Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med 2014;371:1577-87. DOI: 10.1056/NEJMoa1407426

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Supplementary Appendix

Supplement to: Gillespie S, Crook A, McHugh T, et al. REMox TB: Two Four-Month Moxifloxacin-based Regimens for Drug-Sensitive Tuberculosis

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Trial Steering Committee and the Independent Data Safety Monitoring Board

We wish to acknowledge the Trial Steering Committee, which includes Dr. John Magee, Dr. Rick O'Brien, Professor Peter Ormerod.

We also wish to acknowledge the Independent Data Safety Monitoring Board which includes Dr. Katherine Fielding, Dr. Alwyn Mwinga, and Professor Tim Peto.

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ACTG Statement

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Supplementary text

1. Summary of Drug Dosing

Weight adjusted treatment was blinded and matching placebo was provided for all drugs except pyrazinamide (see Supplementary Table S2 for details). Patients co-infected with HIV could be given cotrimoxazole prophylaxis and anti-retrovirals were commenced according to local HIV/AIDS guidelines with efavirenz substituted for nevirapine if required. Treatment was given daily and was observed according to local guidelines.

2. Exclusions from the main analyses

2.1 Exclusion from the modified intention to treat (MITT) analysis

1. Patients with MDR disease documented from samples taken at enrolment or week 1 (late exclusions from the study)
2. Patients without culture confirmation of tuberculosis at enrolment or weeks 1 or 2 around enrolment, from screening to week 2 (late exclusions from the study)
3. Patients withdrawn from treatment because of a protocol violation at enrolment (late exclusions from the study, based on data collected prior to randomisation)
4. Patients who, having completed the treatment phase at Month 6, are lost to follow-up or withdrawn from the study, their last status being culture negative and their last positive culture result ("isolated positive culture") followed by at least two negative culture results (without an intervening positive culture)
5. Women who become pregnant during the 6-month treatment phase and stop their allocated treatment
6. Patients who died during the treatment phase from violent or accidental cause (e.g. road traffic accident). N.B.: This does not include death from suicide, which will be considered an unfavourable outcome.
7. Patients who died during the follow-up phase with no evidence of failure or relapse of their TB, their last status being culture negative and their last positive culture result ("isolated positive culture") followed by at least two negative culture results, and who have not already been classified as unfavourable.
8. Patients who, after being classified as having culture negative status, are re-infected with a new strain different from that with which they were originally infected. "Reinfection" will be defined specifically as a patient infected with a strain that is different from the initial strain as defined by MIRU and IS6110 typing. Assessments of relapse vs. reinfection will be made before database lock and unblinding.
9. Patients who are able to produce sputum at 18 months, but whose 18-month visit sputum samples are all (L-J and MGIT) contaminated or missing, who cannot be brought back for repeat cultures, provided they have not already been classified as unfavourable and provided their last positive culture was followed by at least two negative cultures. N.B.: This does not apply to patients who are unable to produce sputum at 18 months, or to patients who are able to be brought back subsequently and produce negative cultures.

Patients in categories 4-8 above who had already been classified as having an unfavourable outcome will not be excluded.

2.2 Additional exclusions from the per protocol (PP) analysis

1. Patients not meeting the definition of having received an adequate amount of their allocated study regimen (see below), provided they have not already been classified as having an unfavourable outcome

2. Patients lost to follow-up or withdrawn before the Month 6 visit, unless they have already been classified as having an unfavourable outcome.
3. Patients whose treatment was modified or extended for reasons (e.g. an adverse drug reaction or pregnancy) other than an unfavourable therapeutic response to treatment, unless they have already been classified as having an unfavourable outcome
4. Patients who are classified as "major protocol violations", unless they have already been classified as having an unfavourable outcome on the basis of data obtained prior to the protocol violation

2.3 Definition of adequate treatment

The definition of adequate treatment sets limits both for the amount of treatment missed in each treatment phase and the amount of treatment missed overall. For patients allocated to a 4 month regimen, to meet the definition of adequate treatment, the patients must have:

1. Taken a total of at least 42 doses of their allocated intensive phase treatment within 70 days of starting treatment
2. AND taken at least 42 doses of their continuation phase treatment within 84 days of completion of the intensive phase
3. AND missed no more than 28 doses of medication overall

For patients allocated to the 6 month regimen, to meet the definition of adequate treatment, the patients must have:

1. Taken a total of at least 42 doses of their allocated intensive phase treatment within 70 days of starting treatment
2. AND taken at least 84 doses of their continuation phase treatment within 168 days of completion of the intensive phase
3. AND missed no more than 42 doses of medication overall

These definitions are consistent with those used to define per protocol populations in the original trials which determined the effectiveness of the control 6 month isoniazid-rifampicin based regimen.

3. Definition of primary outcome for PP population

3.1 Unfavourable status

1. Patients not classified as having achieved or maintained culture negative status when last seen, or
2. Patients previously classified as having culture negative status who, following the end of treatment, have two positive cultures without an intervening negative culture, or
3. Patients who had a positive culture not followed by at least two negative cultures when last seen, or
4. Patients dying from any cause during the 6 month treatment phase, except from violent or accidental cause (e.g. road traffic accident), not including suicide (e.g., suicide will be considered an unfavourable outcome), or
5. Patients dying from TB related cause during the follow-up phase, or
6. Patients requiring a restart or a change of treatment because of an unfavourable outcome with or without bacteriological confirmation, i.e. on bacteriological, radiographic or clinical grounds

In all cases, “positive culture” refers to the culture being positive for M.tb. Patients found to be re-infected with a strain different from their original isolate are excluded from the analysis), although a sensitivity analysis will be performed in which these patients are classified as having unfavourable outcomes.

3.2 Favourable status

Patients with a negative culture status at 18 months (at or after 72 weeks), who had not already been classified as having an unfavourable outcome, and whose last positive culture result (“isolated positive culture”) was followed by at least two negative culture results.

4. Definition of primary outcome for MITT population

4.1 Unfavourable status

1. Patients not classified as having achieved or maintained culture negative status when last seen, or
2. Patients previously classified as having culture negative status who, following the end of treatment, have two positive cultures without an intervening negative culture, or
3. Patients who had a positive culture not followed by at least two negative cultures when last seen, or
4. Patients dying from any cause during the 6 month treatment phase, except from violent or accidental cause (e.g. road traffic accident), not including suicide (eg, suicide will be considered an unfavourable outcome) or
5. Patients dying from TB related cause during the follow-up phase or
6. Patients requiring an extension of their treatment beyond that permitted by the protocol, a restart or a change of treatment for any reason except reinfection or pregnancy, or
7. Patients failing to complete an adequate course of treatment (as defined above) who were unassessable at 18 months, or
8. Patients lost to follow up or withdrawn from the study before the 6-month visit

In all cases, “positive culture” refers to the culture being positive for M.tb. Patients found to be re-infected with a strain different from their original isolate are excluded from the analysis (and this includes TB deaths), although a sensitivity analysis will be performed in which these patients are classified as having unfavourable outcomes. NB: in the absence of MIRU data, the TB will be assumed to be the original strain. If a patient never achieves culture negative status, the MIRU data will not be used for outcome classification.

4.2 Favourable status

Patients with culture negative status at 18 months (at or after 72 weeks), who had not already been classified as having an unfavourable outcome, and whose last positive culture result (“isolated positive culture”) was followed by at least two negative culture results.

5. Excluded sites

Following partial closure of the Durban site after an investigation for fraud (involving 14 patients), and following an audit at a U.S. based supporting laboratory of the Mexican site (involving 22 patients), the outcome for these patients was deemed “unassessable” for the purposes of all efficacy analyses. The patients were included in safety and sensitivity analyses of efficacy. These decisions were taken before unblinding of the data.

Supplementary figures

Figure S1 REMoxTB Trial schematic describing the regimens and visit schedule

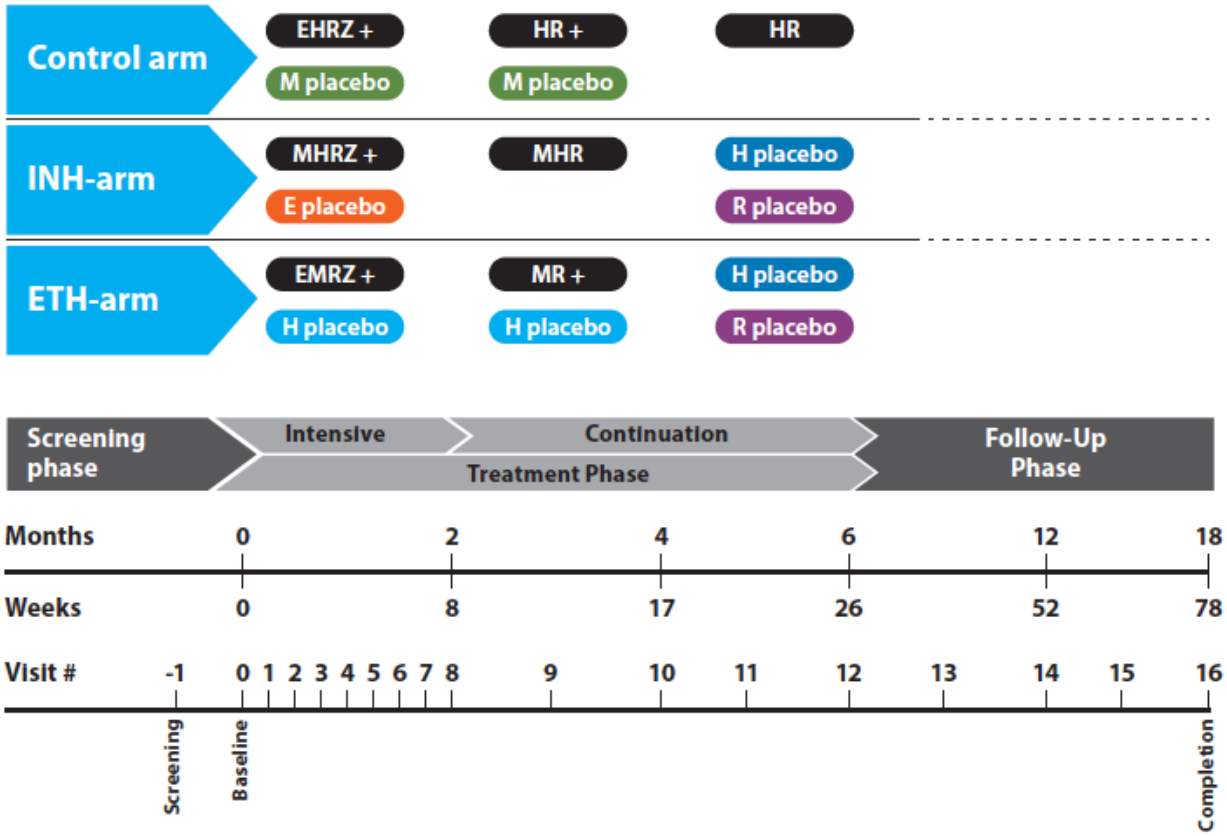


Figure S2 Graphical representation of difference from control with 97.5% confidence intervals.

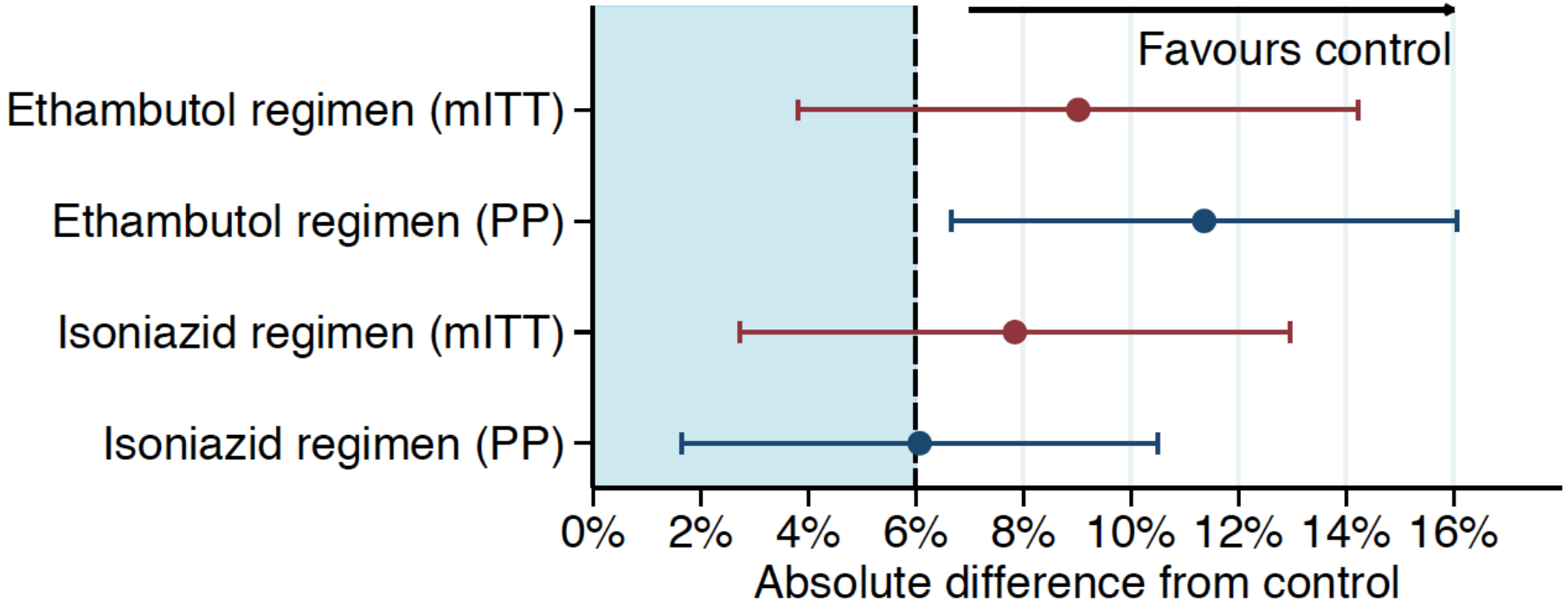
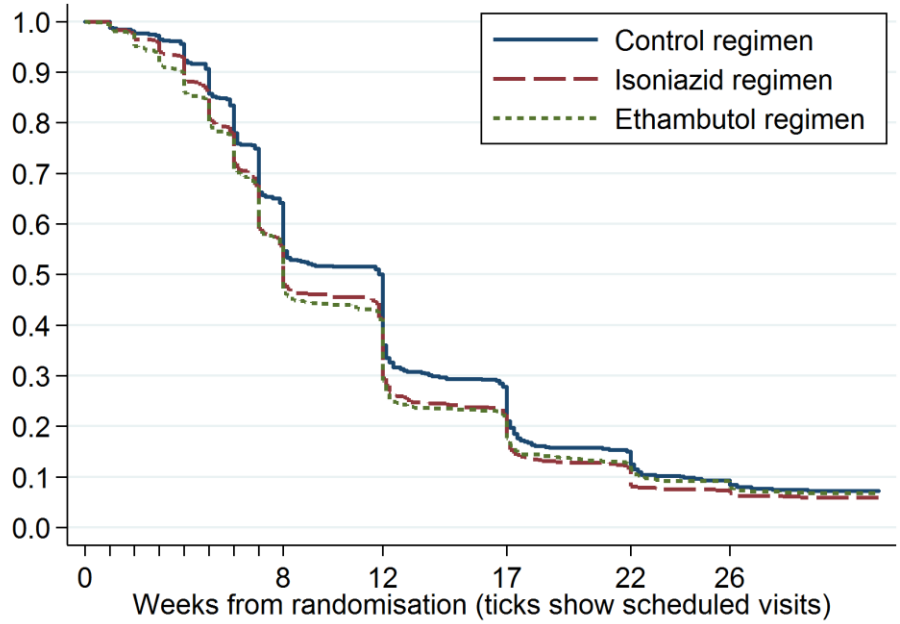


Figure S3 Time to culture negative status using MGIT liquid medium. Analysis include all patients excluding late screening failures



Number at risk

Control	600	561	371	289	159	52
Isoniazid	617	548	323	236	126	40
Ethambutol	604	537	327	240	128	49

Supplementary tables

Table S1 List of all inclusion and exclusion criteria

Inclusion criteria

Signed written consent or witnessed oral consent in the case of illiteracy, before undertaking an trial related activity

Two sputum specimens positive for tubercle bacilli on direct smear microscopy of which one confirmed by the REMoxTB study laboratory at the local laboratory

No history of previous anti-tuberculosis chemotherapy

Aged 18 years and over

A firm home address that is readily accessible for visiting and willingness to inform the study team of any change of address during the treatment and follow-up period

Agreement to participate in the study and to give a sample of blood for HIV testing

Negative pregnancy test (women of childbearing potential)

Pre-menopausal women must be using a barrier form of contraception or be surgically sterilised or have an IUCD in place

Laboratory parameters performed at least 14 days prior to enrolment

Serum aspartate transaminase (AST) and alanine transaminase (ALT) activity less than 3 times the upper limit of normal.
Serum total bilirubin level less than 2.5 times upper limit of normal.
Creatinine clearance (CrCl) level greater than 30 mls/min.
Haemoglobin level of at least 7.0 g/dL.
Platelet count of at least $50x10^9$cells/L.
Serum potassium greater than 3.5 mmol/L

Exclusion criteria

Patients unable to take oral medication.
Previously enrolled in this study

Receiving any investigational drug in the past 3 months or an antibiotic active against *M. tuberculosis*.
Pregnancy or breast-feeding.
Any condition that may prove fatal during the first two months of the study period.
Severe tuberculosis with high risk of a poor outcome (e.g., meningitis).
A pre-existing condition likely to prejudice the response to, or assessment of treatment, a condition likely to lead to uncooperative behaviour
A contraindication to any medications in the study regimens
A congenital or sporadic cardiac syndrome or taking medications that could result in QTc prolongation
Patients already receiving anti-retroviral therapy.
Weight less than 35kg.
HIV infection with CD4 count less than 250 cells/μL.
End stage liver failure (class Child-Pugh C).
Patients whose initial isolate was shown to be multiple drug resistant or mono-resistant to rifampicin, or any fluoroquinolone were excluded.

Table S2 Drug Dose for daily therapy

Moxifloxacin	400 mg
Rifampicin	
	< 45 kg 450 mg
	> 45 kg 600 mg
Isoniazid 300 mg	
Pyrazinamide	
	< 40 kg 25 mg/kg rounded to nearest 500 mg*
	40-55 kg 1000 mg
	> 55 kg – 75 kg 1500 mg
	> 75 kg 2000 mg
Ethambutol	
	< 40 kg 15 mg/kg rounded to nearest 100 mg
	40-55 kg 800 mg
	> 55 kg – 75 kg 1200 mg
	> 75 kg 1600 mg

* for pyrazinamide dosing in patients < 40 kg, 1000 mg used instead of 500 mg

Table S3A Summary of sensitivity analyses

	Control arm	Isoniazid arm		Ethambutol arm	
Analysis	N unfavourable / N assessable (%)	N unfavourable / N assessable (%)	Difference from control (97.5% CI)	N unfavourable / N assessable (%)	Difference from control (97.5% CI)
Per Protocol Analyses (PP)					
Primary analysis: adjusted for stratification factors	43/510 (8%)	78/514 (15%)	6.07% (1.65%, 10.50%)	105/524 (20%)	11.36% (6.66%, 16.06%)
Adjusted for additional covariates			5.13% (0.56%, 9.71%)		10.74% (6.02%, 15.47%)
Unadjusted			6.74% (2.25%, 11.24%)		11.61% (6.81%, 16.40%)
All deaths as unfavourable	48/515 (9%)	84/520 (16%)	6.28% (1.77%, 10.78%)	105/524 (20%)	10.51% (5.76%, 15.25%)
Primary endpoint based on only LJ results	43/501 (9%)	78/500 (16%)	7.02% (2.42%, 11.61%)	105/507 (21%)	12.13% (7.21%, 17.04%)
Primary endpoint based only on MGIT result	65/498 (13%)	98/498 (20%)	6.59% (1.55%, 11.63%)	131/512 (26%)	12.52% (7.14%, 17.89%)
Status at end of active treatment phase (EOT)	16/474 (3%)	17/489 (3%)	0.10% (-2.53%, 2.73%)	26/506 (5%)	1.76% (-1.12%, 4.64%)
18m status in those favourable at EOT	21/458 (5%)	63/472 (13%)	8.76% (4.63%, 12.90%)	84/480 (18%)	12.91% (8.45%, 17.38%)
12m status in those favourable at EOT	27/435 (6%)	64/459 (14%)	7.74% (3.28%, 12.19%)	81/462 (18%)	11.33% (6.59%, 16.06%)
Modified Intention to Treat (MITT)					
Primary analysis: adjusted for stratification factors	87/555 (16%)	132/568 (23%)	7.84% (2.73%, 12.95%)	132/551 (24%)	9.02% (3.81%, 14.23%)
Adjusted for additional covariates			7.36% (2.27%, 12.45%)		8.29% (3.16%, 13.42%)
Unadjusted			7.56% (2.30%, 12.83%)		8.28% (2.94%, 13.63%)
Reinfections as unfavourable	97/565 (17%)	145/581 (25%)	7.92% (2.66%, 13.18%)	151/570 (26%)	9.59% (4.25%, 14.93%)
Pinetown and Mexico as unfavourable	97/565 (17%)	140/576 (24%)	7.81% (2.63%, 12.99%)	150/569 (26%)	9.76% (4.46%, 15.06%)
All deaths as unfavourable	92/560 (16%)	135/571 (24%)	7.33% (2.14%, 12.52%)	132/551 (24%)	8.20% (2.93%, 13.46%)
Secondary bacteriological endpoint	75/555 (14%)	127/567 (22%)	8.86% (3.93%, 13.79%)	129/551 (23%)	10.27% (5.19%, 15.35%)
Primary endpoint based on only LJ results	87/546 (16%)	132/554 (24%)	8.10% (2.90%, 13.30%)	132/534 (25%)	9.55% (4.24%, 14.86%)
Primary endpoint based only on MGIT result	109/543 (20%)	153/553 (28%)	7.60% (1.90%, 13.30%)	158/539 (29%)	9.46% (3.66%, 15.26%)
Status at end of active treatment phase	16/485 (3%)	19/503 (4%)	0.48% (-2.16%, 3.11%)	27/513 (5%)	1.96% (-0.90%, 4.83%)
18m status in those favourable at EOT	31/469 (7%)	75/484 (15%)	8.06% (3.49%, 12.64%)	90/486 (19%)	11.14% (6.48%, 15.81%)
12m status in those favourable at EOT	37/446 (8%)	76/471 (16%)	6.94% (1.90%, 11.98%)	87/468 (19%)	9.59% (4.59%, 14.59%)
All randomised patients					
Missing outcome as unfavourable	172/640 (27%)	219/655 (33%)	6.79% (1.12%, 12.47%)	217/636 (34%)	7.12% (1.44%, 12.80%)
Missing outcome as favourable	87/640 (14%)	132/655 (20%)	6.73% (2.24%, 11.21%)	132/636 (21%)	7.75% (3.15%, 12.36%)
Missing outcomes as last observation carried forward	119/640 (19%)	165/655 (25%)	6.51% (1.45%, 11.58%)	164/636 (26%)	7.27% (2.15%, 12.38%)
All randomised patients excluding late screening failures					
Missing outcome as unfavourable	132/600 (22%)	181/617 (29%)	7.48% (1.97%, 12.99%)	185/604 (31%)	8.76% (3.18%, 14.33%)
Missing outcome as favourable	87/600 (14%)	132/617 (21%)	7.06% (2.29%, 11.83%)	132/604 (22%)	8.02% (3.17%, 12.87%)
Missing outcomes as last observation carried forward	101/600 (17%)	148/617 (24%)	7.24% (2.19%, 12.30%)	152/604 (25%)	8.68% (3.58%, 13.78%)

Table S3B Summary of sub-group analyses. All sub-group analyses use the per protocol classification and are unadjusted.

		Control arm	Isoniazid arm			Ethambutol arm		
Baseline characteristic	Category	N unfavourable / N assessable (%)	N unfavourable / N assessable (%)	Difference from control (97.5% CI)	Test for interaction	N unfavourable / N assessable (%)	Difference from control (97.5% CI)	Test for interaction
Site location	Stellenbosch	9/97 (9%)	19/119 (16%)	6.69% (-3.32%, 16.70%)		24/122 (20%)	10.39% (-0.03%, 20.82%)	
	Cape Town	9/74 (12%)	16/82 (20%)	7.35% (-5.64%, 20.34%)		11/67 (16%)	4.26% (-8.99%, 17.50%)	
	Other SA	5/61 (8%)	8/56 (14%)	6.09% (-7.02%, 19.20%)		13/53 (25%)	16.33% (0.92%, 31.74%)	
	India	12/103 (12%)	17/94 (18%)	6.43% (-4.94%, 17.81%)		23/111 (21%)	9.07% (-2.09%, 20.23%)	
	East Africa	5/120 (4%)	12/104 (12%)	7.37% (-0.75%, 15.50%)		24/121 (20%)	15.67% (6.57%, 24.76%)	
	East Asia	3/55 (5%)	6/59 (10%)	4.71% (-6.46%, 15.89%)	p=0.999	10/50 (20%)	14.55% (0.13%, 28.96%)	p=0.620
Gender	Female	13/154 (8%)	12/163 (7%)	-1.08% (-7.88%, 5.72%)		20/155 (13%)	4.46% (-3.39%, 12.31%)	
	Male	30/356 (8%)	66/351 (19%)	10.38% (4.65%, 16.10%)	p=0.004	85/369 (23%)	14.61% (8.69%, 20.53%)	p=0.023
BMI	<18.4 kg/m^2	21/258 (8%)	51/266 (19%)	11.03% (4.41%, 17.65%)		63/266 (24%)	15.54% (8.57%, 22.52%)	
	≥18.4 kg/m^2	22/252 (9%)	27/248 (11%)	2.16% (-3.80%, 8.12%)	p=0.026	42/258 (16%)	7.55% (1.04%, 14.06%)	p=0.061
Weight band	< 40 kg	4/50 (8%)	7/44 (16%)	7.91% (-7.15%, 22.97%)		9/58 (16%)	7.52% (-6.18%, 21.21%)	
	40-45 kg	8/80 (10%)	17/90 (19%)	8.89% (-3.03%, 20.81%)		27/82 (33%)	22.93% (9.08%, 36.78%)	
	45-55 kg	21/206 (10%)	35/210 (17%)	6.47% (-0.98%, 13.93%)		39/204 (19%)	8.92% (1.15%, 16.70%)	
	≥75 kg	10/174 (6%)	19/170 (11%)	5.43% (-1.28%, 12.14%)	p=0.946	30/180 (17%)	10.92% (3.54%, 18.30%)	p=0.225
Age	<31 years	17/262 (6%)	34/272 (13%)	6.01% (0.37%, 11.65%)		43/262 (16%)	9.92% (3.76%, 16.08%)	
	≥31 years	26/248 (10%)	44/242 (18%)	7.70% (0.63%, 14.76%)	p=0.676	62/262 (24%)	13.18% (5.86%, 20.50%)	p=0.446
Race	Asian	15/160 (9%)	23/154 (15%)	5.56% (-2.69%, 13.81%)		33/161 (20%)	11.12% (2.32%, 19.93%)	
	Black	19/238 (8%)	26/210 (12%)	4.40% (-2.04%, 10.84%)		49/237 (21%)	12.69% (5.60%, 19.78%)	
	Mixed race	9/111 (8%)	27/148 (18%)	10.14% (0.95%, 19.32%)	p=0.516	23/126 (18%)	10.15% (0.49%, 19.80%)	p=0.883
HIV status	Negative	38/472 (8%)	68/477 (14%)	6.20% (1.65%, 10.76%)		91/489 (19%)	10.56% (5.72%, 15.40%)	
	Positive	5/38 (13%)	10/37 (27%)	13.87% (-6.60%, 34.34%)	p=0.413	14/35 (40%)	26.84% (4.58%, 49.10%)	p=0.113
Resistance to isoniazid	Sensitive	38/470 (8%)	69/473 (15%)	6.50% (1.90%, 11.10%)		95/479 (20%)	11.75% (6.79%, 16.71%)	
	Resistant	5/29 (17%)	6/34 (18%)	0.41% (-21.09%, 21.90%)	p=0.533	8/39 (21%)	3.27% (-18.11%, 24.65%)	p=0.382
Cavitation	Absent	6/96 (6%)	6/104 (6%)	-0.48% (-8.03%, 7.06%)		13/108 (12%)	5.79% (-3.15%, 14.73%)	
	Present	34/368 (9%)	60/357 (17%)	7.57% (1.99%, 13.15%)	p=0.058	83/367 (23%)	13.38% (7.43%, 19.33%)	p=0.118
MGIT Time to positivity	<5 days	19/229 (8%)	36/239 (15%)	6.77% (0.16%, 13.37%)		62/254 (24%)	16.11% (8.82%, 23.41%)	
	>=5 days	23/266 (9%)	40/263 (15%)	6.56% (0.27%, 12.85%)	p=0.960	43/258 (17%)	8.02% (1.54%, 14.50%)	p=0.064

Table S4 Recruitment by randomisation stratification factors: centre and weight band at randomisation.

		Control	INH-arm	ETH-arm	Total
Country and site					
South Africa	Stellenbosch	119	140	136	**395**
	Cape Town	101	103	86	**290**
	Johannesburg	35	28	29	**92**
	Durban	18	19	24	**61**
	Brits	17	16	19	**52**
	ACTG	8	7	4	**19**
India	Multiple sites	121	128	127	**376**
Tanzania	Mbeya	48	42	51	**141**
	Moshi	26	22	23	**71**
Kenya	Nairobi	44	49	43	**136**
Thailand	CDI, Nonthaburi	24	19	23	**66**
	RVH, Bangkok	16	19	18	**53**
Malaysia	Kuala Lumpur	23	26	20	**69**
Zambia	Lusaka	23	23	20	**66**
China	Beijing, Tianjin	8	9	5	**22**
Mexico		9	5	8	**22**
Weight band at randomisation					
	< 40 kg	63 (10%)	61 (9%)	62 (10%)	186 (10%)
	40-45 kg	101 (16%)	115 (18%)	101 (16%)	317 (16%)
	45-55 kg	256 (40%)	254 (39%)	249 (39%)	759 (39%)
	55-75 kg	204 (32%)	209 (32%)	209 (33%)	622 (32%)
	>75 kg	16 (3%)	16 (2%)	15 (2%)	47 (2%)
Total randomised		**640**	**655**	**636**	**1931**

Table S5 Baseline characteristics of all randomised patients. A single patient had missing HIV status. Resistance results were missing for isoniazid for 62 patients, for rifampicin for 61 patients, for moxifloxacin for 77 patients and for pyrazinamide for 94 patients. Cavitation status was missing in 218 patients. 1 patient had missing race.

		Control regimen	Isoniazid regimen	Ethambutol regimen	Total
Total randomised		640	655	636	1931
Male N (%)	**Male**	448 (70%)	450 (69%)	448 (70%)	1346 (70%)
BMI (kg/m^2)	**Median (min-max)**	18.4 (12.1-50.9)	18.3 (12.0-40.7)	18.5 (12.2-34.5)	18.4 (12.0-50.9)
Weight band N(%)	**< 40 kg**	63 (10%)	61 (9%)	62 (10%)	186 (10%)
	40-45 kg	101 (16%)	115 (18%)	101 (16%)	317 (16%)
	45-55 kg	256 (40%)	254 (39%)	249 (39%)	759 (39%)
	55-75 kg	204 (32%)	209 (32%)	209 (33%)	622 (32%)
	>75 kg	16 (3%)	16 (2%)	15 (2%)	47 (2%)
Age N (%)	**<25 years**	187 (29%)	205 (31%)	175 (28%)	567 (29%)
	25-<35 years	186 (29%)	212 (32%)	209 (33%)	607 (31%)
	35+ years	267 (42%)	238 (36%)	252 (40%)	757 (39%)
Race N(%)	**Black**	194 (30%)	202 (31%)	194 (31%)	590 (31%)
	Asian	296 (46%)	277 (42%)	291 (46%)	864 (45%)
	Mixed race	140 (22%)	169 (26%)	142 (22%)	451 (23%)
	Other	10 (1%)	7 (1%)	8 (1%)	25 (1%)
Smoking History N (%)	**Never**	299 (47%)	292 (45%)	280 (44%)	871 (45%)
	Past	155 (24%)	155 (24%)	166 (26%)	476 (25%)
	Current	186 (29%)	208 (32%)	190 (30%)	584 (30%)
HIV status N (%)	**Positive**	46 (7%)	46 (7%)	48 (8%)	140 (7%)
Resistance to Isoniazid (%)	**Resistant**	46 (7%)	52 (8%)	49 (8%)	147 (8%)
Resistance to Rifampicin (%)	**Resistant**	9 (1%)	9 (1%)	7 (1%)	25 (1%)
Resistance to Moxifloxacin (%)	**Resistant**	13 (2%)	8 (1%)	9 (1%)	30 (2%)
Resistance to Pyrazinamide (%)	**Resistant**	25 (4%)	11 (2%)	12 (2%)	48 (2%)
Cavitation (%)	**Present**	457 (79%)	442 (76%)	428 (76%)	1327 (77%)

Time to positivity (%)	**≥ 5 days**	322 (50%)	337 (51%)	320 (50%)	979 (51%)
	< 5 days	291 (45%)	290 (44%)	294 (46%)	875 (45%)
	Not available	27 (4%)	28 (4%)	22 (3%)	77 (4%)

Table S6 Baseline characteristics of patients assessable in the MITT population. Resistance results were missing for isoniazid for 24 patients and for pyranamide in 29 patients. Cavitation status was missing in 166 patients.

		Control regimen	Isoniazid regimen	Ethambutol regimen	Total
Total randomised (MITT)		555	568	551	1674
Male N (%)	**Male**	387 (70%)	392 (69%)	387 (70%)	1166 (70%)
BMI (kg/m^2)	**Median (min-max)**	18.3 (12.1-50.9)	18.3 (12.0-40.7)	18.4 (12.2-32.6)	18.3 (12.0-50.9)
Weight band N(%)	**< 40 kg**	58 (10%)	53 (9%)	59 (11%)	170 (10%)
	40-45 kg	91 (16%)	98 (17%)	86 (16%)	275 (16%)
	45-55 kg	222 (40%)	226 (40%)	215 (39%)	663 (40%)
	55-75 kg	171 (31%)	177 (31%)	184 (33%)	532 (32%)
	>75 kg	13 (2%)	14 (2%)	7 (1%)	34 (2%)
Age N (%)	**<25 years**	171 (31%)	172 (30%)	157 (28%)	500 (30%)
	25-<35 years	159 (29%)	185 (33%)	181 (33%)	525 (31%)
	35+ years	225 (41%)	211 (37%)	213 (39%)	649 (39%)
Race N(%)	**Black**	178 (32%)	177 (31%)	172 (31%)	527 (31%)
	Asian	256 (46%)	232 (41%)	250 (45%)	738 (44%)
	Mixed race	120 (22%)	157 (28%)	129 (23%)	406 (24%)
	Other	1 (<0.5%)	2 (<0.5%)	0	3 (<0.5%)
Smoking History N (%)	**Never**	263 (47%)	255 (45%)	243 (44%)	761 (45%)
	Past	128 (23%)	125 (22%)	142 (26%)	395 (24%)
	Current	164 (30%)	188 (33%)	166 (30%)	518 (31%)
HIV status N (%)	**Positive**	43 (8%)	40 (7%)	40 (7%)	123 (7%)
Resistance to Isoniazid (%)	**Resistant**	32 (6%)	41 (7%)	41 (7%)	114 (7%)
Resistance to Pyrazinamide (%)	**Resistant**	16 (3%)	7 (1%)	6 (1%)	29 (2%)
Cavitation (%)	**Present**	398 (72%)	389 (68%)	383 (70%)	1170 (70%)
Time to positivity (%)	**≥ 5 days**	284 (51%)	290 (51%)	272 (49%)	846 (51%)
	< 5 days	254 (46%)	260 (46%)	263 (48%)	777 (46%)
	Not available	17 (3%)	18 (3%)	16 (3%)	51 (3%)

Table S7 Time to culture negative status of all randomised patients excluding late screening failures.

		Control	INH-arm	No INH-arm
Total randomised		640	655	636
Total in analysis		600	617	604
LJ solid media	**Person years in follow-up**	95.1	80.2	80.8
	Culture negative	570	576	580
	Rate per 10 person years (95% CI)	59.93 (55.20, 65.05)	71.83 (66.19, 77.94)	71.79 (66.18, 77.88)
	Median time to culture negative status / wks (95% CI)	6.0 (6.0, 6.1)	6.0 (5.1, 6.0)	6.0 (5.7, 6.0)
	Hazard ratio, compared to control		1.25	1.21
	95% confidence interval		(1.10, 1.40)	(1.07, 1.35)
	97.5% confidence interval		(1.08, 1.42)	(1.05, 1.37)
	Log-rank test, compared to control		p=0.0001	p=0.0011
MGIT liquid media	**Person years in follow-up**	156.5	143.2	145.0
	Culture negative	550	553	559
	Rate per 10 person years (95% CI)	35.14 (32.32, 38.20)	38.61 (35.52, 41.97)	38.54 (35.47, 41.87)
	Median time to culture negative status / wks (95% CI)	11.9 (8.1, 12.0)	8.0 (8.0, 9.9)	8.0 (8.0, 8.1)
	Hazard ratio, compared to control		1.17	1.17
	95% confidence interval		(1.03, 1.31)	(1.03, 1.31)
	97.5% confidence interval		(1.01, 1.33)	(1.01, 1.33)
	Log-rank test, compared to control		p=0.0091	p=0.0045

Table S8 Status at end of 8 week intensive phase including all randomised patients excluding late screening failures.

		Control 2EHRZ/4HR	INH-arm 2MHRZ/2MHR	No INH-arm 2EMRZ/2MR
Total randomised		640	655	636
Analysis population		600	617	604
LJ solid media	**Unassessable**	126	100	90
	N Assessable	474	517	514
	Negative (% N)	393 (83%)	439 (85%)	448 (87%)
	Positive (% N)	77 (16%)	73 (14%)	63 (12%)
	Died (% N)	4 (1%)	5 (1%)	3 (1%)
	Difference from control in culture negative (97.5% CI)		2.52% (-2.41%, 7.45%)	3.09% (-1.93%, 8.12%)
	Chi-sq test for independence		p = 0.391 (Chi2=0.74)	p = 0.061 (Chi2=3.51)
MGIT liquid media	**Unassessable**	128	112	120
	N Assessable	472	505	484
	Negative (% N)	267 (57%)	309 (61%)	295 (61%)
	Positive (% N)	201 (43%)	191 (38%)	186 (38%)
	Died (% N)	4 (1%)	5 (1%)	3 (1%)
	Difference from control in culture negative (97.5% CI)		4.37% (-2.43%, 11.17%)	4.62% (-2.31%, 11.54%)
	Chi-sq test for independence		p = 0.142 (Chi2=2.15)	p = 0.169 (Chi2=1.89)

Table S9 Time to unfavourable outcome according to PP classification. Analysis includes all randomised patients excluding late screening failures. *Since the proportion of unfavourable outcomes is much less than 50% it is not possible to estimate *median* time to unfavourable outcome without extrapolation. The 10th centile of time to unfavourable outcome shows the time before which 10% of patients had an unfavourable outcome.

	Control	INH-arm	No INH-arm
Total randomised	640	655	636
Total in analysis	600	617	604
Person years in follow-up	771.2	736.8	725.9
Unfavourable outcomes	43	78	105
Rate per 10 person years (95% CI)	0.56 (0.41, 0.75)	1.06 (0.85, 1.32)	1.45 (1.19, 1.75)
10th centile time to unfavourable outcome*	84.9 (68.9, 137.1)	39.3 (35.3, 50.7)	31.6 (26.1, 38.9)
Hazard ratio, compared to control		1.87	2.56
95% confidence interval		(1.17, 2.57)	(1.65, 3.47)
97.5% confidence interval		(1.07, 2.67)	(1.51, 3.60)
Log-rank test, compared to control		p=0.0009	P<0.0001

Table S10 Serious Adverse Events and Deaths. The table below presents the total number of SAE events and the number and percentage of subjects experiencing each event for system organ classes in which >1% of patients experienced an SAE.

		2EHRZ/4HR N=639		2MHRZ/2MHR N=655		2EMRZ/2MR N=636	
Deaths		16 (3%)		15 (2%)		12 (2%)	
TB-Related Deaths		11 (2%)		10 (2%)		9 (1%)	
SAEs							
System Organ Class	**Preferred Term**	**Evt.**	**n (%)**	**Evt.**	**n (%)**	**Evt.**	**n (%)**
Any	Any	105	59(9%)	132	62(9%)	112	52(8%)
Gastrointestinal Disorders	Any	10	6(1%)	11	6(1%)	17	10(2%)
	Abdominal Distension	0	0(0%)	0	0(0%)	1	1(0%)
	Abdominal Mass	0	0(0%)	1	1(0%)	0	0(0%)
	Abdominal Pain	1	1(0%)	0	0(0%)	2	2(0%)
	Abdominal Pain Lower	0	0(0%)	3	2(0%)	0	0(0%)
	Abdominal Tenderness	0	0(0%)	1	1(0%)	0	0(0%)
	Acute Abdomen	1	1(0%)	0	0(0%)	0	0(0%)
	Ascites	0	0(0%)	0	0(0%)	1	1(0%)
	Diarrhoea	1	1(0%)	0	0(0%)	0	0(0%)
	Gastrointestinal Disorder	0	0(0%)	1	1(0%)	0	0(0%)
	Haematemesis	1	1(0%)	0	0(0%)	0	0(0%)
	Haematochezia	2	1(0%)	0	0(0%)	0	0(0%)
	Nausea	1	1(0%)	2	2(0%)	2	2(0%)
	Pancreatitis	1	1(0%)	0	0(0%)	0	0(0%)
	Peptic Ulcer Perforation	1	1(0%)	0	0(0%)	0	0(0%)
	Vomiting	1	1(0%)	3	3(0%)	11	6(1%)
Infections And Infestations	Any	14	13(2%)	24	19(3%)	14	12(2%)
	Appendicitis	0	0(0%)	1	1(0%)	0	0(0%)
	Diarrhoea Infectious	0	0(0%)	1	1(0%)	0	0(0%)
	Disseminated Tuberculosis	1	1(0%)	0	0(0%)	1	1(0%)
	Gangrene	0	0(0%)	1	1(0%)	0	0(0%)
	Hepatitis B	0	0(0%)	1	1(0%)	0	0(0%)

		2EHRZ/4HR N=639		2MHRZ/2MHR N=655		2EMRZ/2MR N=636	
Deaths		16 (3%)		15 (2%)		12 (2%)	
TB-Related Deaths		11 (2%)		10 (2%)		9 (1%)	
SAEs							
System Organ Class	**Preferred Term**	**Evt.**	**n (%)**	**Evt.**	**n (%)**	**Evt.**	**n (%)**
	Aspartate Aminotransferase Increased	1	1(0%)	0	0(0%)	1	1(0%)
	Blood Bilirubin Increased	0	0(0%)	1	1(0%)	0	0(0%)
	Blood Creatinine Increased	0	0(0%)	1	1(0%)	1	1(0%)
	Breath Sounds Abnormal	0	0(0%)	1	1(0%)	0	0(0%)
	Gamma-Glutamyltransferase Increased	2	2(0%)	0	0(0%)	2	2(0%)
	Haemoglobin Decreased	0	0(0%)	0	0(0%)	1	1(0%)
	Hepatic Enzyme Increased	3	3(0%)	3	3(0%)	4	4(1%)
	International Normalised Ratio Increased	0	0(0%)	1	1(0%)	0	0(0%)
	Liver Function Test Abnormal	1	1(0%)	0	0(0%)	0	0(0%)
	Prothrombin Time Prolonged	0	0(0%)	2	1(0%)	0	0(0%)
	Respiratory Rate Increased	0	0(0%)	0	0(0%)	1	1(0%)
	Weight Decreased	2	2(0%)	2	2(0%)	4	2(0%)
Respiratory, Thoracic And Mediastinal Disorders	Any	24	14(2%)	28	14(2%)	20	13(2%)
	Asphyxia	0	0(0%)	1	1(0%)	0	0(0%)
	Asthma	0	0(0%)	1	1(0%)	0	0(0%)
	Bronchospasm	0	0(0%)	0	0(0%)	1	1(0%)
	Cough	1	1(0%)	0	0(0%)	0	0(0%)
	Dysphonia	0	0(0%)	1	1(0%)	0	0(0%)
	Dyspnoea	6	5(1%)	2	2(0%)	8	6(1%)

		2EHRZ/4HR N=639		2MHRZ/2MHR N=655		2EMRZ/2MR N=636	
Deaths		16 (3%)		15 (2%)		12 (2%)	
TB-Related Deaths		11 (2%)		10 (2%)		9 (1%)	
SAEs							
System Organ Class	**Preferred Term**	**Evt.**	**n (%)**	**Evt.**	**n (%)**	**Evt.**	**n (%)**
	Haemoptysis	8	7(1%)	7	6(1%)	2	2(0%)
	Haemothorax	1	1(0%)	0	0(0%)	0	0(0%)
	Hydropneumothorax	0	0(0%)	3	1(0%)	0	0(0%)
	Hypoventilation	0	0(0%)	1	1(0%)	0	0(0%)
	Oropharyngeal Pain	1	1(0%)	0	0(0%)	0	0(0%)
	Pleural Effusion	1	1(0%)	0	0(0%)	1	1(0%)
	Pneumonia Aspiration	0	0(0%)	1	1(0%)	0	0(0%)
	Pneumothorax	5	2(0%)	3	3(0%)	6	3(0%)
	Rales	0	0(0%)	3	2(0%)	0	0(0%)
	Respiratory Distress	0	0(0%)	0	0(0%)	1	1(0%)
	Respiratory Failure	1	1(0%)	1	1(0%)	1	1(0%)
	Rhonchi	0	0(0%)	2	1(0%)	0	0(0%)
	Wheezing	0	0(0%)	2	1(0%)	0	0(0%)