BEAT Tuberculosis Trial

(Building Evidence for Advancing New Treatment for Tuberculosis)

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BEAT Tuberculosis Study design

An open label, randomized controlled trial to establish the efficacy and safety of a **Study Strategy** consisting of 6 months of bedaquiline (B), delamanid (D), and linezolid (L), with levofloxacin (Lfx) and clofazimine (C) compared to the current South African Standard of Care (**Control Strategy**)

ClinicalTrials.gov Identifier: **NCT04062201**
PACTR Trial ID: **PACTR201908619497716**

Primary Objectives

Efficacy

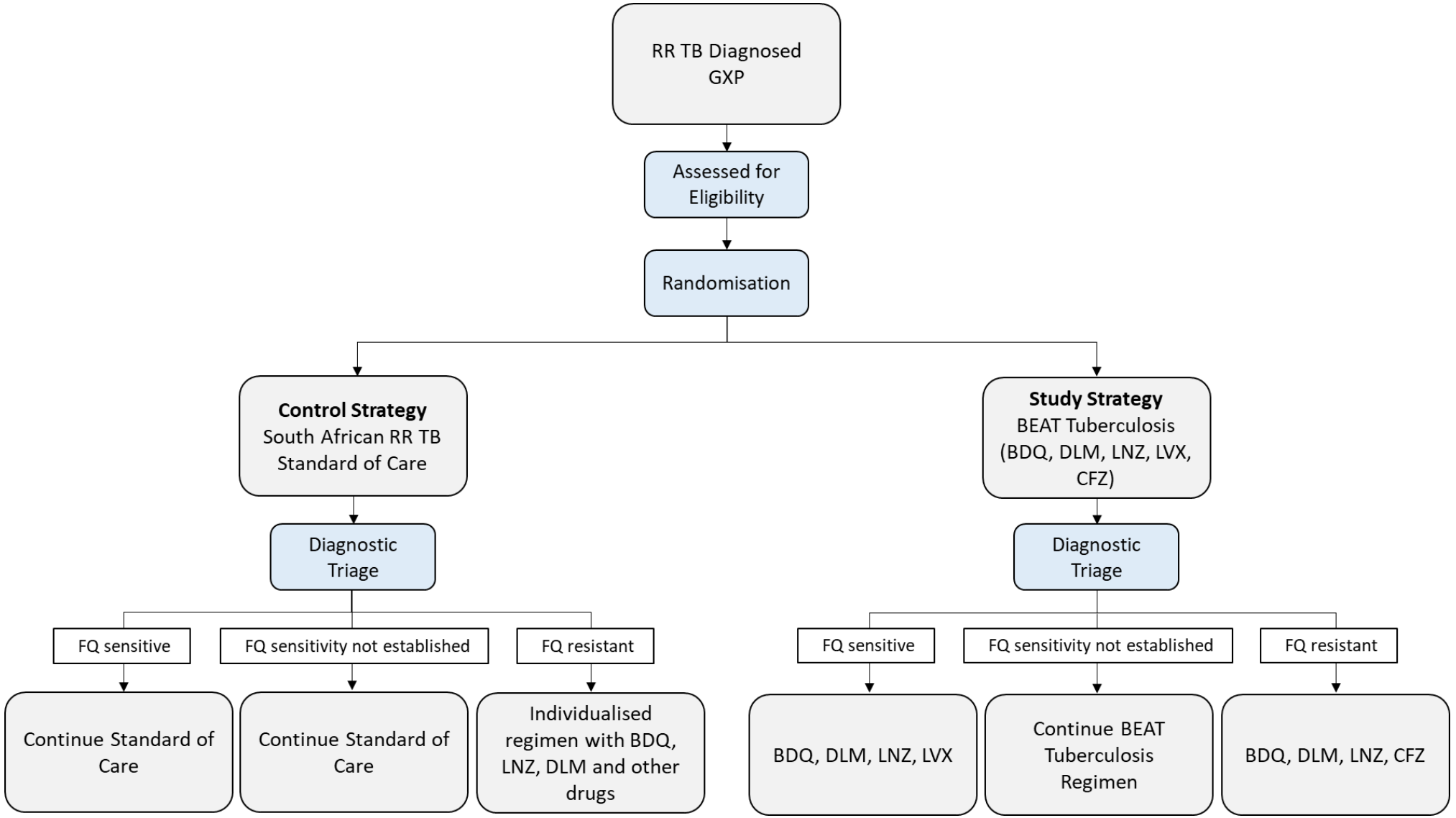
Successful treatment is assessed at the end of treatment

and

the end of follow-up (76 weeks post randomisation)

Safety

Grade 3 or greater adverse events during treatment



World Health Organization

END TB

Major inclusion criteria

- Male or female, aged **6 years or older, including breastfeeding and/or pregnant women**
- Weigh more than or equal to **16kg**
- Pulmonary RR-TB
- Participants above the age of 12 years, must have confirmed pulmonary TB with initial laboratory result of resistance to at least rifampicin as confirmed by genotypic or phenotypic susceptibility testing in the last three months
- Participants between the ages of 6 – 12 years, must have **either confirmed pulmonary RR-TB or probable pulmonary RR-TB and a decision has been made by the referring clinician or investigator to treat the child for RR-TB**
- Participants who are pregnant, should have an ultrasound done to confirm a viable intrauterine pregnancy prior to enrolment
- Willing to have an HIV test and if positive, is willing to be treated with appropriate antiretroviral therapy

Demographics

BEAT participants

	Control Strategy	Study Strategy	Total
Total randomised			
	200	203	403
Study site			
Port Elizabeth	182 (91%)	184 (91%)	366 (91%)
Durban	18 (9%)	19 (9%)	37 (9%)
Age (years)			
Median (IQR)	34.5 (27.0, 44.0)	35.0 (28.0, 43.0)	35.0 (28.0, 43.0)
Under 18	17 (8%)	13 (6%)	30 (7%)
Gender			
Female	85 (42%)	85 (42%)	170 (42%)
Race			
Black	160 (80%)	150 (74%)	310 (77%)
Mixed	40 (20%)	50 (25%)	90 (22%)
White	0	3 (1%)	3 (1%)
BMI (kg/m²)			
Median (IQR)	19.3 (17.2, 22.4)	19.1 (17.0, 22.0)	19.2 (17.1, 22.2)
Under 18.5	82 (41%)	85 (42%)	167 (41%)
HIV Status			
HIV Positive	100 (50%)	105 (52%)	205 (51%)
CD4 Median (IQR)	229.0 (87.0, 395.0)	168.0 (85.0, 298.5)	194.0 (87.0, 362.0)

Efficacy

Primary outcome

Primary Outcome	Control Strategy	Study Strategy	Total
Total randomized	**200**	**202**	**402**
Successful outcome at end of treatment and follow-up Total	**172 (86.0%)**	**174 (86.1%)**	**346 (86.1%)**
Cured at end of treatment, and end of follow-up	**162 (81.0%)**	**161 (79.7%)**	323 (80.3%)
Cured at end of treatment, culture negative when last seen	10 (5.0%)	13 (6.4%)	23 (5.7%)

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Primary outcome

Primary Outcome	Control Strategy	Study Strategy	Total
Total	**22 (11.0%)**	**14 (6.9%)**	**36 (9.0%)**
Treatment failed	10 (5.0%)	7 (3.5%)	17 (4.2%)
Lost to follow-up on treatment	4 (2.0%)	2 (1.0%)	6 (1.5%)
Died while on treatment	7 (3.5%)	4 (2.0%)	11 (2.7%)
Not Evaluated	1 (0.5%)	1 (<0.5%)	2 (<0.5%)
Unsuccessful end of follow-up	**6 (3.0%)**	**14 (6.9%)**	**20 (5.0%)**
Recurrence after cure at end of treatment	4 (2.0%)	10 (5.0%)	14 (3.5%)
Died after cure at end of treatment	2 (1.0%)	4 (2.0%)	6 (1.5%)

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Safety

Grade 3-5 AE

	Control Strategy	Study Strategy	Total	RD (95% CI)
Randomised and starting treatment	**200**	**202**	**402**	
Grade 3-5 AEs	76 (38.0%)	69 (34.2%)	145 (36.1%)	3.8% (-5.5%, 13.2%)
Grade 3-5 AEs during treatment	74 (37.0%)	63 (31.2%)	137 (34.1%)	5.8% (-3.4%, 15.1%)

Grade 3-5 AEs (occurring in 3 or more participants)

	Control Strategy	Study Strategy	Total
Total randomized	**200**	**202**	**402**
No Grade 3-5 AE	**124 (62.0%)**	**133 (65.8%)**	**257 (63.9%)**
Any Grade 3-5 AE	**76 (38.0%)**	**69 (34.2%)**	**145 (36.1%)**
Anaemia	29 (14.5%)	33 (16.3%)	62 (15.4%)
Neuropathy peripheral	12 (6.0%)	15 (7.4%)	27 (6.7%)
Alanine aminotransferase increased	9 (4.5%)	4 (2.0%)	13 (3.2%)
Electrocardiogram QT prolonged	7 (3.5%)	6 (3.0%)	13 (3.2%)
Optic neuritis	2 (1.0%)	5 (2.5%)	7 (1.7%)

Children

Primary Efficacy

Primary Outcome	Control Strategy	Study Strategy	Total
Total randomized (ITT population)	**17**	**13**	**30**
Successful outcome at end of treatment and follow-up			
Total	**17 (100.0%)**	**13 (100.0%)**	**30 (100.0%)**
Cured at end of treatment, and end of follow-up	17 (100.0%)	13 (100.0%)	30 (100.0%)

Primary Safety

	Control Strategy	Study Strategy	Total	RD (95% CI)
Randomised and starting treatment	**17**	**13**	**30**	
Grade 3-5 AEs	7 (41.2%)	3 (23.1%)	10 (33.3%)	18.1% (-14.6%, 50.8%)
Grade 3-5 AEs during treatment	6 (35.3%)	3 (23.1%)	9 (30.0%)	12.2% (-20.0%, 44.5%)

Grade 3-5 AEs

	Control Strategy	Study Strategy	Total
Total randomized	17	13	30
No Grade 3-5 AE	10 (58.8%)	10 (76.9%)	20 (66.7%)
Any Grade 3-5 AE	7 (41.2%)	3 (23.1%)	10 (33.3%)
Neuropathy peripheral	3 (17.6%)	1 (7.7%)	4 (13.3%)
Anaemia	2 (11.8%)	1 (7.7%)	3 (10.0%)
Optic neuritis	1 (5.9%)	1 (7.7%)	2 (6.7%)
Neutropenia	1 (5.9%)	0	1 (3.3%)
Treatment failure	1 (5.9%)	0	1 (3.3%)
Weight decreased	1 (5.9%)	0	1 (3.3%)

Pregnancy

Pregnancy outcomes

Participant	Arm	Randomization	Pregnancy reported	Outcome Date	Outcome	Weeks*
1	Study	18/Mar/2021	18/Mar/2021	01/May/2021	Full term live birth	6.3
2	Control	22/Jul/2021	19/Jul/2021	22/Sep/2021	Premature live birth	8.9
3	Control	27/Sep/2022	20/Sep/2022	20/Dec/2022	Full term live birth	12.0
4	Control	28/Sep/2022	12/Oct/2022	27/Dec/2022	Full term live birth	12.9
5	Study	27/May/2022	27/May/2022	27/Sep/2022	Full term live birth	17.6
6	Control	17/Sep/2021	17/Sep/2021	26/Jan/2022	Full term live birth	18.7
7	Study	09/Nov/2021	09/Jun/2021	25/Mar/2022	Full term live birth	19.4
8	Control	21/Jan/2022	17/Feb/2022	22/Jul/2022	Full term live birth	26.0
9	Control	01/Feb/2022	16/Mar/2022	21/Oct/2022	Full term live birth	37.4
10	Study	07/Sep/2021	09/Mar/2022	30/May/2022	Full term live birth	37.9

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Primary efficacy outcome among pregnant women

Primary Outcome	Control Strategy	Study Strategy	Total
Total randomized (ITT population)	**6**	**4**	**10**
Successful outcome at end of treatment and follow-up			
Total		**3 (75.0%)**	**9 (90.0%)**
Cured at end of treatment, and end of follow-up	6 (100.0%)	3 (75.0%)	9 (90.0%)
Unsuccessful end of follow-up			
Total	0	1 (25.0%)	1 (10.0%)
Recurrence after cure at end of treatment	0	1 (25.0%)	1 (10.0%)

One participant experienced recurrence 7 months after full-term delivery of the infant.

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Grade 3-5 AEs by MedDRA Coding among Pregnant Women

	Control Strategy	Study Strategy	Total
Total randomized	6	4	10
No Grade 3-5 AE	4 (66.7%)[9]	4 (100.0%)	8 (80.0%)
Any Grade 3-5 AE	2 (33.3%)	0	2 (20.0%)
Acute abdomen	1 (16.7%)	0	1 (10.0%)
Premature rupture of membranes	1 (16.7%)	0	1 (10.0%)

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Acquisition of resistance

31 treatment failures

- 14 recurrences
- 17 treatment failures

FQ-S disease (n=14)

- BDQ resistance testing was not done at baseline
  - One patient on control strategy developed BDQ resistance (treatment failure) FQ-resistant disease

FQ-R disease (17)

- **Recurrence** after cure at the end of treatment
  - Two patients acquired BDQ resistance on the study strategy
- **Treatment failure**
  - Three patients acquired BDQ resistance on study strategy
  - Three patients acquired BDQ resistance on control strategy

Conclusion

- BDLL/C is an effective and safe treatment strategy to use compared to the standard of care for the treatment of MDR/RR-TB and pre-XDR
- BEAT TB conducted in India showed similar results:

- 139 of 153 patients (91%) had a favorable outcome.
- Fourteen patients (9%) had unfavorable outcomes: 4 deaths, 7 treatment changes, 2 bacteriological failures, and 1 withdrawal. During treatment, 85 patients (52%) developed myelosuppression, 69 (42%) reported peripheral neuropathy, and none had QTc(F) prolongation >500 ms.
- At 48 weeks of follow-up, 131 patients showed sustained treatment success with the resolution of adverse events in the majority.

Bedaquiline, Delamanid, Linezolid, and Clofazimine for Treatment of Pre-extensively Drug-Resistant Tuberculosis

Chandrasekaran Padmapriyadarsini,[1] Vikram Vohra,[2] Anuj Bhatnagar,[3] Rajesh Solanki,[4] Rathinam Sridhar,[5] Lalitkumar Anande,[6] M. Muthuvijaylakshmi,[1] Meera Bhatia Rana,[2] Bharathi Jeyadeepa,[1] Gaurav Taneja,[3] S. Balaji,[1] Prashant Shah,[4] N. Saravanan,[1] Vijay Chavan,[6] Hemanth Kumar,[1] Chinnayin Ponnuraja,[1] Viktoriya Livchits,[7] Monica Bahl,[8] Umesh Alavadi,[7] K. S. Sachdeva,[9] and Soumya Swaminathan[10,1], for the BEAT India Team[a]

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Implementation considerations

Management of patients with anemia before starting treatment

Pregnancy

- First trimester
- Second and third trimester
- Breastfeeding

Treatment interruptions or missed doses

- Healthcare worker directed
- Adherence issue

Treatment Extensions

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Anemia before starting treatment

All the short regimens are to be given as a package.

Linezolid is a critical component of the treatment

All medications need to be given for as long as possible

Causes of anemia in a patient with TB disease

- TB
- HIV infection
- Iron/ folate deficiency

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Management strategies

Grade 3 anaemia HB less than 8 g/dl

- Signs of decompensation

Delay treatment and correct anaemia with transfusion

Start BDLLfxC and repeat HB measurement weekly

Use a Linezolid free regimen

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Pregnancy and breastfeeding

When to start treatment in pregnancy?

- As soon as the diagnosis of RR-TB is made
- There is no evidence in the preclinical work of teratogenicity
- Watch out for anaemia
- Aim for culture conversion by time of delivery

When to start treatment in breastfeeding?

- As soon as the diagnosis of RR-TB is made
- Continue breastfeeding if possible
- TPT for the infant: levofloxacin

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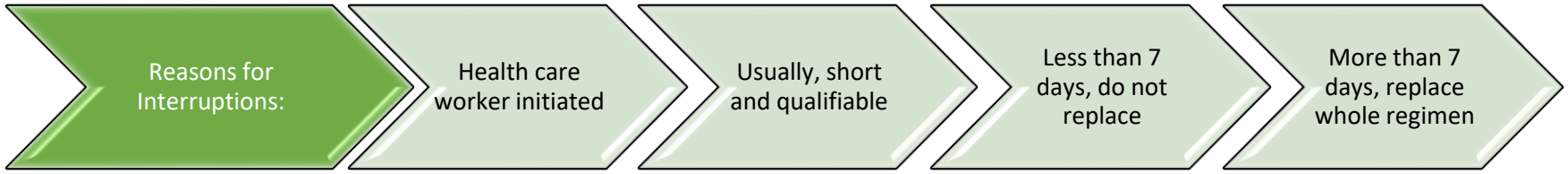
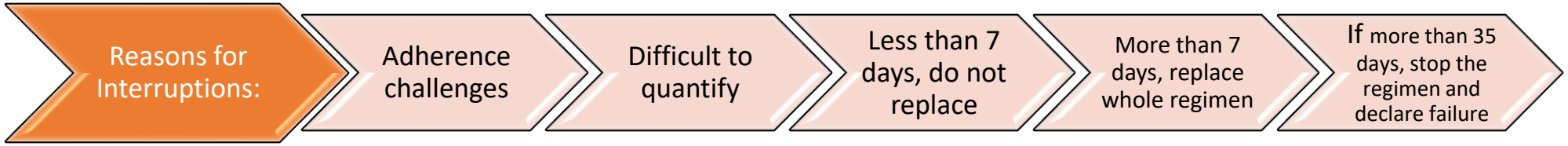
How to manage treatment interruptions





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When to extend BDLLfxC treatment

According to the protocol, if culture conversion has not taken place by week 16

Reasons for late conversion

- Poor adherence
- Undiagnosed resistance that could have been transmitted or acquired
- Extensive pulmonary disease

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Conclusion

- The strategy of BDLLfxC for 6 months is an alternative to BPAL M
- Extended indications for children under the age of 14 and pregnant and lactating women
- More costly than BPaLM

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