TRUNCATE-TB

Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for drug-sensitive TB

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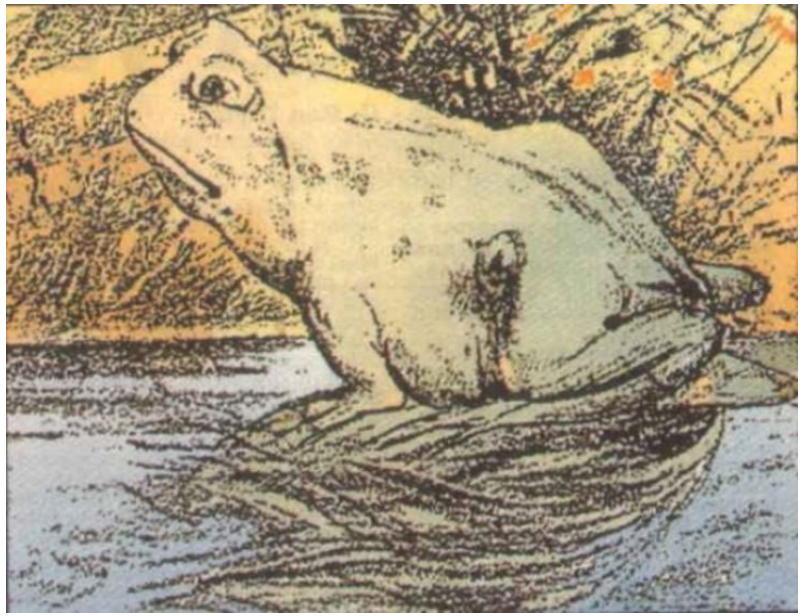
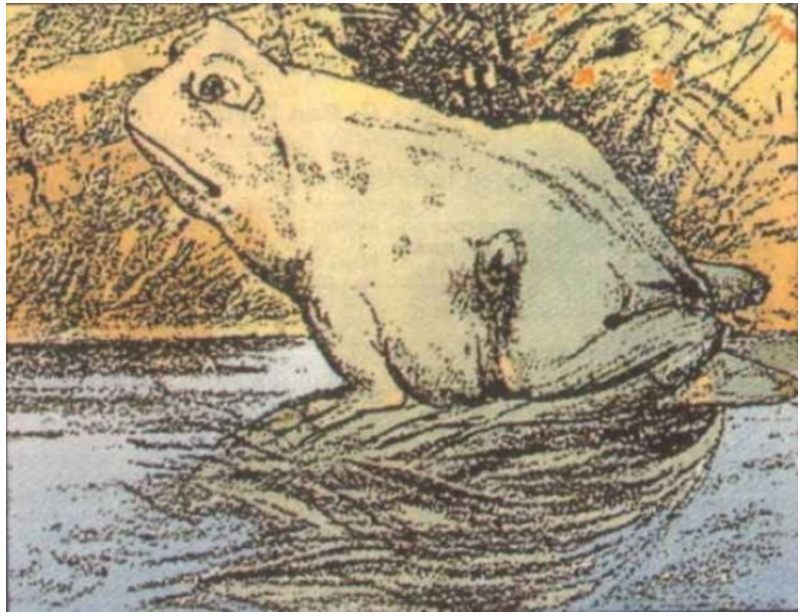
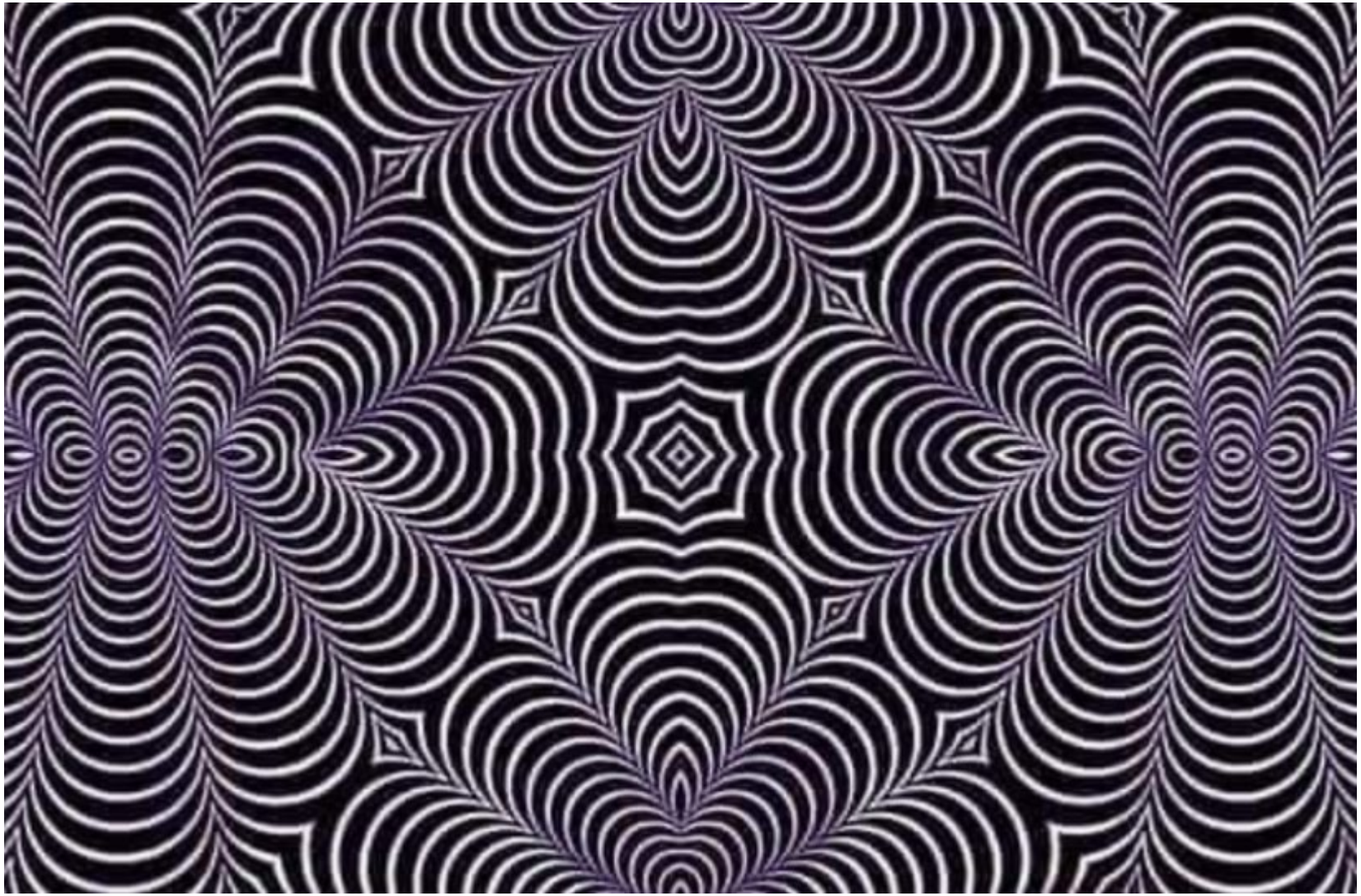
Approaches to shortening Rx for TB

- Find new drugs/regimens
  - Drug/regimen licensing trials
  - Non-inferiority design, unfavourable outcome
- Immune-based therapy (adjunctive)
  - Neglected area
  - Still at early stage; looking at culture conversion outcomes (or misc. clinical)
- Strategic approaches (using existing drugs)
  - (Very) neglected area
  - Program-relevant design
  - Need different (and broader) outcomes







TRUNCATE-TB Rationale

Table 1.11 Short-course chemotherapy studies of smear-negative pulmonary tuberculosis in Hong Kong. Patients with negative cultures or with drug-sensitive cultures initially.

Study no. (date of start)	Initial culture results	Regimen	Duration (months)	Patients assessed for relapse	Relapse rate (%) follow-up for 2 years*	Relapse rate (%) follow-up for 5 years*	Reference
1 (1976)	Negative	SC†	–	176	53 (40)	57 (41)	212
		SHRZ	2	165	7 (4)	11 (6)	213
		SHRZ	3	162	4 (2)	7 (3)	214
		3SPH/S_2H_2	12	160	1 (0)	2 (1)	
	Positive	SHRZ	2	72	22 (15)	32 (23)	
		SHRZ	3	69	12 (9)	13 (10)	
		3SPH/S_2H_2	12	78	1 (0)	5 (1)	
2 (1978)	Negative	SHRZ	3	364	2	6 (3)	215
		$S_3H_3R_3Z_3$	3	345	3	8 (3)	
		$S_3H_3R_3Z_3$	4	325	2	4 (1)	
	Positive	SHRZ	4	157	3	3 (3)	
		$S_3H_3R_3Z_3$	4	136	1	2 (1)	
		$S_3H_3R_3Z_3$	6	166	2	5 (2)	

* Percentage bacteriologically confirmed in parentheses.
† Selective chemotherapy group. Treatment started when bacteriological or radiographic evidence of activity occurred during follow-up.

Fox Int J Tubercl Lung Dis 1999

Regimens of less than six months for treating tuberculosis (Review)

Gelband H

THE COCHRANE COLLABORATION®

- With standard 6m Rx we're over-treating the majority to prevent relapse in a minority

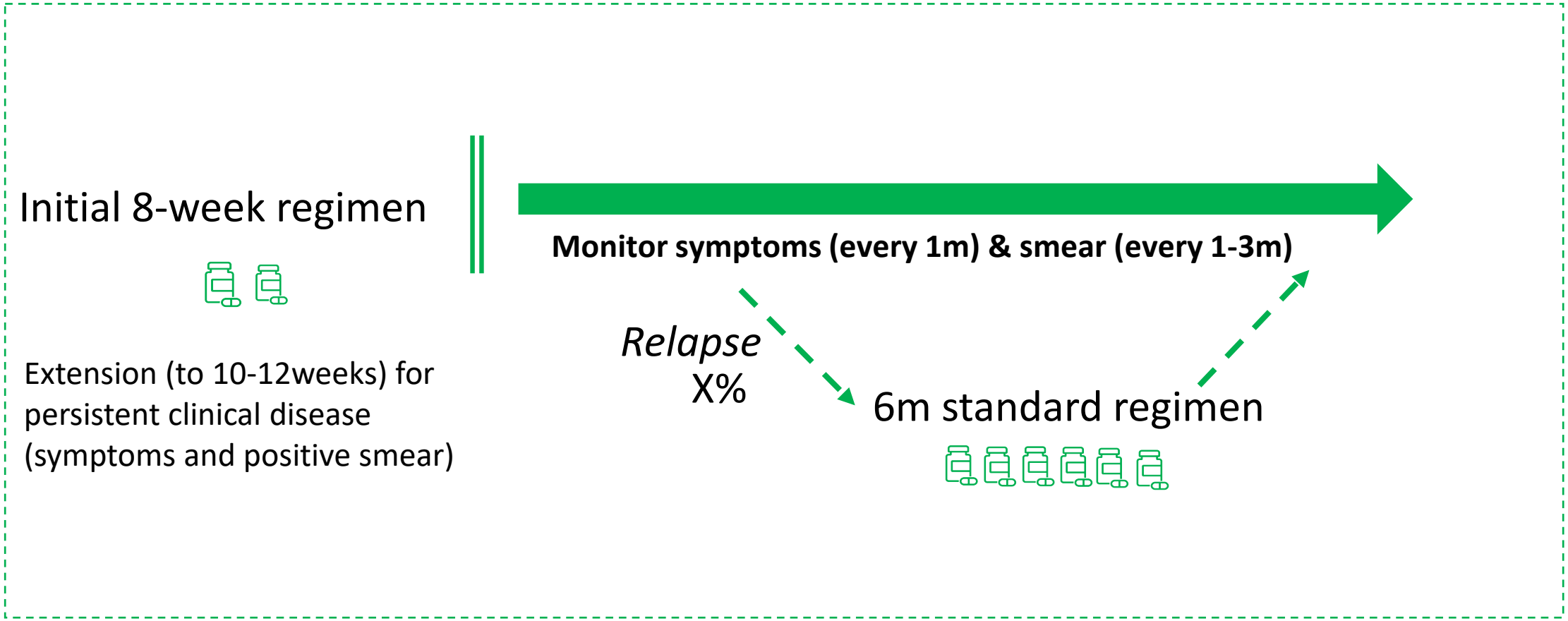
TRUNCATE-TB Rationale

Overall outcomes may be as good (or better) in programme setting if:

- Treat everyone with a shorter duration needed for the majority
- Shift resources to early detection and re-treatment of relapses in the minority

- Potential advantages for people with tuberculosis and for programmes

TRUNCATE Strategy



TRUNCATE-TB Trial design

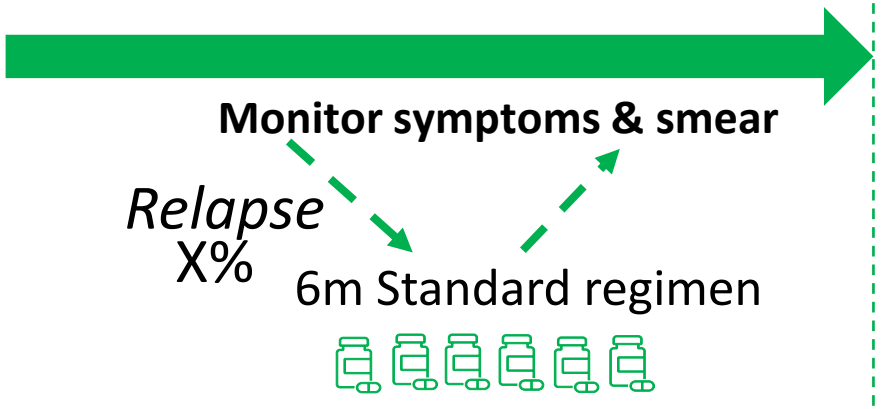
Standard treatment (strategy)

24w standard treatment

vs

TRUNCATE strategy

8w initial regimen



TRUNCATE-TB Trial design

Standard treatment (strategy)

24w standard treatment

Monitor symptoms & smear

vs

TRUNCATE strategy

8w initial regimen

Monitor symptoms & smear

Relapse X%

6m Standard regimen

Primary outcome:
Unsatisfactory clinical outcome at **W96**
- Died or
- Active TB or
- On TB treatment

Secondary outcomes:
Participant-centred:
Total time on treatment, acceptability, motivation, QoL

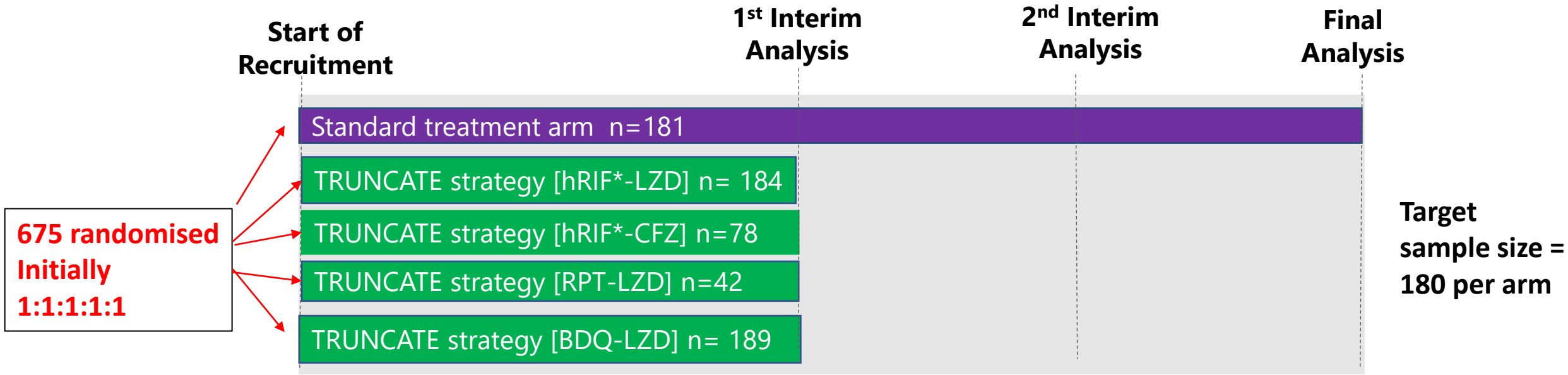
Safety:
Adverse events
Respiratory disability

Programme-centred:
Adherence, default, new drug resistance, estimated transmission risk

Trial Regimens

Standard Treatment	24w	Rifampicin 10mg/kg	Isoniazid	Pyrazinamide (first 8w)	Ethambutol (first 8w)	
hRIF-LZD	8w	↑ Rifampicin 20-35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg
hRIF-CFZ	8w	↑ Rifampicin 35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Clofazimine 200mg
RPT-LZD	8w	Rifapentine 1200mg	Isoniazid	Pyrazinamide	Levofloxacin 1000mg	Linezolid 600mg
BDQ-LZD	8w	Bedaquiline 400/200mg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg

Recruitment to arms – adaptive changes



IDMC Stopping guidelines at interim analysis:

High rate of early relapse (>20%)

Time to culture conversion worse than control (HR < 0.9)

Poor tolerability/toxicity

TSC Stopping decisions:

TRUNCATE strategy [RPT-LZD]: high pill burden and new regulatory guidance on quinolone toxicity

TRUNCATE strategy [hRIF-CFZ]: regulator refused replacement CFZ importation

*hRIF dose decreased from 35mg/kg (first 88 enrolled) to 20mg/kg (subsequent 96 enrolled) in the hRIF–LZD arm following drug induced liver injury event

Main eligibility Criteria

Selected inclusion criteria

- Age 18 to 65 years
- Clinical symptoms consistent with pulmonary TB and/or evidence of pulmonary TB on CXR
- Sputum Xpert MTB/RIF positive

Selected exclusion criteria

- Rifampicin resistance on Xpert MTB/RIF
- Previous active TB disease
- Extra-pulmonary TB
- Severe clinical PTB
- Sputum smear 3+ *
- Cavity size >4cm on screening CXR*
- HIV positive*
- Poorly-controlled diabetes
- Cardiac disease
- Severe chronic lung disease
- Peripheral neuropathy

*Removed/modified in stage 3 of trial

Analysis of the primary outcome

Primary outcome: % unsatisfactory outcome (death, active TB disease at week 96, on treatment at week 96)

Compared each complete (full sample size) TRUNCATE strategy arm and standard treatment arm

Estimate 97.5% confidence interval for the difference (adjustment for 2 comparisons)

Non-inferiority declared if limit of 97.5% CI is < 12%

Main analysis done in an intention to treat population (excluded only those randomised in error)

TRUNCATE-TB sites

18 trial sites, 5 countries

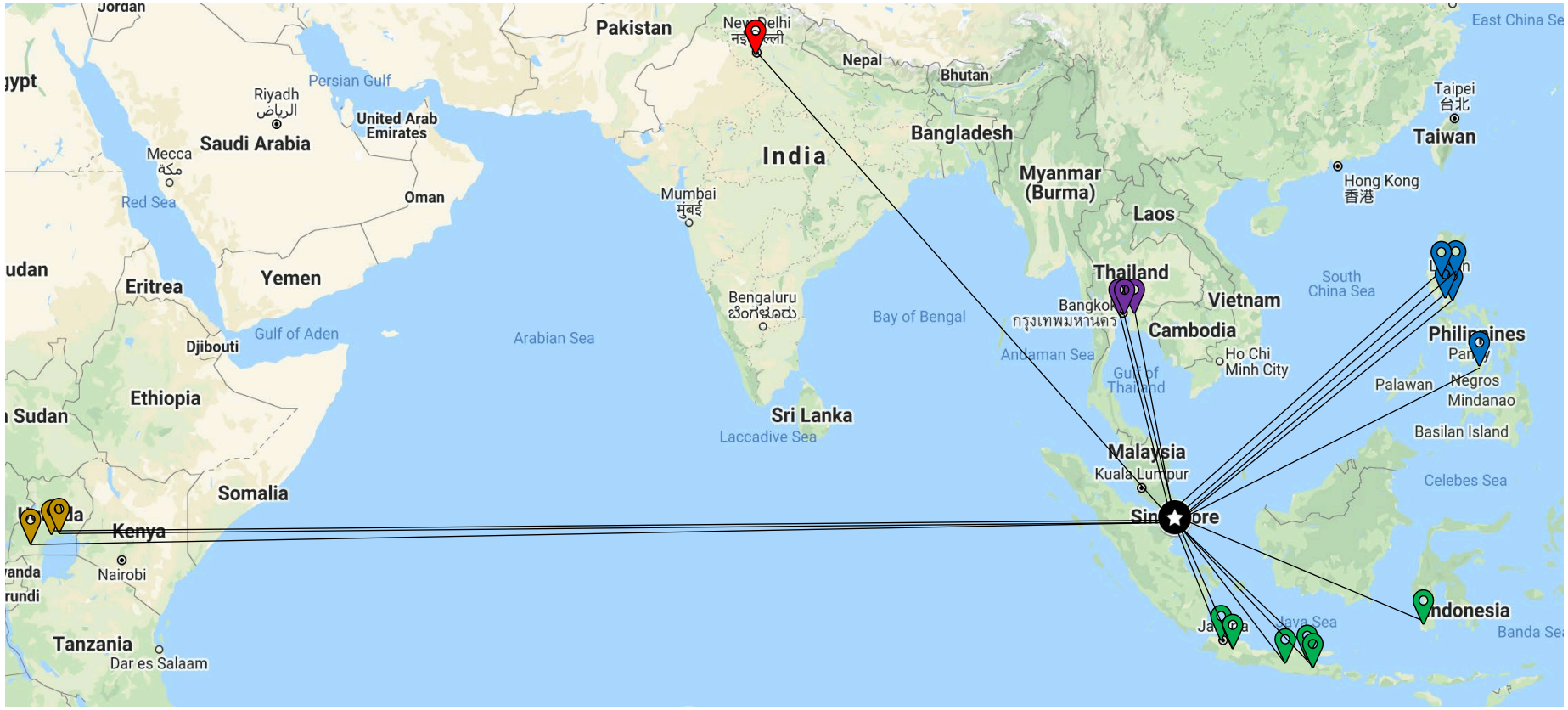
INDONESIA
21 Universitas Padjadjaran, Bandung
22 Universitas Hasanuddin, Makassar
23 Dr Soetomo Hospital, Surabaya
24 Universitas Indonesia, Jakarta
25 Dr Moewardi Hospital, Solo
26 Dr Saiful Anwar Hospital, Malang

THAILAND
31 King Chulalongkorn Memorial Hospital, Bangkok
32 Central Chest Institute of Thailand, Nonthaburi
33 Taksin Hospital, Bangkok

PHILIPPINES
41 Lung Center of Philippines, Quezon City
42 Quezon Institute, Quezon City
43 De La Salle Health Sciences Institute, Cavite
44 Perpetual Succour Hospital, Cebu
45 Tropical Disease Foundation, Makati City

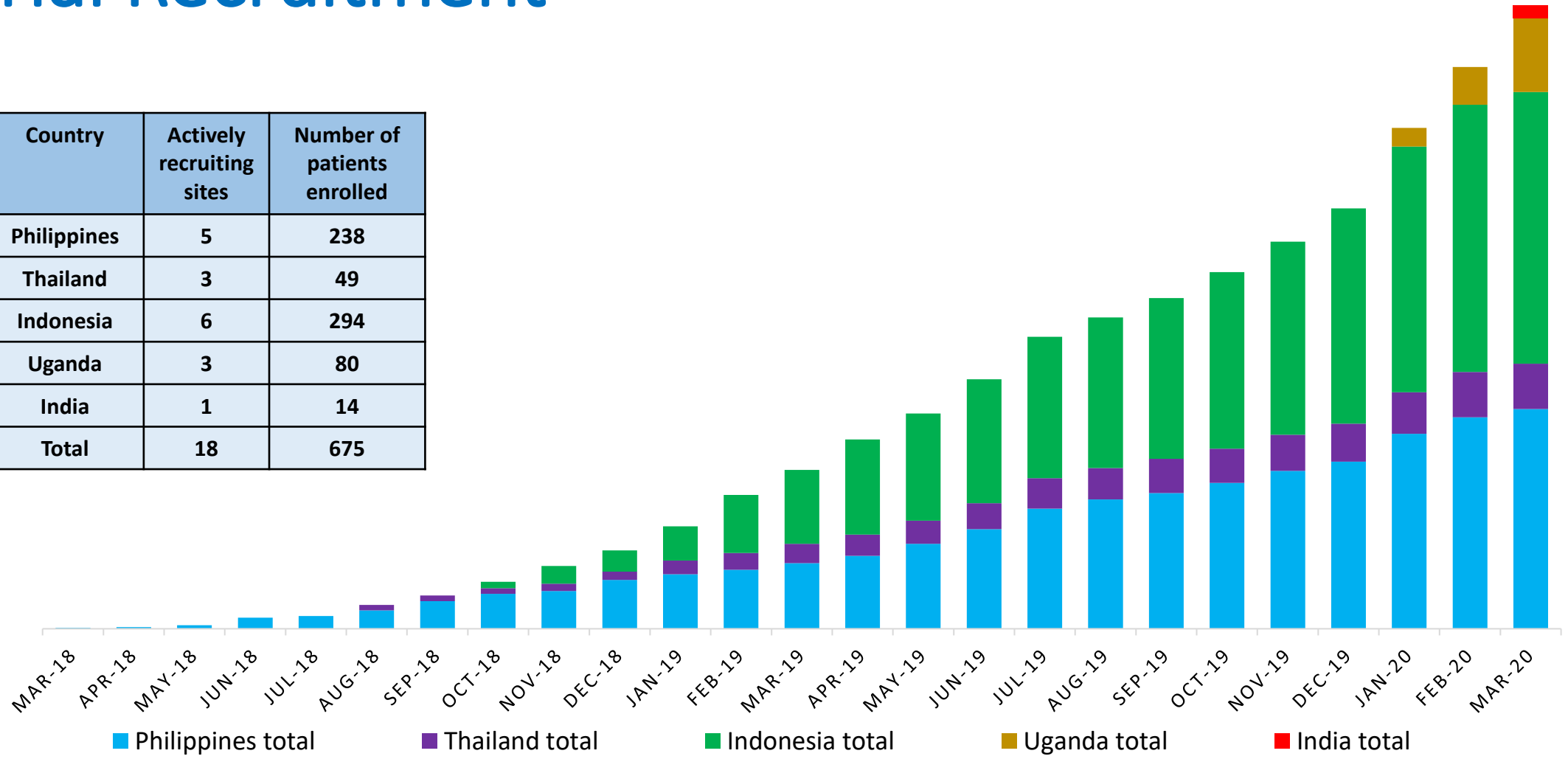
INDIA
61 NITRD, New Delhi

UGANDA
71 Infectious Diseases Institute, Kampala
72 Joint Clinical Research Centre, Lubowa
73 Joint Clinical Research Centre, Mbrara



Trial Recruitment

Country	Actively recruiting sites	Number of patients enrolled
Philippines	5	238
Thailand	3	49
Indonesia	6	294
Uganda	3	80
India	1	14
Total	18	675



Retention in trial

- Randomised in trial: 675
  - Randomised in error and immediately withdrawn: 1

- Intention to treat population: 674
  - Lost to follow-up or withdrawal: 4 (0.6%)
  - Died before week 96: 10 (1.5%)

- Alive and under follow-up at W96: 660
  - Evaluated at W96: 660
  - 643 (97%) in person
  - 17 (3%) by telephone

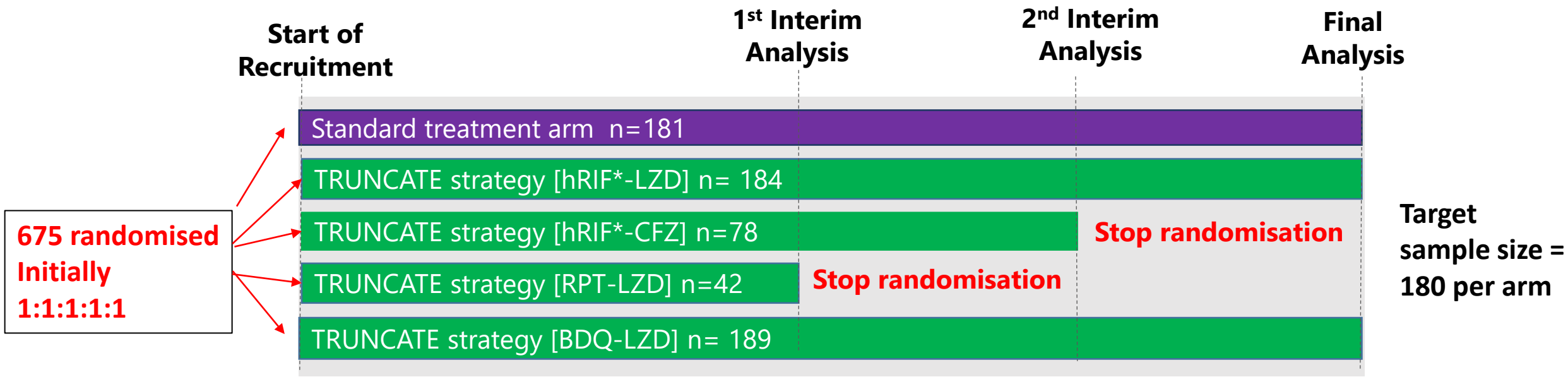
Baseline characteristics (1)

Characteristic	Standard treatment (N= 181)	TRUNCATE strategy (hRIF/LZD) (N=184)	TRUNCATE strategy (hRIF/CFZ) (N=78)	TRUNCATE strategy (RPT/LZD) (N=42)	TRUNCATE strategy (BDQ/LZD) (N=189)	Overall (N=674)
Male sex – no. (%)	66%	61%	62%	60%	61%	62%
Age group – no. (%)						
<35 yr	57%	59%	65%	62%	50%	57%
35-50 yr	33%	31%	27%	26%	37%	32%
≥50 – 65 yr	10%	10%	8%	12%	13%	11%
Country – no. (%)						
Indonesia	43%	40%	49%	55%	43%	44%
Philippines	34%	36%	41%	36%	33%	35%
Thailand	6%	8%	10%	10%	6%	7%
Uganda †	15%	14%	0	0	14%	12%
India †	2%	3%	0	0	3%	2%
Median BMI (range) -kg/m^2	19 (14-29)	19 (14-33)	19 (14-29)	18 (12-25)	19 (13-30)	19 (12-33)

Baseline characteristics (2)

Characteristic	Standard treatment (N= 181)	TRUNCATE strategy (hRIF/LZD) (N=184)	TRUNCATE strategy (hRIF/CFZ) (N=78)	TRUNCATE strategy (RPT/LZD) (N=42)	TRUNCATE strategy (BDQ/LZD) (N=189)	Overall (N=674)
CXR cavitation present	52%	55%	47%	55%	56%	54%
CXR proportion lung affected						
<25%	25%	34%	36%	29%	28%	30%
25-50%	52%	47%	46%	57%	52%	50%
>50%	23%	19%	18%	14%	20%	20%
WHO smear grade						
Negative	26%	31%	33%	29%	26%	28%
Scanty	15%	15%	15%	17%	13%	15%
1+	21%	26%	32%	32%	28%	26%
2+	24%	20%	10%	17%	20%	20%
3+	14%	8%	9%	5%	13%	11%
Xpert MTB/RIF result						
Very low	14%	13%	11%	8%	9%	12%
Low	23%	28%	30%	30%	28%	27%
Medium	42%	46%	42%	40%	40%	42%
High	21%	13%	17%	22%	23%	19%

Recruitment to arms – adaptive changes



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Treatment received

	Standard N=181	**hRIF/LZD N=184**	**BDQ/LZD N=189**
8-week arms: completed assigned Rx	**-**	**169 (92)**	**179 (95)**
Completed 56 days exactly	-	143 (78)	162 (86)
Extended up to 70 days	-	21 (11)	13 (7)
Extended up to 84 days	-	5 (3)	4 (2)
Standard Rx: completed assigned Rx *	**178 (98)**	-	-
Did not complete assigned Rx	3 (2)	15 (8)	10 (5)
Adherence during first 56 days	99%	96%	98%

* switch, cessation, withdrew, died during initial Rx

Primary efficacy outcome, ITT population TRUNCATE strategy (hRIF/LZD) arm

Outcome	Standard treatment (N= 181)	TRUNCATE strategy (hRIF/LZD) (N=184)	Adjusted difference (97.5% CI)
Unsatisfactory outcome – no. (%)	**7 (3.9)**	**21 (11.4)**	**7.2 (1.7 –13.2)**
On tuberculosis treatment at W96	2 (1.1)	8 (4.3)	-
Tuberculosis disease activity at W96	1 (0.6)	4 (2.2)	-
Death before W96	2 (1.1)	5 (2.7)	-
Telephone evaluation W96 – insufficient evidence of disease clearance when last seen	2 (1.1)	3 (1.6)	-
No evaluation W96 - insufficient evidence of disease clearance when last seen	0	1 (0.5)	-
Participants with unassessable outcome – no. (%)	**1 (0.6)**	**1 (0.5)**	**-**
Single positive culture at W96	0	1 (0.5)	-
Death (not related to tuberculosis)	1 (0.6)	0	-
No evaluation W96 – evidence of disease clearance when last seen	0	0	-
Participants with satisfactory outcome – no. (%)	**173 (95.6)**	**162 (88.0)**	**-**

Primary efficacy outcome, ITT population: TRUNCATE strategy (BDQ/LZD) arm

Outcome	Standard treatment (N= 181)	TRUNCATE strategy (BDQ/LZD) (N=189)	Adjusted difference (97.5% CI)
Unsatisfactory outcome – no. (%)	**7 (3.9)**	**11 (5.8)**	**0.8 (-3.4 to 5.1)**
On tuberculosis treatment at W96	2 (1.1)	5 (2.6)	-
Tuberculosis disease activity at W96	1 (0.6)	3 (1.6)	-
Death before W96	2 (1.1)	1 (0.5)	-
Telephone evaluation W96 – insufficient evidence of disease clearance when last seen	2 (1.1)	1 (0.5)	-
No evaluation W96 - insufficient evidence of disease clearance when last seen	0	1 (0.5)	-
Participants with unassessable outcome – no. (%)	**1 (0.6)**	**2 (1.1)**	-
Single positive culture at W96	0	0	-
Death (not related to tuberculosis)	1 (0.6)	0	-
No evaluation W96 – evidence of disease clearance when last seen	0	2 (1.1)	-
Participants with satisfactory outcome – no. (%)	**173 (95.6)**	**176 (93.1)**	-

Participant-centred secondary outcomes

	Standard treatment (N= 181)	TRUNCATE strategy (hRIF/LZD) (N=184)	TRUNCATE strategy (BDQ/LZD) (N=189)
Total treatment days to week 96	180.2 ± 37.9	105.7 ± 80.1	84.8 ± 65.3
Quality of life (MOS-HIV)			
Mental health summary score	57.5 ± 0.5	57.5 ± 0.5	57.8 ± 0.5
Physical health summary score	56.7 ± 0.5	56.8 ± 0.5	56.7 ± 5.6
Illness-related missed work or study – days	2.6 ± 9.1	3.3 ± 9.4	3.1 ± 12.9
Body weight			
Change from baseline – kg	5.8 ± 4.8	5.6 ± 4.7	6.1 ± 4.8
Change from baseline - %	11.9 ± 10.0	11.4 ± 9.8	12.1 ± 9.8

Participant acceptability (1)

	Standard treatment (N= 181)	TRUNCATE strategy (hRIF/LZD) (N=184)	TRUNCATE strategy (BDQ/LZD) (N=189)
Difficulty			
Acceptable on difficulty domain, overall (%)	90%	79%	88%
Acceptable, swallowing pills (%)	93%	85%	90%
Acceptable, post-treatment visits (%)	95%	89%	94%
Anxiety			
Acceptable on anxiety domain (%)	66%	62%	66%
Acceptable, risk of side effects (%)	88%	89%	89%
Acceptable, risk of TB recurrence (%)	83%	84%	83%
Acceptable, risk of infecting others (%)	76%	70%	74%

Participant acceptability (2)

	Standard treatment (N= 181)	TRUNCATE strategy (hRIF/LZD) (N=184)	TRUNCATE strategy (BDQ/LZD) (N=189)
Motivation			
Motivation score	6.2 ± 3.9	8.0 ± 3.0	8.1 ± 2.9
Strategy increased motivation:			
None (%)	21%	5%	4%
A little (%)	12%	10%	13%
Some (%)	24%	22%	18%
A lot (%)	40%	59%	61%
Recommendation to others			
2-month treatment (%)	NA	69%	75%
6-month treatment (%)	NA	19%	13%
No preference (%)	NA	8%	7%

Safety outcomes

	Standard treatment (N= 181)	TRUNCATE strategy (hRIF/LZD) (N=184)	P value	TRUNCATE strategy (BDQ/LZD) (N=189)	P value
Any grade 3 or 4 adverse event – no. (%)	29 (16.0)	32 (17.4)	0.664	30 (15.9)	0.666
Any serious adverse event – no. (%)	11 (6.1)	18 (9.8)	0.168	14 (7.4)	0.530
Death no. (%)	3 (1.7)	5 (2.7)	0.724	1 (0.5)	0.362
Respiratory disability at W96					
MRC breathlessness scale ≥ 3 – no. (%)	0	2.7 (1.5)	0.122	2.7 (1.4)	0.499
FEV1 < 50% of Predicted value	24.3 (13.4)	20.5 (11.1)	0.597	22.4 (11.8)	0.378

Programme-centred secondary outcomes

	Standard treatment (N= 181)	TRUNCATE strategy (hRIF/LZD) (N=184)	TRUNCATE strategy (BDQ/LZD) (N=189)
Treatment adherence			
Adherence over first 56 days - %	98.8 ± 5.5	95.9 ± 10.0	98.4 ± 6.6
Default within first 56 days – no. (%)	1 (0.6)	3 (1.6)	1 (0.5)
Relapse-associated transmission risk			
Transmission risk period – days	0.5 ± 4.3	2.4 ± 8.3	3.2 ± 14.1
New exposed household contacts – no.	0.01 ± 0.15	0.01 ± 0.10	0.06 ± 0.4
Acquired drug resistance - no. (%)	0	0	2 (1.1)

Acquired drug resistance

Participant 1

- Baseline INH resistance
- Missed 14 days (12 consecutive) of all drugs during the first 4 weeks
- Relapsed at W52 with new phenotypic resistance to BDQ (and CFZ) [with compatible mutations]
- Retreatment with standard treatment (with quinolone added) was successful.

Participant 2

- No baseline drug resistance
- Adherent to initial 8-week treatment
- Relapsed at W36 with new phenotypic resistance to BDQ (and CFZ) [with compatible mutations]
- Retreatment with standard treatment was successful.

No acquired drug resistance in the other TRUNCATE strategy or standard treatment arm

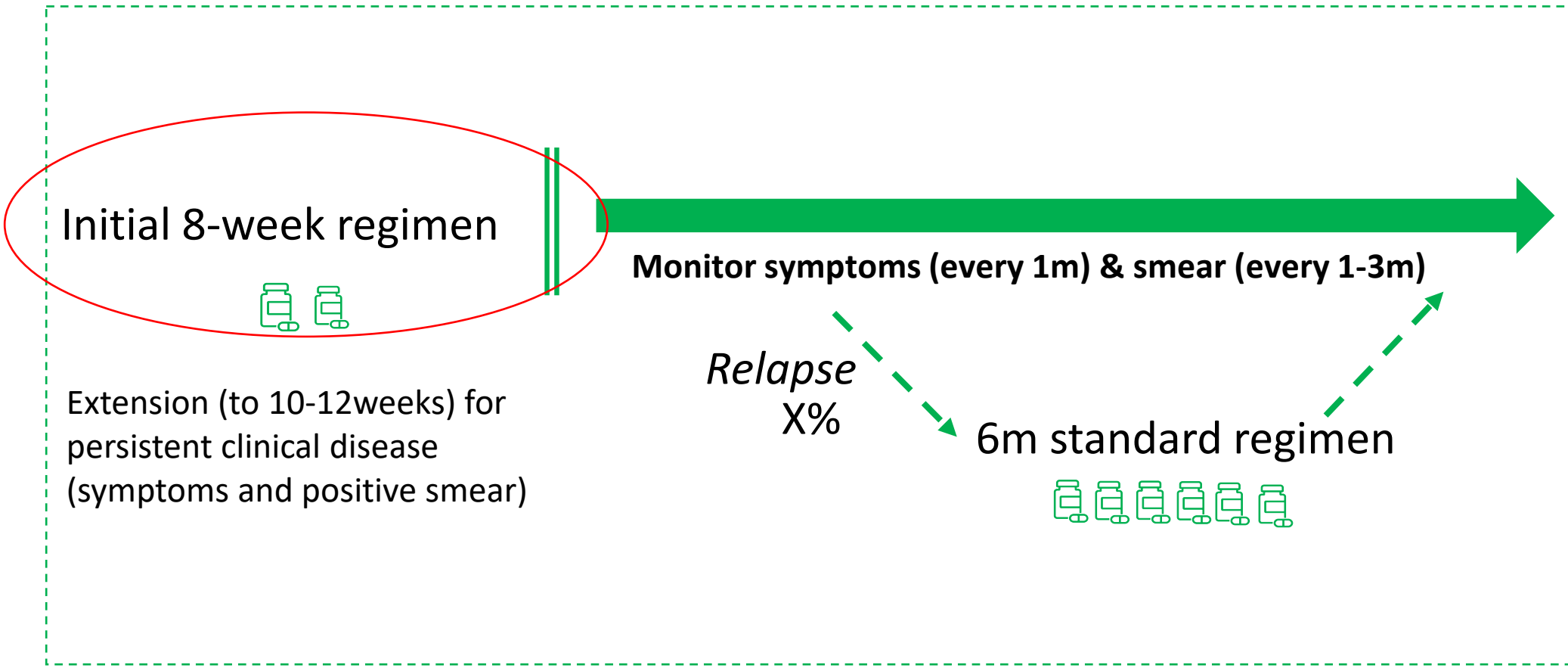
Summary of strategy analysis

- Non-inferior to standard treatment on clinical outcome at week 96 (with initial BDQ-LZD, but not with initial hRIF-LZD) - consistent in subgroup analyses
- Safe – no excess severe/serious AEs, death, respiratory disability.
- Substantial reduction in overall days on treatment; increased adherence motivation
- Had low risk of drug resistance (and only with BDQ regimen)

- Alternatives to over-treating the large majority of people with TB can be successful
- Important new research direction
- TRUNCATE strategy may be refined in future to improve outcomes using:
  - Alternative drug regimens (short duration, well tolerated)
  - Alternative algorithm for treatment extension (biomarkers)
  - Alternative strategies for monitoring

* Paton N, Cousins C, Suresh C et al. NEJM published online 20 Feb 2023: DOI: 10.1056/NEJMoa2212537

TRUNCATE Strategy



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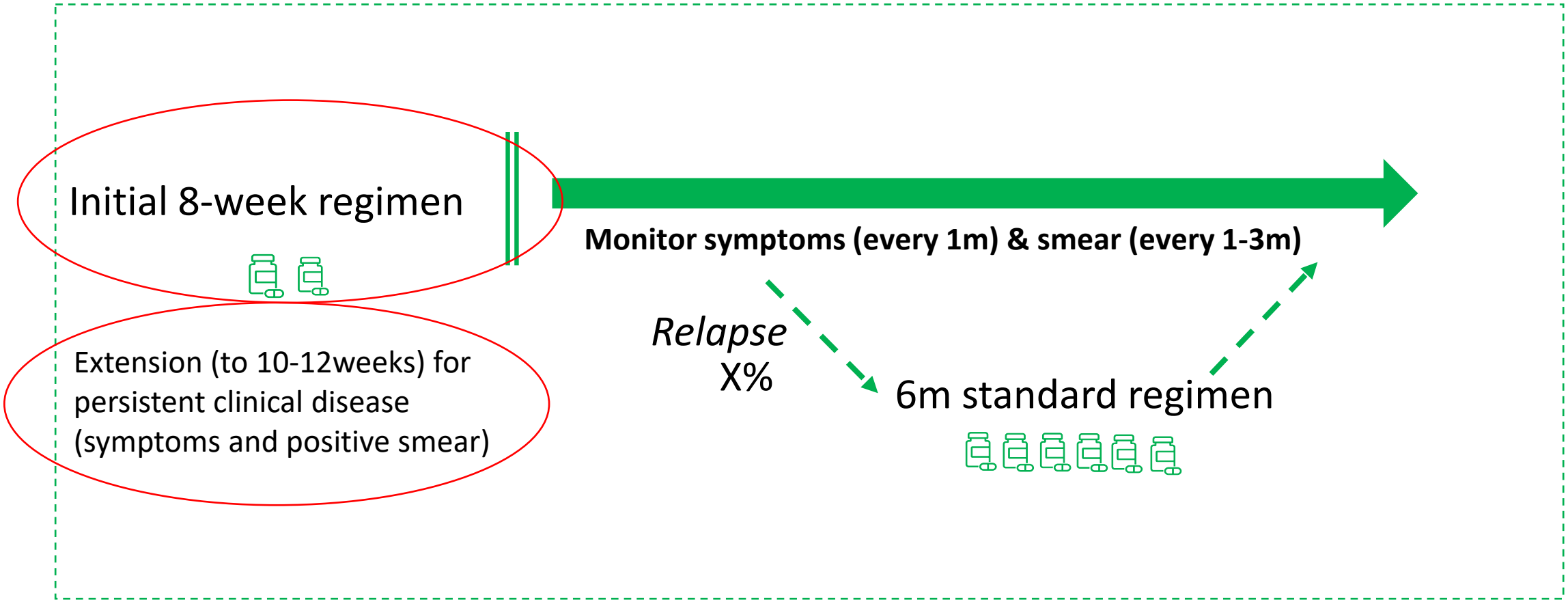

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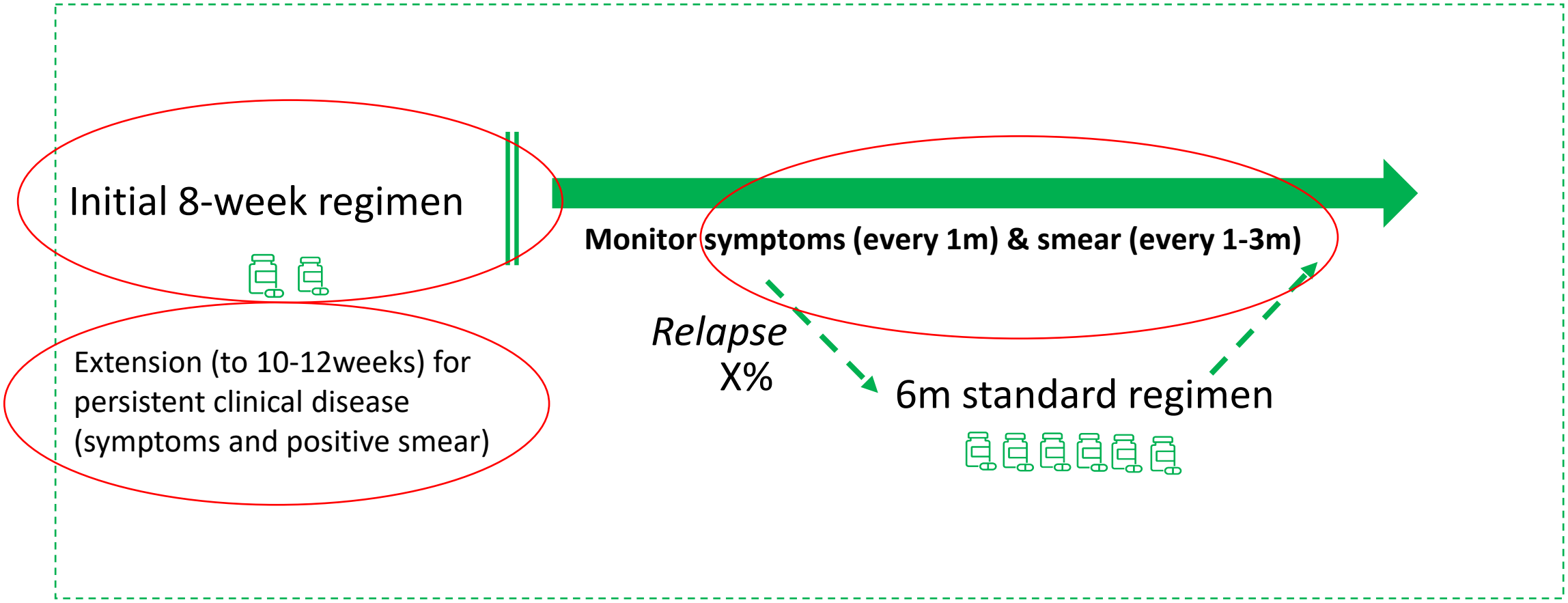

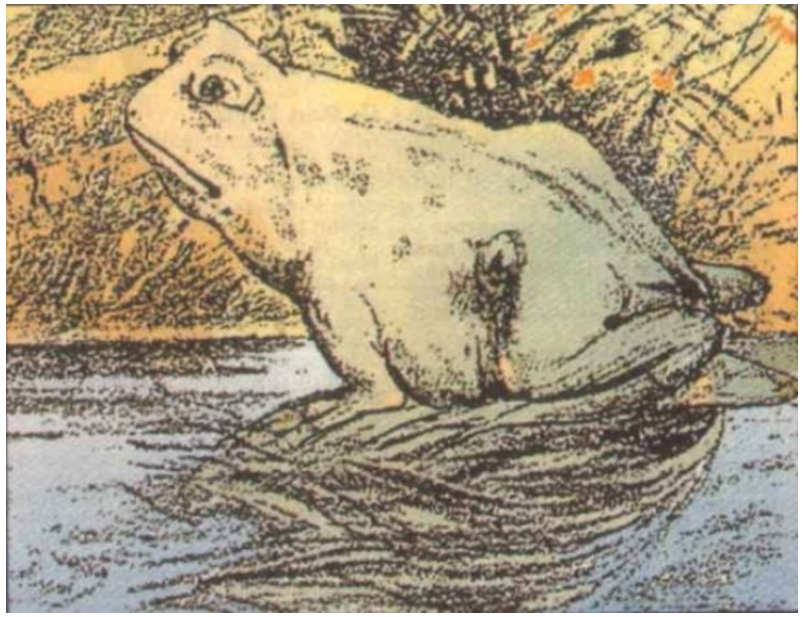

Regimen analysis

Aims of this analysis

- To evaluate the efficacy and safety of the main 8-week regimens tested in the TRUNCATE-TB trial (as distinct from the strategy in which they were deployed)
- To examine whether can identify subgroups in which the 8-week regimens do less well / better
- Unfavourable outcome

Regimen analysis: unfavourable outcome

	24 weeks Standard Rx (N=181)	8 weeks hRIF/LZD (N=184)	8 weeks BDQ/LZD (N=189)
Unfavourable outcome – no (%)	7 (3.9%)	46 (25.0%)	26 (13.8%)
Treatment failure at switch to standard Rx	0 (0.0)	0 (0.0)	1 (0.5)
Treatment failure at end of treatment	0 (0.0)	0 (0.0)	1 (0.5)
Confirmed relapse	4 (2.2)	39 (21.2)	20 (10.6)
Un-confirmed relapse	0 (0.0)	0 (0.0)	3 (1.6)
Death by W96, possible TB-related cause	2 (1.1)	5 (2.7)	0 (0.0)
Did not attend W96, lacks evidence of cure at last attended visit	1 (0.6)	2 (1.1)	1 (0.5)
Unassessable outcome	6 (3.3)	29 (15.8)	16 (8.5)

Unfavourable outcome

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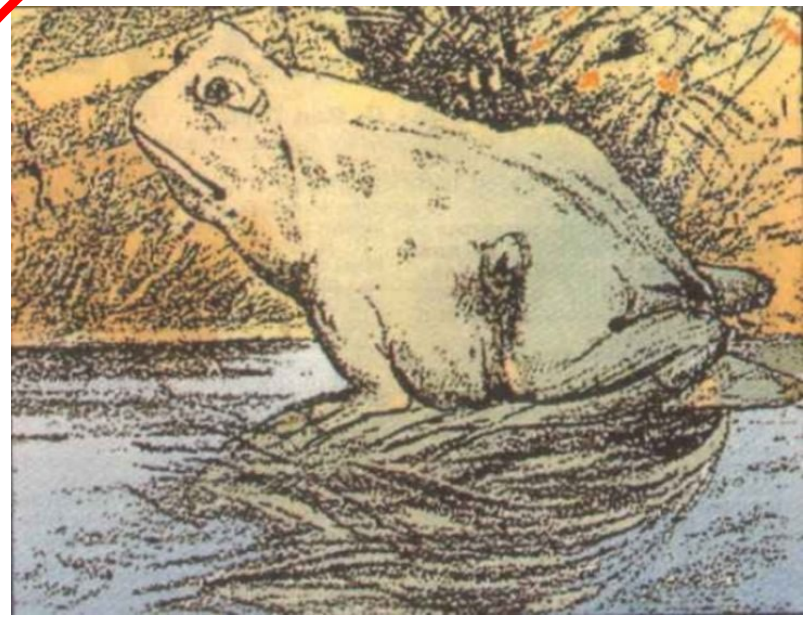
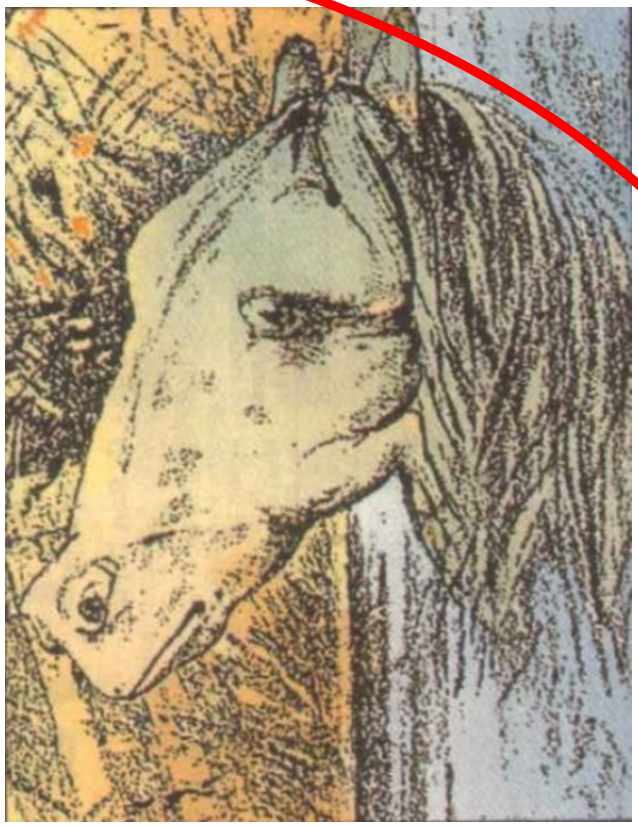
Unfavourable outcome: Bayesian analysis

	24 weeks Standard Rx (N=181)	8 weeks hRIF/LZD (N=184)	8 weeks BDQ/LZD (N=189)
Adjusted proportion (95% BCI)*	3.4% (1.3 to 6.3%)	23.7% (17.2 to 30.9%)	12.5% (7.9 to 18.1%)
Probability that proportion difference <12%*	-	0.01	0.85

Estimate using Bayesian model with flat (uninformative") prior; adjusted for country and baseline relapse risk
Following approach described by Laptook et al, JAMA 2017; DOI: 10.1001/jama.2017.14972





Probability of achieving absolute relapse rate < 20% by regimen and subgroup

	Probability of unfavourable outcome < 20%		
	24 wk Standard treatment	**8wk hRIF/LZD**	**8wk BDQ/LZD**
	(N=181)	**(N=184)**	**(N=189)**
All participants			
Smear grade			
Negative			
Scanty/1+			
2+			
3+			
Xpert MTB/RIF burden			
Very low/low			
Medium			
High			
CXR % lung affected			
< 25%			
25-50%			
> 50%			

>0.8

0.5 to 0.8

<0.5

Probability of achieving absolute relapse rate < 20% by regimen and subgroup

	Probability of unfavourable outcome < 20%		
	24 wk Standard treatment	**8wk hRIF/LZD**	**8wk BDQ/LZD**
	(N=181)	**(N=184)**	**(N=189)**
All participants	1		
Smear grade			
Negative			
Scanty/1+			
2+			
3+			
Xpert MTB/RIF burden			
Very low/low			
Medium			
High			
CXR % lung affected			
< 25%			
25-50%			
> 50%			

>0.8

0.5 to 0.8

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Probability of achieving absolute relapse rate < 20% by regimen and subgroup

	Probability of unfavourable outcome < 20%		
	24 wk Standard treatment	**8wk hRIF/LZD**	**8wk BDQ/LZD**
	(N=181)	**(N=184)**	**(N=189)**
All participants	1		
Smear grade			
Negative	1		
Scanty/1+	1		
2+	0.994		
3+	0.964		
Xpert MTB/RIF burden			
Very low/low	1		
Medium	1		
High	0.94		
CXR % lung affected			
< 25%	1		
25-50%	1		
> 50%	0.99		

>0.8

0.5 to 0.8

<0.5

Probability of achieving absolute relapse rate < 20% by regimen and subgroup

	Probability of unfavourable outcome < 20%		
	24 wk Standard treatment	**8wk hRIF/LZD**	**8wk BDQ/LZD**
	(N=181)	**(N=184)**	**(N=189)**
All participants	1	0.052	
Smear grade			
Negative	1		
Scanty/1+	1		
2+	0.994		
3+	0.964		
Xpert MTB/RIF burden			
Very low/low	1		
Medium	1		
High	0.94		
CXR % lung affected			
< 25%	1		
25-50%	1		
> 50%	0.99		

>0.8

0.5 to 0.8

<0.5

Probability of achieving absolute relapse rate < 20% by regimen and subgroup

	Probability of unfavourable outcome < 20%		
	24 wk Standard treatment (N=181)	**8wk hRIF/LZD (N=184)**	**8wk BDQ/LZD (N=189)**
All participants	1	0.052	
Smear grade			
Negative	1	0.819	
Scanty/1+	1	0.433	
2+	0.994	0	
3+	0.964	0.265	
Xpert MTB/RIF burden			
Very low/low	1	0.913	
Medium	1	0.019	
High	0.94	0.001	
CXR % lung affected			
< 25%	1	0.808	
25-50%	1	0.015	
> 50%	0.99	0.13	

>0.8

0.5 to 0.8

<0.5

Probability of achieving absolute relapse rate < 20% by regimen and subgroup

	Probability of unfavourable outcome < 20%		
	24 wk Standard treatment (N=181)	**8wk hRIF/LZD (N=184)**	**8wk BDQ/LZD (N=189)**
All participants	1	0.052	0.989
Smear grade			
Negative	1	0.819	
Scanty/1+	1	0.433	
2+	0.994	0	
3+	0.964	0.265	
Xpert MTB/RIF burden			
Very low/low	1	0.913	
Medium	1	0.019	
High	0.94	0.001	
CXR % lung affected			
< 25%	1	0.808	
25-50%	1	0.015	
> 50%	0.99	0.13	

>0.8

0.5 to 0.8

<0.5

Probability of achieving absolute relapse rate < 20% by regimen and subgroup

	Probability of unfavourable outcome < 20%		
	24 wk Standard treatment (N=181)	**8wk hRIF/LZD (N=184)**	**8wk BDQ/LZD (N=189)**
All participants	1	0.052	0.989
Smear grade			
Negative	1	0.819	0.994
Scanty/1+	1	0.433	0.956
2+	0.994	0	0.779
3+	0.964	0.265	0.31
Xpert MTB/RIF burden			
Very low/low	1	0.913	0.996
Medium	1	0.019	0.994
High	0.94	0.001	0.062
CXR % lung affected			
< 25%	1	0.808	0.987
25-50%	1	0.015	0.897
> 50%	0.99	0.13	0.785

>0.8

0.5 to 0.8

<0.5

Safety analysis

Number of participants with adverse event (%)	**Standard treatment (N= 181)**	**hRIF/LZD regimen (N=184)**	**BDQ/LZD regimen (N=189)**
Any grade 3 or 4 adverse event	25 (13.8)	20 (10.9)	21 (11.1)
Blood & lymphatic system disorders	8 (4.4)	3 (1.6)	13 (6.9)
Nervous system disorders	1 (0.6)	1 (0.5)	1 (0.5)
Hepatobiliary disorders	6 (3.3)	6 (3.3)	1 (0.5)
Any serious adverse event	7 (3.9)	8 (4.3)	5 (2.6)
Death	2 (1.1)	1 (0.5)	0

Conclusions of regimen analysis

Regimen efficacy

- Unfavourable outcome more frequent with 8wk regimens than 24wk standard regimen, as expected
- Difference modest with 5-drug BDQ/LZD regimen (high probability <12%); excess relapses can be managed within the TRUNCATE strategy*
- Biomarkers can identify subgroups with low probability of achieving target relapse rate (< 20%) with 8wk regimen. Refining criteria for treatment extension may improve strategy outcomes further.

Regimen safety

- Regimens were safe overall (severe AEs, serious AEs uncommon)
- Toxicity burden from linezolid appeared manageable
- BDQ resistance in two (1.1%) is a caution; needs monitoring in other studies

* Paton N, Cousins C, Suresh C et al. NEJM published online 20 Feb 2023: DOI: 10.1056/NEJMoa2212537

Overall implications of the findings

Alternatives to over-treating the large majority of people with TB can be successful
Important new research direction, with the promise to improve outcomes for patients and programmes

TRUNCATE strategy may be refined in future to improve outcomes using:

- Alternative drug regimens (short duration, well tolerated)
- Alternative stopping rules
- Alternative monitoring approaches (biomarkers to decide Rx cessation; or improve relapse detection)

Ongoing analyses from the TRUNCATE-TB trial will further enhance our understanding:

- Strategy implementation and health economics
- Safety, efficacy and PK-PD of the regimens tested
- Analysis of biomarkers (standard and new)

Need implementation studies of TRUNCATE strategy in broader populations (especially including HIV+)

Acknowledgements

Christopher Cousins

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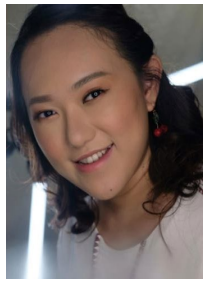

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