8/445 (2)	13/450 (3)	–1.1 (–3.1 to 0.9)



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Primary Efficacy Analysis (Modified Intention-to-Treat Population).

Table 2. Primary Efficacy Analysis (Modified Intention-to-Treat Population).*

Outcome	4-Month Treatment (N=572)	6-Month Treatment (N=573)	Difference (95% CI)	
			Adjusted Analysis†	Unadjusted Analysis
			percentage points	
Unfavorable status — no. (%)	16 (3)	18 (3)	−0.4 (−2.2 to 1.5)	−0.3 (−2.3 to 1.6)
Death from any cause after 4 mo	7 (1)	12 (2)		
Loss to follow-up after 4 mo but during treatment period	0‡	1 (<1)		
Treatment failure				
Tuberculosis recurrence	6 (1)	4 (1)		
Extension of treatment	2 (<1)	0		
Restart of treatment§	1 (<1)	1 (<1)		
Favorable status — no. (%)	556 (97)	555 (97)		

Primary Safety Outcome, Serious Adverse Events, Deaths, Adverse Drug Reactions, and Suspected Bacterial Infections Leading to Hospitalization.

Table 3. Primary Safety Outcome, Serious Adverse Events, Deaths, Adverse Drug Reactions, and Suspected Bacterial Infections Leading to Hospitalization.*

Event	4-Month Treatment (N=602)	6-Month Treatment (N=602)	Total (N=1204)
Primary safety outcome — no. of events	49	66	115
No. of participants with ≥1 event (%)†	47 (8)	48 (8)	95 (8)
At ≤4 mo			
No. of adverse events of grade ≥3	35	52	87
No. of participants with ≥1 event (%)	33 (5)	40 (7)	73 (6)
At >4 mo			
No. of adverse events of grade ≥3	14	14	28
No. of participants with ≥1 event (%)	14 (2)	12 (2)	26 (2)
Serious adverse event — no. of events	88	104	192
No. of participants with ≥1 serious adverse event (%)†	75 (12)	75 (12)	150 (12)
At ≤4 mo			
No. of serious adverse events	35	50	85
No. of participants with ≥1 serious adverse event (%)	33 (5)	40 (7)	73 (6)
At >4 mo			
No. of serious adverse events	53	54	107
No. of participants with ≥1 serious adverse event (%)	47 (8)	44 (7)	91 (8)
Death — no. (%)	12 (2)	19 (3)	31 (3)
At ≤4 mo			
No. of deaths (%)	5 (1)	6 (1)	11 (1)
No. of deaths considered to be related to tuberculosis (%)	3 (<1)	2 (<1)	5 (<1)
At >4 mo			
No. of deaths (%)	7 (1)	13 (2)	20 (2)
No. of deaths considered to be related to tuberculosis (%)	2 (<1)	6 (1)	8 (1)
Adverse drug reaction — no. of participants (%)‡	6 (1)	11 (2)	17 (1)
Bacterial infection leading to hospitalization — no. of events	40	40	80
No. of participants with ≥1 event (%)	36 (6)	30 (5)	66 (5)

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Questions?

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