

PROTOCOL

BEAT Tuberculosis (Building Evidence for Advancing new Treatment for Tuberculosis)

An open label, randomized controlled trial to establish the efficacy and safety of a Study Strategy consisting of 6 months of bedaquiline (BDQ), delamanid (DLM), and linezolid (LNZ), with levofloxacin (LVX) and clofazimine (CFZ) compared to the current South African Standard of Care (Control Strategy) for 9 months for the treatment of rifampicin resistant tuberculosis (RR-TB)

Sponsored by:

United States Agency for International Development (USAID)

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PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to South African legal and regulatory requirements and ICH GCP guidelines.

Principal Investigator

Signed: _____

Name: _____

Date: _____

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PROTOCOL TEAM ROSTER

Principal Investigator	Dr Francesca Conradie Clinical HIV Research Unit, Wits Health Consortium University of the Witwatersrand fconradie@witshealth.co.za
Investigators Pharmacokinetic-pharmacodynamics sub-study Dried blood spot (DBS) validation sub-study Pharmacogenetics sub-study	Prof Gary Maartens The Division of Clinical Pharmacology, University of Cape Town gary.maartens@uct.ac.za Dr Richard Court The Division of Clinical Pharmacology, University of Cape Town richard.court@uct.ac.za
Investigators ECG sub-study: multi-lead mobile technology for monitoring cardiac repolarization	John Metcalfe Associate Professor University of California, San Francisco San Francisco General Hospital 1001 Potrero Ave. Rm 5K1, San Francisco, CA John.Metcalfe@ucsf.edu Jacqueline Shreibati VP, Medical Affairs, AliveCor 444 Castro St, Suite 600 Mountain View, CA 94041 jacqueline@alivecor.com
Trial Steering Committee	Dr Norbert Ndjeka Director, Drug-Resistant TB, TB & HIV, South African National Department of Health norbertndjeka@gmail.com Prof Gary Maartens The Division of Clinical Pharmacology, University of Cape Town gary.maartens@uct.ac.za Prof Graeme Meintjes The Institute of Infectious Disease and Molecular Medicine, University of Cape Town graemein@mweb.co.za Prof Nazir Ismail The Centre for Tuberculosis, National Institute for Communicable Diseases Naziri@nicd.ac.za

	Dr Hannetjie Ferreira MDR/XDR TB Unit, Tshepong Hospital herbadoc@webmail.co.za Dr Thandi Dlamini DR-TB technical advisor, Right to Care Thandi.Dlamini@righttocare.org Dr Jennifer Hughes Desmond Tutu Tuberculosis Centre, Stellenbosch University jhughes@sun.ac.za Dr Iqbal Master MDR TB unit, King Dinizulu Hospital iqbal.master@gmail.com Mr. Phinda Galela Clinical HIV Research Unit, Wits Health Consortium University of the Witwatersrand pgalela@witshealth.co.za
Trial Statistician	Dr Patrick Phillips University of California San Francisco Patrick.Phillips@ucsf.edu
Trial Pharmacist	Ms Coreen Barker Clinical HIV Research Unit, Wits Health Consortium University of the Witwatersrand cbarker@witshealth.co.za
Trial Manager	Ms Katerina Selibas Clinical HIV Research Unit, Wits Health Consortium University of the Witwatersrand kselibas@witshealth.co.za
Data Manager	Dr Ravindre Panchia Perinatal HIV Research Unit, Wits Health Consortium University of the Witwatersrand panchiar@phru.co.za
Clinical Medical Monitors	Dr Pauline Howell Clinical HIV Research Unit, Wits Health Consortium University of the Witwatersrand phowell@witshealth.co.za

	Dr Nokuphiwa Mvuna Clinical HIV Research Unit, Wits Health Consortium University of the Witwatersrand nmvuna@witshealth.co.za
Data Monitoring Committee	Prof C. Robert Horsburgh, Jr. School of Public Health Boston University rhorsbu@bu.edu Dr Neel Gandhi Rollins School of Public Health and Emory School of Medicine, Emory University Neel.r.gandhi@emory.edu Dr Daniel Grint Tropical Epidemiology Group, London School of Hygiene & Tropical Medicine Daniel.Grint@lshtm.ac.uk Dr Rodolfo Romero Clinical Head- District Clinical Specialist Team, Namakwa District leyetromero@gmail.com

ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
ACTG	AIDS Clinical Trial Group
ADR	Adverse Drug Reaction
ART	Anti-retroviral therapy
BCAP	Bedaquiline Clinical Access Program
BDQ	Bedaquiline
CFZ	Clofazimine
DLM	Delamanid
DMC	Data Monitoring Committee
DOT	Directly Observed Therapy
DR-TB	Drug-resistant Tuberculosis
DST	Drug Susceptibility Testing
E	Ethambutol
ECG	Electrocardiogram
FQ	Fluoroquinolone
HIV	Human Immunodeficiency Virus
INH	Isoniazid
LPA	Line probe assay
LNZ	Linezolid
LVX	Levofloxacin
MDR-TB	Multidrug-resistant Tuberculosis
<i>Mtb</i>	<i>Mycobacterium Tuberculosis</i>
NHLS	National Health Laboratory Service
PK/PD	Pharmacokinetics / Pharmacodynamics
QTcF	Fridericia-corrected QT interval
RIF	Rifampicin
RR TB	Rifampicin Resistant Tuberculosis
SAE	Serious Adverse Event
SAHPRA	South African Health Products Regulatory Authority
SANTP	South African National Tuberculosis Program
SOC	Standard of Care
STR	Shorter Treatment Regimen
TEAE	Treatment Emergent Adverse Events
WHO	World Health Organization
XDR-TB	Extensively Drug-resistant Tuberculosis
Z	Pyrazinamide

SYNOPSIS

Protocol Title	BEAT Tuberculosis (B uilding Evidence for A dvancing new T reatment)
Clinical Phase	Phase 3
Treatment Indication	Rifampicin Resistant Tuberculosis (RR-TB) with or without resistance to isoniazid (INH) and/or fluoroquinolones.
Trial Aim	To compare the efficacy and safety of a Study Strategy consisting of 6 months of bedaquiline (BDQ), delamanid (DLM), and linezolid (LNZ), with levofloxacin (LVX) and clofazimine (CFZ) compared to the current South African Standard of Care (Control Strategy) for 9 months for the treatment of rifampicin resistant (RR-TB) Tuberculosis. Both the Study and the Control Strategies will be modified once fluoroquinolone sensitivity has been established.
Objectives	Primary Objectives: 1. <u>Efficacy</u>: To assess whether the proportion of participants with a successful outcome at the end of treatment and at the end of follow up at 76 weeks after randomization on the Study Strategy is not inferior to that on the Control Strategy. 2. <u>Safety</u>: To compare the proportion of participants who experience grade 3 or greater adverse events during treatment on the Study Strategy as compared to the Control Strategy. Secondary Objectives: 1. <u>Composite efficacy and safety</u>: To assess if the proportion of participants with a successful composite outcome at 76 weeks after randomization on the Study Strategy is superior to the Control Strategy. 2. <u>Pharmacokinetics / Pharmacodynamics (PK/PD)</u>: to be described in the body of the protocol.
Criteria for Evaluation	<u>Primary efficacy endpoints</u> A successful treatment outcome measured at the end of treatment and is defined as one of the following: • <u>Cured</u>: Adequate treatment adherence (at least 80% of doses taken) as per protocol without evidence of failure AND the last two negative

	sputum specimens at the end of treatment being culture negative. These specimens must be separated by at least 14 days • <u>Treatment completed</u>: Adequate treatment adherence (at least 80% of doses taken) as per protocol without evidence of failure BUT no record that two or more consecutive cultures taken at least 14 days apart are negative An unsuccessful treatment outcome measured at the end of treatment and is defined as one of the following: • Treatment failed ▪ lack of sputum culture conversion by the end of treatment OR ▪ bacteriological reversion after sputum culture conversion to negative OR ▪ If two or more anti-TB drugs are substituted due to Adverse Drug Reactions (ADRs) • Death during the treatment from any cause • Lost to follow-up: A participant who missed 28 consecutive days of treatment, not directed by the clinician • Not evaluated: A participant for whom no treatment outcome is assigned (this includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown) A successful end of follow up outcome measured at 76 weeks post treatment initiation and is defined as one of the following: • <u>Cured</u>: Sputum Culture negative at the end of follow up OR • <u>Culture negative when last seen</u>, if the participant is lost before the end of follow up and provided they have a successful treatment outcome at the last study visit attended An unsuccessful end of follow up outcome measured at 76 weeks post treatment initiation and is defined as one of the following:
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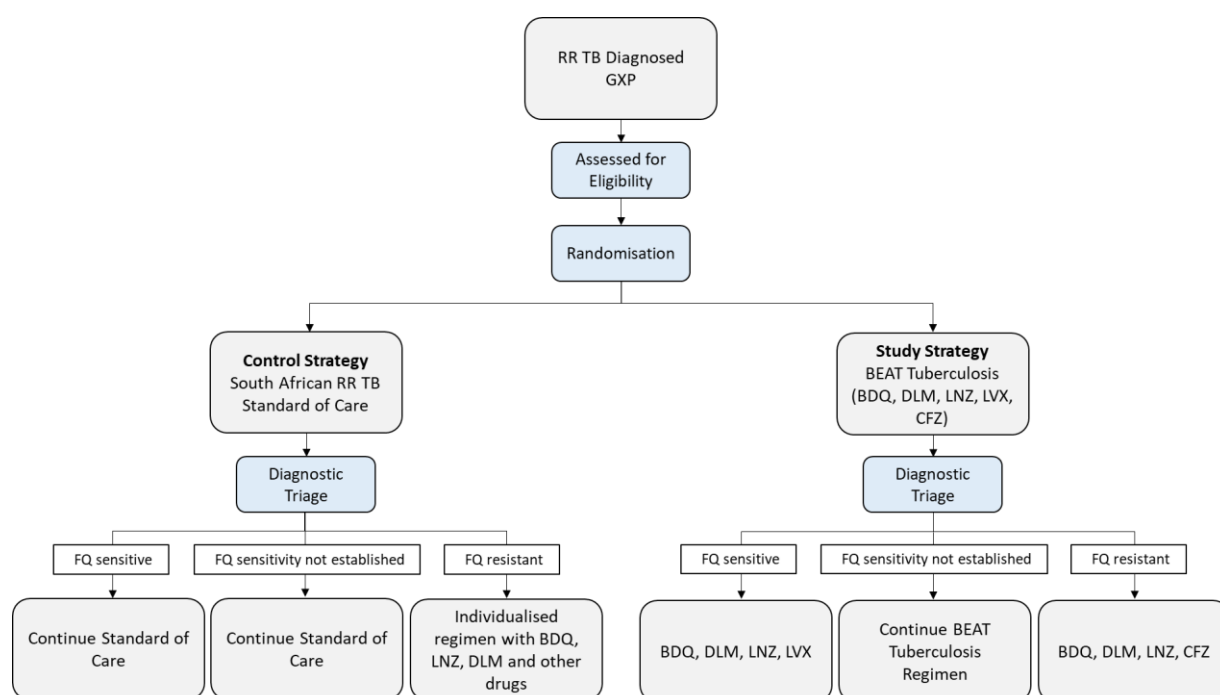
	• Relapse: ▪ Two consecutive positive cultures separated by at least 14 days OR ▪ One positive after confirmed culture conversion culture with clinical signs and symptoms of TB or no improvement or worsening of radiological changes since baseline. Please note: an isolated positive smear or culture without clinical or radiographic deterioration after treatment completion provides insufficient evidence to define recurrent TB • Death in follow up from any cause • Loss to follow up with clinical signs and/or symptoms of TB when last seen OR sputum culture positive when last seen OR not sputum culture negative and with clinical signs and symptoms of TB when last seen
	<u>Primary safety endpoint</u> The incidence of all (expected and/or unknown/unsuspected adverse events of the drugs being used) Treatment Emergent Adverse Events (TEAEs) of Grade 3 or higher using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events by treatment arm and up to 30 days following the end of treatment.
	<u>Secondary endpoints</u> 1. Composite efficacy / safety: The proportion of participants with a successful end of follow up outcome and no grade 3 or higher adverse events during treatment 2. Safety endpoints 1. The quantitative and qualitative clinical laboratory result measurements, including observed and changes from baseline by treatment arm graded by

	the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events 2. The proportion of participants who have a Fridericia-corrected QT interval (QTcF) >500 ms at any time during treatment, by treatment arm 3. The proportion of participants who have an increase from baseline in QTcF of greater than 60 ms at any time during treatment, by treatment arm
Sample Size	400 participants (87.3% power to show non-inferiority assuming a proportion cure of 0.60 in the Control Strategy and 0.65 in the Study Strategy (an absolute increase of 0.05))
Trial Duration	The trial duration per participant is 76 weeks
Trial Design	BEAT Tuberculosis is an open label, multi-centre, randomized controlled trial Participants will have a screening period of up to 30 days and will be randomized to receive either the Study Strategy or the Control Strategy Study Strategy a) Bedaquiline b) Linezolid c) Delamanid d) Clofazimine e) Levofloxacin If culture conversion has not occurred by week 16, the full treatment duration can be extended to 36 weeks. As per standard practice, at the time of treatment initiation, a sputum sample will be sent for ascertainment of fluoroquinolone sensitivity. • If the sample shows fluoroquinolone sensitivity by line probe assay, then clofazimine will be stopped. • If the sample shows fluoroquinolone resistance by line probe assay, then levofloxacin will be stopped. • If the line probe assay is indeterminate or missing, both levofloxacin and clofazimine will be continued for the duration of the treatment. • If the fluoroquinolone sensitivity is known prior to treatment initiation, clofazimine or levofloxacin will not be given, depending on the result.

	• If there is fluoroquinolone sensitivity by genotype, then clofazimine will be stopped. Additionally, the genotypic result will be confirmed by phenotype as per the national testing guidelines and treatment modified as required, if there is a discrepancy. Discuss with the PI or Clinical Medical Monitors. Control Strategy The Control Strategy is the South African Standard of care for RR-TB. This will be based on the most up to date, approved SA NTP guidance.* <i>*This amendment in the protocol was submitted as a Clarification Memorandum, on 21 January 2020 to both SAHPRA and Wits HREC.</i> a) Bedaquiline b) Linezolid c) Isoniazid high dose d) Levofloxacin e) Ethambutol f) Pyrazinamide g) Clofazimine This strategy consists of an intensive phase of 16 weeks which may be extended to 24 weeks depending on the participant's response to treatment (i.e. smear conversion and clinical response at 16 weeks of treatment). As per standard practice, at the time of treatment initiation, a sputum sample will be sent for ascertainment of fluoroquinolone sensitivity. • If fluoroquinolone sensitivity is confirmed, the regimen will be continued unchanged. • If fluoroquinolone resistance is confirmed, the regimen will be modified as per the latest NTP guidelines. • If the fluoroquinolone resistance is known prior to treatment initiation, an individualized regimen will be given. • If there is fluoroquinolone sensitivity by genotype, the regimen will continue unchanged. Additionally, this genotypic result will be confirmed by phenotype as per the national testing guidelines and treatment modified as
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	required, if there is a discrepancy. Discuss with the PI or Clinical Medical Monitors. <u>Follow up:</u> All participants will be followed up for 76 weeks from randomization.
Data Monitoring Committee	Interim safety and efficacy data will be reviewed by the Data Monitoring Committee (DMC) as follows: • Approximately every 6 months after the first participant is enrolled; • Ad hoc meetings can be called by the DMC based on rates of Serious Adverse Events (SAEs) or if safety concerns arise during the trial
Population	Participants ≥ 6 years of age diagnosed with confirmed or probable pulmonary Rifampicin Resistant Tuberculosis (RR TB)
Randomization	1:1 with stratification by HIV status and by clinical trial site

Figure 1: BEAT Tuberculosis Algorithm



TABLES

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1. Rationale for the BEAT Tuberculosis study

1.1. Background: treatment of RR-TB

For many years Rifampicin-Resistant Tuberculosis (RR-TB) patients have been treated with a World Health Organization (WHO)-recommended standardized RR-TB regimen which generally has an intensive phase of treatment of up to 8 months and a total duration of treatment of up to 24 months. In 2016, the WHO issued guidelines for the use of a shorter treatment regimen (STR) for eligible patients with rifampicin-resistant and multidrug-resistant tuberculosis (MDR-TB). The regimen includes the repurposed anti-leprosy drug, clofazimine, in combination with four to six months of kanamycin, moxifloxacin, pyrazinamide (Z), ethambutol (E), ethionamide (or prothionamide) and high dose isoniazid INH (INH_{high dose}) followed by 5 months of moxifloxacin, Z and E.ⁱ This STR was adopted by the South African National Tuberculosis Program (SANTP) in 2017. By September 2017, all nine South African provinces had adopted this regimen and most eligible patients who were treated within the TB program were started on this regimen. The next major communication from the WHO was in September 2018 when the Rapid Communication: Key changes to treatment of Multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) was released.ⁱⁱ In this document, inter alia, the categorization of medicines for MDR/RR-TB was changed. Bedaquiline (BDQ), linezolid (LNZ) and fluoroquinolones have been moved to Category A and should be included in all regimens as core drugs. Clofazimine and terizidone as Category B drugs should be added to all regimens.

In addition to the shorter RR-TB regimen recommended by the WHO, there are other shorter regimens currently being evaluated in clinical trials. Many of these regimens employ new or repurposed medicines such as BDQ, DLM, and LNZ, which have each been shown to be effective in clinical trials. Some of the regimens forgo the use of a second-line injectable, which is associated with a high rate of adverse events and is programmatically difficult to administer. Although these regimens are currently undergoing testing in clinical trials, the programmatic use of these regimens under operational and pragmatic research conditions can also provide important data to the global TB community about their effectiveness and safety, while also providing more information about programmatic implementation and expanding access to their potential benefits.

1.2. Treatment of RR-TB in South Africa

In parallel with the adoption of the STR, the SANTP has introduced a new medication for the treatment of RR-TB: bedaquiline. This process began in January 2013 when the SANTP, with the support of non-governmental and academic partners, established the BDQ Clinical Access Program (BCAP) so that patients with pre-extensively drug-resistant tuberculosis (pre-XDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) at specialized public health facilities in South Africa could receive BDQ. Early

results of the BCAP cohort showed high rates of culture conversion and encouraging outcomes, including improved survival. Final outcomes of this program were better than expected. The clinicians at the TB treatment sites selected patients who had few, if any, other treatment options. This cohort of patients with high levels of resistance to TB treatment was one of the first to receive BDQ outside of a clinical trial, and over two thirds of them were living with HIV. Despite this, we found that 146 out of 200 (73.0%) had favorable outcomes and only 25 out of 200 (12.5 %) died ⁱⁱⁱ. Following with BCAP, the SANTP, led by Dr. Ndjeka, pioneered the use of this novel medication. With the early success of the BCAP, it was decided that all patients with XDR and pre-XDR TB be offered BDQ. In addition, any patient with treatment-limiting toxicity to the standard regimen would be offered BDQ. The most common reason for toxicity in the program is ototoxicity due to the injectable agent. The SANTP also has an extensive program for monitoring of hearing at sites where MDR-TB medication is given. By 2017, around 70% of patients with RR-TB were either started on BDQ in a regimen without kanamycin or had a medication substitution with BDQ (Personal Communication by Dr Ndjeka).

1.3. Current Standard of care (SOC) for RR-TB with fluoroquinolone sensitivity in South Africa

This consists of a 9 -11 month all oral regimen as contained in the current RR TB guidelines.

1.4. Current Standard of care (SOC) for RR-TB with fluoroquinolone and / or injectable resistance in South Africa

Should the patient have resistance to the fluoroquinolones and/or the injectable, the patient is started on a strengthened regimen that may include BDQ, LNZ and DLM with other added agents depending on prior exposure and any other available resistance testing. This regimen then needs to be individualized taking into account prior treatment history, Drug Sensitivity Test (DST) results and drug toxicity and intolerance. Although the SOC does not contain an injectable agent, the presence of resistance to these agents is a potential marker of more advanced resistance, including to E and Z.

1.5. Current Standard of care (SOC) for RR-TB in children from the age of 6 years and older in South Africa

The diagnosis of TB disease in children is often made on patient history, clinical and radiological grounds with consideration of RR-TB disease based on risk factors for RR- TB, such as recent RR-TB exposure or failure of first-line TB treatment with good adherence. However, children with clinically diagnosed TB may have culture-confirmed RR-TB as well and may even be the index RR-TB case. Bacteriological confirmation should always be attempted; at least two good quality specimens should be collected and sent for Xpert MTB/RIF Ultra and mycobacterial culture and DST. Many children will

not have bacteriological confirmation due to paucibacillary disease or some forms of extra-pulmonary disease.

The shorter treatment regimen is considered to be a package regimen, where the same initial regimen is given to all persons with RR-TB with only minimal modifications allowed. Data on the dosing and safety of bedaquiline in children aged 6 years and older has been established and because bedaquiline can be used safely in this group, they qualify for the shorter regimen. Data on the dosing and safety of bedaquiline in children under the age of 6 years has not yet been established and thus bedaquiline cannot be routinely used in this population. For this reason, children under the age of 6 years need to receive an individualised regimen whose composition and duration will be based on their clinical status, disease severity, resistance pattern, and site of disease.

Traditionally, the efficacy of anti-tuberculosis regimens has been extrapolated to children, and Phase I/II studies of the PK and safety of individual TB drugs have been considered the priority research area in children^{iv}. Inclusion of this population group in BEAT Tuberculosis will contribute to efficacy data.

Since children tend to have paucibacillary TB (approximately 30-40% culture-confirmed and <10% sputum smear-positive for acid-fast bacilli [AFB] in pediatric pulmonary TB) children can reasonably be expected to respond to TB treatment better than adults. Dramatically better treatment outcomes among children with MDR-TB (75-90% successfully treated)^{v vi} compared to adults (50% successfully treated) in routine care settings^{vii} are already achieved despite substantially lower drug exposures in children for many key second-line drugs^{viii ix}.

Additionally, although relative to adults with MDR-TB, children have better treatment outcomes^x, there may be scope to further reduce morbidity and mortality, especially in HIV co-infected children and in children with more severe forms of disease, by combining highly effective anti-tuberculosis drugs to which there is little pre-existing resistance.

1.6. Current Standard of care (SOC) for RR-TB in pregnant and breastfeeding women

The burden of tuberculosis in pregnant women is substantial with prevalence estimates amongst pregnant and post-partum women ranging from 0.06% to 7.2%, and as high as 11% in HIV-infected settings^{xi}. Untreated tuberculosis in pregnancy poses a significant threat to the mother, foetus and family. While standard treatment regimens for drug-susceptible tuberculosis are usually considered acceptable for pregnant women, little is known about the efficacy, safety and dosing of second-line tuberculosis drugs for treatment of RR-TB during pregnancy. There are fewer than 15 case reports describing the safety and outcomes of second-line tuberculosis treatment during pregnancy, most of which included women receiving older treatment regimens^{xii}. As RR-TB regimens have shortened and

improved in both efficacy and safety, many of the older and more toxic medications have been removed from standard regimens, including second line injectable agents and ethionamide, to be replaced by novel or repurposed drugs. Pregnant women have generally been excluded from the studies on which the latest WHO RR-TB treatment recommendations were based, and therefore guidance for treatment of RR-TB in pregnant women still remains extremely limited due to lack of safety and efficacy data^{xiii}. The FDA categorises bedaquiline as a Group B drug in pregnancy (animal studies indicate no risk of teratogenicity and there are no human studies) and all the other agents except delamanid as Group C drugs (animal studies indicate a risk of teratogenicity and there are no human studies). The FDA has not registered delamanid yet. In South Africa, pregnant women with RR-TB at all stages of pregnancy are treated with the same drug regimens as their non-pregnant counterparts. A recently published observational study of 108 pregnant women with RR-TB in the KwaZulu Natal province of South Africa reported high rates of favourable pregnancy, infant and RR-TB outcomes, particularly among women receiving treatment with novel and repurposed agents^{xi}.

1.7. Study Strategy

The rationale behind the selection of this strategy is that upon the diagnosis of RR-TB, fluoroquinolone resistance is usually unknown. The principle is to “hit early and to hit hard” with the agents most likely to be effective. This trial will provide a treatment regimen containing three novel agents as core drugs (BDQ, LNZ, and DLM) against which there is no expected *Mtb* resistance in the community. In addition, there will be two other support medications: LVX and CFZ. Treatment will be changed on receipt of the second-line line probe assay (LPA) results. The BEAT Tuberculosis strategy has been designed that all possible eventualities will be covered from rifampicin mono resistant TB to XDR-TB with an all oral regimen.

Proof of concept for this approach is the Global TB Alliance study Nix-TB-(B-L-Pa). At the time of the drafting of this protocol, Nix-TB was an ongoing open label, single arm study at three South African sites and it evaluated the safety and efficacy of BDQ, pretomanid and LNZ (1200 mg per day) given orally for 26 weeks for XDR-TB or MDR-TB treatment intolerant or MDR-TB patients failing treatment. An interim analysis assigned outcomes to the first 75 participants followed to the primary endpoint of bacteriologic failure, relapse or clinical failure at six months after treatment end. Of the first 75 participants, six died during the early stages of treatment, one in follow-up and one after withdrawal due to relapse. All remaining participants completed six months of therapy with no extensions. Two participants (3%) relapsed. Durable cure at six months was found in 66 participants (80%). The expected LNZ toxicities of peripheral neuropathy and myelosuppression were common and manageable at site level, usually requiring protocol mandated reductions of dose and/or interruptions

in LNZ dosing in the majority of participants. There were no withdrawals for reasons other than death or relapse. Interim results of this simplified, shortened all oral regimen for drug-resistant TB continue to be encouraging in terms of both efficacy and safety.^{xiv}

Nix-TB is the proof of concept of an all oral regimen for the treatment of XDR-TB. BEAT Tuberculosis is building on this, using DLM in place of pretomanid. Additionally, in BEAT Tuberculosis the regimen has two additional medications: CFZ and LVX. This allows for a broader RR-TB patient population.

1.7.1. Bedaquiline

BDQ is a diarylquinoline that was FDA-approved in December of 2012 and by the South African Medicines Control Council in December 2014 for the treatment of MDR-TB. It inhibits the proton pump of *Mycobacterium tuberculosis* (*M. tuberculosis*) ATP synthase, a novel mechanism of action for an anti-mycobacterial drug. It is active in vitro against both replicating and non-replicating bacilli, and it has significant bactericidal and sterilizing activity in the murine model of TB infection. In vitro, it is equally active against drug sensitive, MDR, Pre-XDR, and XDR strains of *M. tuberculosis*. The distinct target and mode of action of BDQ minimizes the potential for cross-resistance with existing anti-TB drugs. BDQ is well-absorbed with a T_{max} of 5 h. Dose-proportionality of C_{max} and AUC was seen up to 700 mg with single doses and 400 mg with multiple doses. The average terminal elimination half-life of BDQ is 132 days and is 112 days for its M2 metabolite. Administration with food increased bioavailability by 95%. BDQ is metabolized by oxidative metabolism via the CYP3A4 isoenzyme to its N-desmethyl metabolite, M2. The M2 metabolite has activity against *Mtb*, but it is 3- to 6-fold less potent. For the treatment of TB infection, a dose of 400 mg daily (four 100 mg tablets) for 2 weeks, followed by 200 mg three times per week (with at least 48 hours between the doses) to complete 6 months of treatment is recommended.^{xv}

As of September 2018, the most recent Randomized Controlled Trial to report on the efficacy and safety of BDQ for the treatment of MDR-TB was the phase 2b trial which began enrolling patients in 2009. The enrolled patients received BDQ or placebo in addition to a standardized, long course (24 month) regimen for multi-drug resistant tuberculosis typically consisting of kanamycin, ofloxacin, ethionamide, cycloserine or terizidone, and pyrazinamide. The phase 2b trial had indicated that, among the modified intention to treat population, while rates of culture conversion (at 24 weeks: 52 of 66 BDQ patients [79%] and 38 of 66 placebo arm patients [58%]) and cure (at 120 weeks: 38 of 66 BDQ patients [58%] and 21 of 66 patients [32%]) were higher for BDQ, there was a statistically significant imbalance in mortality. 10 of 79 (13%) BDQ patients and 2 of 81 patients (2%) in the placebo

arm died, but almost all of these deaths occurred after BDQ had been discontinued, suggesting that the observed imbalance in mortality was a chance finding.^{xvi}

However, in the phase 2, multicenter, open-label, single-arm trial (TMC207-C209), newly diagnosed or previously treated patients with MDR-TB (including pre-XDR-TB or XDR TB) received BDQ for 24 weeks with a background regimen of anti-TB drugs continued according to National TB Programme treatment guidelines. Patients were assessed during and up to 120 weeks after starting BDQ. In this study only 16 patients (6.9%) died. In the efficacy population (n=205), culture conversion (missing outcome classified as failure) was 72.2% at 120 weeks.^{xvii}

A randomized controlled trial funded by USAID, Janssen and the MRC UK called STREAM 2 is currently underway in a number of countries including South Africa (ISRCTN 18148631). This is the phase 3 registration trial for BDQ. This three-arm trial is the phase 3 study for BDQ. The standard short course is compared to a 9-month injection-free regimen with BDQ. Results of this trial are expected in 2022. Finally a paper recently published in Lancet Respiratory Medicine using data from the electronic data base of the SANTP, EDR.web, reported that the addition of BDQ was associated with a reduction in the risk of all-cause mortality for patients with MDR-TB or RR-TB (hazard ratio [HR] 0.35, 95% CI 0.28–0.46) and XDR-TB (0.26, 0.18–0.38) compared with standard regimens.^{xviii}

BDQ is associated with relatively few side effects. Patients taking BDQ were seen to have a mean maximum increase in QT interval of 14.2 ms; those also receiving CFZ had a mean increase of 31.9 ms.^{xix}

In August 2018, the WHO released a rapid communication of the Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Medicines for the treatment of MDR/RR-TB have been regrouped into three categories and ranked based on the latest evidence about the balance of effectiveness to safety. BDQ has been moved to a Group A medicines and its use has been prioritized.

1.7.2. Delamanid

DLM is a nitro-dihydro-imidazoxazole derivative that inhibits mycolic acid synthesis and enhances killing by generating nitric oxide in *Mtb* in anaerobic conditions. It is active in vitro against actively-dividing and dormant mycobacteria with similar MICs against drug-sensitive and MDR-TB strains. The distinct target and mode of action of DLM minimizes the potential for cross-resistance with existing anti-TB drugs. Clinical trial evidence indicates improved treatment outcomes when added to an optimized background regimen without increased adverse events. Based on the preliminary evidence of effectiveness and safety, the WHO has issued interim guidance for the use of DLM in 2016^{xx}. Subsequent to this, phase III, multicenter, randomized, double-blind, placebo-controlled clinical trial

to evaluate the safety and efficacy of DLM (Trial #242-09-213, hereafter referred to as 'Trial 213') was released. There was no statistically significant difference between the DLM and placebo study arms in treatment success, all-cause mortality, or culture conversion. Importantly, there was no significant difference in TEAEs between participants receiving DLM and those receiving placebo, including the prolongation of the QTcF. 5/285 (1.8%) participants who received DLM developed additional resistance to the fluoroquinolones, compared to 5/139 participants (3.6%) in the placebo arms. In a subset of the intention-to-treat population for whom DST was conducted, 6/320 (1.9%) in the DLM arm developed resistance to first-line drugs, compared to 9/139 (6.5%) in the placebo arm.^{xxi} This points to the role of DLM as a medication that protects the other medications in the regimen in terms of resistance development.

The endTB study is a multi-center observational study of the effectiveness and safety of DLM and BDQ sponsored by Medicines Sans Frontiers. In the endTB cohort, 658 patients were included in the DLM analysis. In general, patients receiving DLM had a high rate of comorbidities, including HIV (18%) and diabetes. The endTB observational study follows patients who receive treatment regimens containing BDQ or DLM in 17 countries on four continents. In the endTB cohort, 79% of patients who received DLM as part of a multidrug regimen converted their sputum culture within six months. This culture conversion rate was consistent with the Phase III trial.^{xxii}

1.7.3. Combination of bedaquiline and delamanid

The major obstacle in combining BDQ and DLM has been that both can cause cardiotoxicity. A prolonged heart rate-corrected QTcF (adjusted for heart rate using the Fridericia correction formula) interval is defined as above 450 ms in men and 470 ms in women, and it is recognized as a well-known risk factor for ventricular arrhythmias and sudden cardiac death. During phase 2 clinical trials with both BDQ and DLM, a prolongation of QTcF interval of about 12 ms was observed with each drug, but in the larger DLM phase 3 trial the QTcF prolongation was much lower.

The AIDS Clinical Trial Group (ACTG) is conducting a randomized controlled clinical trial (A5343) with the combination of BDQ and DLM. A5343 has as its primary hypothesis that the co-administration of BDQ and DLM with multidrug background treatment for MDR-TB will increase the duration of the QT interval compared to administration of either drug alone, but the combined effects on the QT interval will be no greater than additive. This safety study, with rigorous measurement of the QTcF, is underway at three sites: two in South Africa and one in Peru. The study is fully enrolled and results are expected in quarter 4 of 2019. An interim analysis was shared with WHO in July 2018, which showed no grade 3 or 4 QTcF prolongation and that the QTcF effects of the combination of BDQ and DLM was no more than additive.

1.7.4. Linezolid

LNZ, an oxazolidinone class antimicrobial approved for Gram-positive bacterial infections, is increasingly being used off-label for drug resistant TB disease. LNZ works by inhibiting ribosomal protein synthesis. It is highly bioavailable and rapidly absorbed as an oral tablet of 600mg. Its T_{max} is 1-2 hours, it is hepatically metabolized, and its clearance varies with age and gender. It is present in high concentrations in the epithelial lining fluid.

A systematic review of 11 studies reporting outcomes for 148 patients systematically treated with LNZ for DR-TB showed a pooled proportion of treatment success of 67.99% (95% CI 58.0-78.99%). There was no significant difference in success comparing daily dose of LNZ of less than or equal to 600 mg daily with more than 600 mg daily dosing. The pooled estimate for adverse events was 61% (95% CI 40.15-82.8%) with 36.23% discontinuing LNZ due to adverse events.^{xxiii}

In a clinical trial evaluating the addition of LNZ as a single drug to a failing XDR-TB regimen, by 4 months 79% of patients in the immediate start group compared with 35% of patients in the delayed start group had culture converted, and 87% of patients had a negative sputum culture within 6 months of starting LNZ. Follow up data from this study as of November 2013, has shown that of the 30 patients who had completed treatment there was no relapses detected at 12 months follow up^{xxiv}. Even though resistance to LNZ did occur in some patients in this study, these data suggest that LNZ may have a high barrier for development of resistance given that LNZ was added in as a single drug in the regimen in patients likely to have been failing treatment, a strategy that would normally be predicted to have high rates of resistance.

There are multiple adverse events associated with LNZ use, especially when administered over long periods. These events include neurologic effects (optic and peripheral neuropathy), lactic acidosis, and hematologic effects (anemia, thrombocytopenia, and leucopenia). The hematologic side effects are reversible and appear to be dose related with significantly less anemia (2.5% vs 60%) associated with LNZ given at 600 mg or less daily than at greater than 600mg daily^{xxv}.

The optimal dose for LNZ treatment of TB is not known. Cohort studies of TB treatment with LNZ have used daily and twice daily dosing and doses ranging from 300 mg daily to 1200 mg daily. The randomized trials of LNZ have used 600 mg daily (two trials), and 1200 mg daily for 4-6 weeks reducing to 300-600 mg daily. Pre-clinical studies suggest a dose response effect for LNZ between the ranges of 300-1200mg daily.^{xxvi xxvii}

The optimal duration of LNZ required within a regimen is unknown. In MDR-TB treatment in humans a systematic review did not show any difference in treatment success comparing studies with a duration of LNZ treatment longer than 7 months compared with studies where LNZ was given for less than or equal to 7 months.^{xxviii}

In August 2018 the WHO released a rapid communication of the Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Medicines for the treatment MDR/RR-TB of have been regrouped into three categories and ranked based on the latest evidence about the balance of effectiveness to safety. LNZ has been moved to a Group A medicine and its use has been prioritized.

1.7.5. Levofloxacin

LVX is a fluoroquinolone approved for bacterial infections, notably sinusitis, lower respiratory tract, urinary tract and soft-tissue infections. Fluoroquinolones are bactericidal and act by inhibiting DNA gyrase, interfering with reproduction of bacterial DNA. High-dose LVX is used in the treatment of DR-TB sensitive to fluoroquinolones. High-dose LVX significantly improves treatment outcomes in adults with RR-TB and MDR-TB. Fluoroquinolones are considered to be the most important component of the core MDR-TB regimen and the benefits from their use outweigh potential risks. They should therefore always be included unless there is evidence for absolute contraindication for their use. LVX is preferred to moxifloxacin as it has minimal QT prolonging effects.^{xxix xxx} LVX has remained as a Group A medicine and its use has been prioritized.

1.7.6. Clofazimine

Clofazimine is a fat-soluble iminophenazine and is a brick-red dye that has in vitro activity against several species of mycobacteria and was initially found to be effective in the treatment of leprosy. Clofazimine binds to the guanine bases of bacterial DNA, inhibiting bacterial proliferation. WHO recommends clofazimine as a category B drug. One of the main adverse effects of clofazimine is reversible skin discoloration/darkening, which may be distressing to patients, although this has apparently not limited its effectiveness in MDR-TB regimens.

1.8. BEAT Tuberculosis sub-studies

1.8.1. Pharmacokinetics/pharmacodynamics sub-study

Rationale and design

There are limited data describing the association of drug concentrations with efficacy and treatment-related toxicities of many of the anti-TB drugs used in the treatment of rifampicin-resistant TB.

Understanding these pharmacokinetic-pharmacodynamics (PK-PD) relationships can result in dose optimization to improve outcomes in the relevant patient populations. BEAT Tuberculosis is a unique opportunity to explore these relationships.

There are many knowledge gaps in our understanding of the exposure to and PK-PD relationships of drugs used for DR-TB. Least is known about the PK of clofazimine in DR-TB, with no published PK studies at steady state. The QT-prolonging effect of clofazimine monotherapy increased about 20 ms over the 14 day period of an early bactericidal activity study^{xxxix}, indicating that, like almost all drugs that prolong QT, the magnitude of the QT prolongation will be driven by the concentration of clofazimine. However, there are no PK-PD analyses of clofazimine efficacy or toxicity. Linezolid PK in DR-TB is also poorly understood, but Prof Maartens' group is developing a population PK model, which will be used for conducting PK-PD analyses. Levofloxacin exposure in DR-TB has been described in a population PK model in children by Prof Maartens' group^{xxxix} and PK-PD analyses of efficacy will be done in a phase 2 study of higher doses of levofloxacin in MDR-TB (TBTC study 32, Opti-Q: <https://clinicaltrials.gov/ct2/show/NCT01918397>), which will report next year. Bedaquiline exposure has been described in population PK models^{xxxix} and PK-PD analyses have been done of efficacy^{xxxix} and QT prolongation – the latter is driven by the M2 metabolite^{xxxv}. Delamanid exposure will be described in a population PK model being developed in the ACTG study A5343, which is expected to be complete by the end of 2019; PK-PD analysis has shown that the QT prolonging effect is driven by the DM6705 metabolite^{xxxvi}.

The pharmacokinetic modelling will be led by Dr Paolo Denti (head of the UCT pharmacometrics group), with overall supervision of the pharmacokinetic analyses by Professor Gary Maartens. Population pharmacokinetic models are the best method to understand the effect of key co-variables (e.g. sex, weight, renal function, co-morbid disease) and the preferred method to characterize the exposure of drugs that accumulate slowly including bedaquiline and clofazimine. Population PK models are also ideally suited to large populations as in BEAT Tuberculosis as all participants contribute sparse samples (typically trough concentrations) with intensive PK sampling only needed in a small subset. As Prof Maartens' group have (or will have) developed population PK models in South African patients with DR-TB for all of the drugs in the BEAT Tuberculosis regimen except clofazimine, sparse sampling will be adequate to estimate individual participant drug exposure.

A combined intensive and sparse sampling strategy will be used for clofazimine. Intensive sampling will be done in 30 participants at month 1 at the following time points: pre-dose, 2, 4, 6, 8, 10, and 24 hours. In these 30 intensively sample participants ECGs will be done in triplicate at each PK sampling

time point. Pre-dose sparse sampling for all drugs will be done at months 1, 3, and 6. The population PK models will be developed using NONMEM® software.

PK-PD analyses estimate free drug concentrations as only the free drug is active, but free drug concentrations are typically estimated from manufacturers' data from healthy volunteers. Most of the drugs used in the intervention arm are bound to serum albumin, which is a negative acute phase reactant. Therefore, estimates of free drug concentrations based on healthy volunteers are likely to be under-estimates early on in TB. Albumin typically returns to normal after about 8 weeks of TB therapy^{xxxvii}. We will measure free trough drug concentrations weekly for the first 8 weeks of therapy in 20 participants in BEAT Tuberculosis. This will allow more accurate PK-PD analyses in the crucial initial treatment period.

Teasing out the contribution of individual drug exposure to efficacy in a multi-drug regimen is complex, but Prof Maartens' group, in conjunction with Tawanda Gumbo's group, has developed techniques to do this^{xxxviii}. We will use classification and regression tree analysis to perform PK-PD efficacy analyses in the intervention arm. The efficacy measure will be change in time to sputum culture positivity, using a model developed by Prof Maartens' group^{xxxix}, which has been validated externally^{xl} in MDR-TB.

1.8.2. Dried Blood Spot (DBS) validation sub-study

Rationale and design

Dried blood spot (DBS) is an objective measure, which has been recently used to quantify adherence to several drugs, including antiretrovirals^{xli xlii}. DBS has an advantage over plasma in that specimens can be stored at ambient temperatures and easily transported from clinics to laboratories equipped to perform the assays and is therefore utilizable in resource-limited settings^{xliii}. The micro sampling technique used for DBS is also less invasive than standard phlebotomy; blood can be sampled via a skin prick from a heel or finger. An experienced phlebotomist is also not required – a nurse or carer can easily be trained to perform the sampling^{xliv}. DBS has been used for more than 40 years as a screening tool for metabolic disorders in neonates xlv, and has since been widely used in therapeutic drug monitoring and pre-clinical drug discovery. There are no published data on DBS for the drugs used to treat MDR-TB. Considering that treatment completion rates in MDR-TB have historically been recorded at approximately 50%^{xlv}, a simple validated adherence measure will provide critical adherence information to assist in the management of patients with MDR-TB. The pharmacokinetic study nested in BEAT Tuberculosis is a unique opportunity to validate DBS for bedaquiline, levofloxacin, linezolid and clofazimine, which are key drugs in the WHO-recommended treatment regimen for MDR-TB^{xlvi}.

Blood will be sampled for DBS at the same time-points as plasma from 20 participants who are scheduled for intensive sampling at 7 time-points over 24 hours (pre-dose, 2, 4, 6, 8, 10, and 24 hours post-dose). After the drug-specific analyte is spiked into the EDTA tube containing fresh whole blood, 50 µl of preparation is spotted onto a Whatman 903 Protein Saver card, which is then dried at room temperature. The cards will then be stored with three desiccant sachets in a sealable plastic bag at -80°C and transported to the division of Clinical Pharmacology, University of Cape Town, which has experience in the validation of dried blood spots ^{xli xlii xlvii xlviii}. A Bland-Altman plot will be used to analyze agreement between the DBS and the plasma assays taken at the same timepoints.

A validated DBS for the key new and repurposed drugs used in the MDR-TB treatment regimen will lay the platform for further research in the utility of DBS in MDR-TB.

1.8.3. Pharmacogenetics sub-study: Genetic determinants of variability in the pharmacokinetics of anti-TB drugs

Rationale and design

Little is known about the effects of pharmacogenetic variants on multidrug-resistant tuberculosis (MDR-TB) drug exposure, efficacy and toxicity. BEAT Tuberculosis is an ideal setting to explore the effect of pharmacogenetics on the exposure of new and repurposed anti-TB drugs including bedaquiline, clofazimine and levofloxacin. In this sub-study, whole blood from consenting patients, 18 years of age and older, participating in the BEAT Tuberculosis trial will be drawn to perform targeted analyses of candidate genes known to affect drug disposition, in collaboration with David Haas, Department of Medicine, Vanderbilt University School of Medicine, who has significant experience in TB and HIV pharmacogenomics ^{xlix l li}.

We will characterize the plasma PK, efficacy and safety of repurposed and new anti-TB drugs in the BEAT Tuberculosis PK study. Nonlinear mixed effects models (NONMEM®) will be used to describe the population PK of key drugs in semi-mechanistic models. (NONMEM®) accurately ascribes PK variability and can, through simulation, predict improved dosing based on significant fixed effects (e.g. the effects of functionally important genetic variants, adjusting for other significant effects such as lean body mass and drug-drug interactions). We will describe pharmacokinetic-efficacy and pharmacokinetic-toxicity relationships for each anti-TB drug. Therefore, the target plasma exposures will provide the platform to directly interpret the importance of the pharmacogenetic findings and translate them in model-based simulations, to optimize dosing.

Specific objectives

- Identify genetic polymorphisms associated with significant effects on population PK model parameters of exposure for bedaquiline, clofazimine and levofloxacin.
- Quantify the effects of the genetic polymorphisms on plasma exposure, and simulate dose adjustments overcoming these effects.
- Explore polymorphism associations with specific drug toxicities (e.g. QT-prolongation, hepatotoxicity).

After sampling, whole blood will be transported by an accredited courier company to the division of Clinical Pharmacology, University of Cape Town (UCT) for storage at minus 80 degrees Celsius. Thereafter, frozen samples will then be transported in batches to Vanderbilt University School of Medicine in Nashville, Tennessee, United States of America where, after DNA extraction, genotyping will be performed using the Multi-Ethnic Genotyping Array MEGA® chip. <https://emea.illumina.com/science/consortia/human-consortia/multi-ethnic-genotyping-consortium.html>.

Separate informed consent for the pharmacogenomics sub-study will be taken from each participant in either English, Afrikaans or Xhosa. Additional ethics approval will be sought from the UCT Human Research Ethics Committee and the Vanderbilt University School of Medicine Ethics Committee. Participant DNA will not be used for any other research purposes without additional consent. Unused samples will be destroyed within 15 years of study completion.

BEAT Tuberculosis is a unique opportunity to explore genetic associations with plasma drug exposure, efficacy and specific treatment-related toxicities. Knowledge generated in this study will significantly contribute to the optimal use of anti-TB drugs in the future management of patients with MDR-TB.

1.8.4. Pregnancy PK sub-study

Background

There is no existing data on the effect of pregnancy on exposure of the novel and repurposed anti-TB drugs included in the BEAT Tuberculosis trial regimen, several of which are key drugs recommended by the WHO for the treatment of MDR-TB^{lii}. One reason for reduced drug concentrations in pregnancy is the reduction in plasma concentrations of albumin and α 1-acid glycoprotein, which are two common drug-binding proteins^{liii}. Reduction in binding protein concentrations reduces the total (bound and free) concentrations of drugs, but the free fraction typically increases, resulting in free drug concentrations that are similar to non-pregnant women. As only the free drug is pharmacologically active, recommendations to increase the drug doses in pregnancy to approximate total concentrations

in non-pregnant women could increase toxicity. Pregnancy also increases several drug clearance mechanisms, which could reduce free drug concentrations. Therefore, free drug concentration measurements are necessary in order to optimise dosing in pregnancy. Furthermore, data available on the secretion of these drugs into breast milk is limited to case reports^{liv lv lvi}. One report of a study in rats reported bedaquiline concentrations in breast milk to be 6- to 12- fold higher than the concentration in maternal plasma^{lvii}. Information on infant drug exposure through breastfeeding is important not only for safety, but because therapeutic concentrations could potentially be protective in exposed infants, obviating the need for TB preventive therapy and, sub-therapeutic concentrations could select for resistance in infants infected with MDR-TB. Knowledge of the exposure of these drugs in pregnant and breastfeeding women therefore requires rapid accumulation to inform policy in this vulnerable population.

Method

Design: Pregnant women in either treatment strategy will undergo intensive PK sampling (pre-dose, 2, 4, 6, 8 and 24 hours) for bedaquiline, clofazimine and levofloxacin during the third trimester (>28 weeks gestation). The same sampling schedule will be repeated 4-8 weeks postpartum. We will determine concentrations of total, bound and free unbound plasma clofazimine, bedaquiline, and levofloxacin. At delivery, where possible, paired maternal plasma: cord blood samples will also be taken. At the postpartum PK visit breastmilk samples will be obtained pre-dose and at 2, 4, 6, and 8 hours post-dose. A plasma sample will also be obtained from their breastfed infants at a random timepoint (once per infant) over the 8 hour PK visit in order to characterize concentrations of these drugs over an 8 hour dosing interval. If available, an additional sample will also be taken from breastfeeding infants at a time when therapy is near completion, and then on at least one additional occasion 1-3 months after treatment has stopped in order to characterize the washout of long half-life drugs i.e. bedaquiline and clofazimine. Breastmilk assays for bedaquiline, clofazimine and levofloxacin are currently being developed by the Division of Clinical Pharmacology, University of Cape Town (UCT), which has significant experience in the validation of liquid chromatography/mass spectrometry TB drug assays. The laboratory has already developed plasma assays for clofazimine, bedaquiline, and levofloxacin (validated by ACTG's CPQA) and is in the process of developing validated unbound plasma assays for these drugs.

Sample size: This BEAT Tuberculosis PK sub-study in pregnant women is exploratory. We will be pooling data from similar studies in order to power the sample size adequately.

Analysis: Non-compartmental analyses will be conducted for levofloxacin with geometric mean ratios and 90% confidence intervals used to determine differences in AUC₀₋₈ of total and unbound drug

between third trimester and postpartum. For bedaquiline and clofazimine, which accumulate slowly over months, nonlinear mixed-effects modelling will be used to compare exposures in the third trimester of pregnancy with postpartum samples. Professor Denti who heads the UCT pharmacometrics group has developed the first population PK model of clofazimine in MDR-TB, which will be used to estimate exposure differences^{lviii}. A published population PK model will be used for the bedaquiline analyses^{lix}.

Understanding the effect of pregnancy on the exposure of key drugs used to treat MDR-TB will contribute significantly to dose optimisation. Quantification of the secretion of these drugs into breast milk and subsequent infant exposure through breastfeeding will provide much-needed evidence for breastfeeding guidelines in nursing mothers treated for MDR-TB.

1.8.5. ECG sub-study: multi-lead mobile technology for monitoring cardiac repolarization

Design: This sub-study will establish the accuracy and precision of an FDA-approved smartphone-enabled device (AliveCor Triangle) for serial monitoring of electrocardiographic QT intervals compared with standard 12-lead ECGs.

Sample size: 220 independent participants, and 880 total measurements

Intervention: Six-lead ECG measurements with the Triangle device (paired via Bluetooth to smartphones) performed concurrently with 12-lead ECG recordings at three time points centrally read by a cardiology consultant (weeks 4, 12 and 24), and a fourth time point (week 2) read by research staff

Hypotheses and Study Objectives:

Primary Hypothesis: Longitudinal QT measurements obtained with Triangle will predict gold standard 12-lead ECG measurements with acceptable accuracy

Primary Objective: To compare QTcF (the corrected QT based on the Fridericia correction method) intervals with Triangle and measure agreement with standard 12-lead ECGs among BEAT Tuberculosis participants.

Secondary Objective: Assess acceptability, barriers to and facilitators of Triangle among nurses and participants.

Background and Rationale

Monitoring for QT-prolonging effects will be a major programmatic obstacle in scale-up of universal DR-TB treatment regimens. The normal range for the rate-corrected QT interval is similar in males and

females from birth until late adolescence (370 to 440 milliseconds (ms)). Among adults, a prolonged QTcF interval is defined as >450 ms in men and >470 ms in women and is associated with an increased risk of a characteristic life-threatening cardiac arrhythmia, known as torsades de pointes (TdP). A major operational challenge in scale-up of shortened, all-oral regimens in high-burden countries will be the need for serial QT monitoring during treatment. Analogous to audiometry testing for second-line injectables, such monitoring will require specialized equipment, personnel, and dedicated time that could potentially lead to important delays in initiating treatment or proceeding blindly with potentially dangerous treatments; the large burden of iatrogenic deafness due to historic MDR-TB treatment suggests the latter will be common^{lx}. Although recent randomized data suggests that combining BDQ and DLM leads to no more than additive QTcF prolongation for these agents,^{lxi} patients in this trial were carefully screened, electrolytes assiduously repleted, and no additional QT-prolonging medications (including CFZ) were permitted; thus, programmatic use is expected to deviate significantly from these trial conditions, the effect of alternative or additional anti-TB QT-prolonging agents (e.g., FQs, CFZ) is unknown, and further expensive and time-consuming RCTs exploring this question are unlikely. Good clinical practice, along with international and national guidelines, will continue to mandate means for careful cardiac monitoring in resource-limited contexts.

Silicon Valley innovation can have a transformative impact on clinical applications in resource limited settings. Smartphones, now more powerful than a 1980s room-sized supercomputer^{lxii}, have become widely available on a global scale, and are becoming increasingly used for arrhythmia monitoring in ambulatory and outpatient settings^{lxiii}. AliveCor (Mountain View, CA) has been at the cutting edge in development, testing, and marketing of such devices. The currently available KardiaMobile (AliveCor, Mountain View, CA) is a single-lead ECG that received FDA 510k clearance in 2012, and over-the-counter clearance in 2014^{lxiv}. KardiaMobile also has FDA-cleared ECG algorithms for Normal and Atrial Fibrillation. When KardiaMobile's metal electrodes are touched by the right and left hands of the user, a bipolar lead I is created, and the cardiac electric signal is converted to high frequency ultrasound. The application in the smartphone then demodulates the signal to an ambulatory-bandwidth ECG tracing (300 samples/s, 16-bit resolution). The ECG tracing can be viewed in real time and is also stored, being instantly transmitted by the phone to a secure cloud server (Amazon Web Services) for later review.

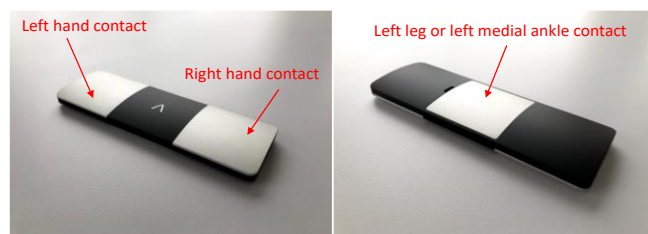


Figure 1. AliveCor's Triangle Hardware

KardiaMobile has been studied for use in QT interval measurement. Chung et al. found reasonable correlation with a KardiaMobile case QT interval and a 12-lead ECG on five patients in normal sinus

rhythm receiving dofetilide, an antiarrhythmic that prolongs the QT interval^{lxv}. Garabelli et al. evaluated the device for QT monitoring in both a healthy population as well as a group of inpatients receiving initiation with sotalol or dofetilide^{lxvi}. The case was accurate in measuring QTc interval in sinus rhythm when compared with 12-lead ECG in healthy volunteers. For patients receiving QT-prolonging antiarrhythmic medications in the hospital setting, KardiaMobile was capable of detecting QTc prolongation as it occurred.



Figure 2. Recording a Six-Lead ECG with Triangle

As the KardiaMobile case above, all current FDA-approved ECG devices rely on a single lead I assessment for technical simplicity. However, because many individuals have flat T waves in lead I, it is well-known that a single-lead ECG device is not ideal for field QT evaluation. On a standard 12-lead ECG, the QT interval is more commonly measured from lead II (or another lead such as V5). Anticipating this challenge, AliveCor has developed an innovative smartphone-enabled multilead ECG device (the Triangle) able to generate a 6-lead ECG (recorded leads I and II; derived lead III (from Einthoven's triangle); and derived leads aVF, aVR, and aVL (from Goldberger's central terminal)) (Fig. 1-3). This device is well positioned to be evaluated in a sub-study of TB medication QT monitoring. Three electrodes are generated when grasped by both hands and held on the left leg or ankle and paired to a smartphone via Bluetooth. The Triangle device has been clinically validated in healthy adult volunteers and adult cardiology patients,^{lxvii} and is currently FDA cleared^{lxviii}

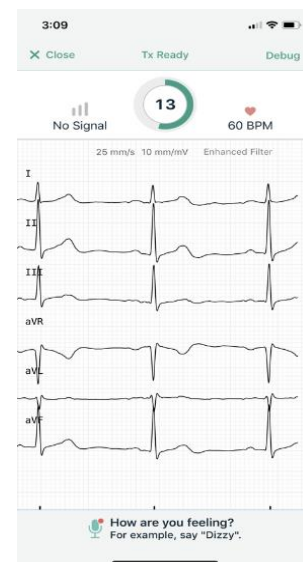


Figure 3. Kardia application read-out

Statistical considerations and Sample Size

Dr. Eric Vittinghoff (University of California, San Francisco) has agreed to be the senior statistician on this project. The 12-lead and device-based QTcF measurements will initially be compared using Bland-Altman plots^{lxix}. We will then estimate a linear mixed model (LMM) for the repeated 12-lead

measurements, with the device-based measurement as the sole predictor. Within-subject correlation of the repeated outcome measurements will be accounted for using random effects. Based on the results of this model, 95% prediction intervals for the outcome will be constructed across the range of the device-based measures, providing estimate of the precision with which the device-based measurements can be used to predict the gold-standard outcome; note that prediction intervals account for residual variability in the outcome as well as error in the estimated expected value, as captured by standard confidence intervals. In addition, exploratory LMMs with restricted cubic spline transformation of the device-based values will be used to assess divergence of the fitted values, plotted against the device-based values, from the line of equality, indicating bias in at least part of the range. In a sensitivity analysis, the time point where the 12-lead ECG is not read centrally will be analyzed separately. Additional exploratory analysis will add time of day to the LMM, to determine whether this can improve prediction accuracy, at some cost in ease of use.

2. Study design

BEAT Tuberculosis is an open label, multi-centre, randomized controlled trial. Participants will be randomized in a 1:1 ratio to receive either the Study Strategy or Control Strategy, with a stratification by clinical site and HIV status.

The study will be open label, as blinding is not feasible. It is not possible to formulate placebos with multiple drugs and durations of treatment. However, the study will be treated as if it were a blinded study in all ways other than the physician and the participant having knowledge of the treatment assignment. Individuals assessing x-rays, cultures, ECGs and other participant information will be blinded to treatment assignment. Moreover, there will be no summary of the study by the randomized treatment arms separately, except for summaries prepared by the trial statistician exclusively for the DMC.

3. Study objectives and endpoints

The objective of this study is to compare the efficacy and safety of a Study Strategy consisting of 6 months of BDQ, DLM, and LNZ, with LVX and CFZ compared to the current South African Standard of Care (Control Strategy) for 9 months for the treatment of rifampicin resistant tuberculosis (RR-TB). Both the Study and the Control Strategies will be modified once fluoroquinolone sensitivity has been established.

3.1. Primary Objectives

3.1.1. Efficacy Objective

To assess whether the proportion of participants with a successful outcome at the end of treatment and at the end of follow up at 76 weeks after randomization on the Study Strategy is not inferior to that on the Control Strategy.

3.1.2. Safety Objective

To compare the proportion of participants who experience grade 3 or greater adverse events during treatment on the Study Strategy as compared to the Control Strategy.

3.2. Secondary objectives

3.2.1. Composite efficacy and safety objective

To assess if the proportion of participants with a successful composite outcome at 76 weeks after randomization on the Study Strategy is superior to the Control Strategy.

3.2.2. Secondary objectives (pharmacokinetics/pharmacodynamics (PK/PD))

- Develop a population PK model of clofazimine exposure
- Estimate individual participant drug exposures for bedaquiline, delamanid, levofloxacin, and linezolid from sparse data using existing population PK models
- Determine PK-PD relationships of toxicity (QT prolongation and increase in ALT from baseline) using estimated individual participant drug exposures of drugs/metabolites known to cause QT prolongation (clofazimine, bedaquiline M2 metabolite, delamanid DM6705 metabolite, and levofloxacin)
- Determine PK-PD relationships of linezolid toxicity (bone marrow suppression, peripheral neuropathy, and optic neuritis)
- Determine the change in the intervention strategy of free concentrations of bedaquiline, delamanid, levofloxacin, and linezolid over the first 8 weeks of therapy in a sub-group
- Determine PK-PD relationships of efficacy (using change in time to sputum culture positivity as the efficacy parameter) in the intervention strategy of bedaquiline, delamanid, levofloxacin, and linezolid

3.3. Study Endpoints

These are based on the WHO outcome definitions, slightly modified for use in a clinical trial and also includes post treatment follow up to 76 weeks after randomization.

3.3.1. Primary efficacy endpoints

3.3.1.1. A successful treatment outcome measured at the end of treatment

Defined as one of the following:

- Cured: Adequate treatment adherence (at least 80% of dosages taken) as per protocol without evidence of failure AND last two negative sputum specimens at the end of treatment being culture negative. These specimens must be separated by at least 14 days.
- Treatment completed: Adequate treatment adherence (at least 80% of dosages taken) as per protocol without evidence of failure BUT no record that two or more consecutive cultures taken at least 14 days apart are negative.

3.3.1.2. An unsuccessful treatment outcome measured at the end of treatment

Defined as one of the following:

- Treatment failed
 - lack of sputum culture conversion by the end of the of treatment
 - OR
 - bacteriological reversion after sputum culture conversion to negative
 - OR
 - If two or more anti-TB drugs are substituted due to Adverse Drug Reactions (ADRs)
- Death during the treatment from any cause
- Lost to follow-up: A participant who missed 28 consecutive days of treatment not directed by the clinician
- Not evaluated: A participant for whom no treatment outcome is assigned (this includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown)

3.3.1.3. A successful end of follow up outcome measured at 76 weeks post treatment initiation

Defined as one of the following:

- Cured: Culture negative at the end of follow up
- OR
- Culture negative when last seen, if the participant is lost before the end of follow up and provided they have a successful treatment outcome at the last study visit attended

3.3.1.4. An unsuccessful end of follow up outcome measured at 76 weeks post treatment initiation

Defined as one of the following:

- Recurrence
 - Two consecutive positive cultures separated by at least 14 days
 - OR
 - One positive culture after confirmed culture conversion with clinical signs and symptoms of TB or no improvement or worsening of radiological changes since baseline. **Please note:** an isolated positive smear or culture without clinical or radiographic deterioration after treatment completion provides insufficient evidence to define recurrent TB
- Death in follow up from any cause
- Loss to follow up with clinical signs and/or symptoms of TB when last seen
- OR
- sputum culture positive when last seen
- OR
- not sputum culture negative and with clinical signs and symptoms of TB when last seen

Strain typing will be available to distinguish between relapse and reinfection. Participants who are re-infected with a different strain can still be considered a successful end of follow up outcome, provided they meet the criteria for this prior to reinfection.

3.3.2. Primary safety endpoint

The incidence of all (expected and/or unknown/unsuspected adverse events of the drugs being used) Treatment Emergent Adverse Events (TEAEs) of Grade 3 or higher using the Division of AIDS (DAIDS)

Table for Grading the Severity of Adult and Pediatric Adverse Events by treatment arm and up to 30 days following the end of treatment

3.3.3. Secondary Composite efficacy / safety endpoint:

The proportion of participants with a successful end of follow up outcome and no grade 3 or higher adverse events during treatment

3.3.4. Secondary safety endpoints

- The quantitative and qualitative clinical laboratory result measurements, including observed and changes from baseline by treatment arm graded by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events
- The proportion of participants who have a QTcF >500 ms at any time during treatment, by treatment arm
- The proportion of participants who have an increase from baseline in QTcF of greater than 60 ms at any time during treatment, by treatment arm

4. Site selection and Participant selection

4.1. Site selection

The clinical trial sites are selected to ensure sufficient numbers of RR-TB cases to meet recruitment targets. The sites are established DR-TB initiation and treating sites and have been approved by the national, provincial and district TB program with the capacity for long term follow up for safety evaluation. The Principal investigator must have experience in the treatment of DR TB and HIV.

The site must have suitable staff and be willing to recruit and retain participants into the trial. All potential participants must be offered an HIV test, as is standard in South Africa, and be willing to take antiretroviral treatment, should they test positive.

4.2. Participant selection

TB patients with evidence of resistance to rifampicin by conventional DST (culture-based) or rapid DST (Xpert MTB/RIF or LPA) will be approached and asked for informed consent to be screened and potentially enrolled to this study.

4.2.1. Inclusion criteria

Potential participants are required to meet all of the following inclusion criteria during the screening period in order to be randomized:

1. Willing and able to give informed consent to be enrolled in the research study prior to any study related procedures (signed or witnessed consent if the participant is unable to read and understand the informed consent document; signed or witnessed consent from a child's biological parent, legal guardian or primary caregiver) and if the participant is a child (6-17 years) is willing to sign assent
2. Willing and able to adhere to the complete follow-up schedule and to study procedures
3. Male or female, aged 6 years or older, including breastfeeding and/or pregnant women
4. Weigh more than or equal to 16kg
5. 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
6. Willing to use effective contraception for females of childbearing potential if sexually active; must be willing to use either an intrauterine contraceptive device or a hormonal method for the duration of the treatment regimen and for three months thereafter
7. Willing to have an HIV test, and if positive, is willing to be treated with appropriate antiretroviral therapy
8. 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
9. Participants who are pregnant, should have an ultrasound done to confirm a viable intrauterine pregnancy prior to enrolment

4.2.2. Exclusion criteria

Potential participants will be excluded from participation if they meet any of the following criteria during the screening period:

1. Had taken more than 28 days, but less than 24 weeks, of second line TB drugs including BDQ, LNZ, CFZ, fluoroquinolones or DLM. **Please note:** Participants with prior successfully treated episodes of DR TB are permitted to enroll.

For data purposes exclusion criterion no.2 has been omitted.

3. Has complicated or severe extra-pulmonary manifestations of TB, including osteo-articular, pericardial and central nervous system infection as per investigator's opinion
4. Is unable to take oral medication
5. Is taking any prohibited medications (see section 5)
6. Has a known allergy or hypersensitivity to any of the medicines in the regimens

7. Is currently taking part in another clinical trial of any medicinal product
8. Has a QTcF interval of > 480 ms. **Please note:** If the QTcF interval is > 480 ms, it may be repeated if participant has reversible contributory factors, i.e. low potassium or to allow washout of previous QT prolonging drugs.
9. Has clinically significant ECG abnormality in the opinion of the site investigator within 60 days prior to entry, including but not limited to second or third degree atrioventricular (AV) block or clinically important arrhythmia
10. Participants with the following laboratory abnormality at screening. **Please note:** These investigations may be repeated if abnormal, provided the results are available within the screening period.
 - a) Haemoglobin level of < 8.0 g/dL
 - b) Platelet count < 75,000/mm³
 - c) Absolute neutrophil count (ANC) < 1000/ mm³
 - d) An estimated creatinine clearance (CrCl) less than 30 mL/min as calculated by the National Health Laboratory Service (NHLS) equation
 - e) Alanine aminotransferase (ALT) ≥3 x ULN
 - f) Total bilirubin grade 3 or greater (>2.0 x ULN, or >1.50 x ULN when accompanied by any increase in other liver function test)
 - g) Serum potassium less than 3.2 mmol/l
11. Peripheral neuropathy of grade 3 or 4 using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events
12. If in the investigator's opinion, the participant is unable to commit to study related procedures or it is unsafe for the participant to take part in the study

If the participant's laboratory results at screening are from the SA National TB Programme (performed by an accredited laboratory), these results can be used to assess the eligibility criteria for that participant, provided these investigations were performed no longer than 14 days prior to the screening visit.

Additionally, if the participant's laboratory tests were performed 14 days or less prior to the screening visit and fulfil the necessary eligibility criteria, the site may randomize the participant based on these results, provided that the randomization visit occurs no longer than 14 days after the earliest screening laboratory result, and all other eligibility criteria are fulfilled as per protocol. This naturally permits the site to screen and randomize a participant on the same day.*

**This amendment in the protocol was submitted as a Clarification Memorandum, on 6 January 2020 to both SAHPRA and Wits HREC.*

5. Prohibited Medications

Concomitant medication should be kept to the minimum during the trial. The following medications are prohibited from the time of screening and during the treatment period.

- a) The systemic use of moderate and strong CYP3A4 inhibitors (including: amiodarone, erythromycin, miconazole, diltiazem, verapamil, conivaptan, clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole)
- b) The systemic use of strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital, St. John's wort, and rifamycins [rifampin, rifapentine] griseofulvin);
- c) The use of any drug that is known to prolong the QTc interval including amiodarone; amitriptyline; amphotericin B; astemizole; azithromycin; citalopram; clarithromycin; clomipramine; erythromycin; escitalopram; esomeprazole; fluoxetine; haloperidol; imipramine (melipramine); ketoconazole; metoclopramide; paroxetine; quinine sulfate, quinidine; risperidone; sertraline; sotalol; terfenadine; thioridazine; tramadol; venlafaxine.

The full list of medications can be found at:

https://crediblemeds.org/index.php/tools/pdfdownload?f=cql_en

(Please note that registration is required)

- d) Selective serotonin reuptake inhibitors (SSRIs) co-administration with linezolid increases the risk for the serotonin syndrome.
- e) Fluconazole is a weak CYP3A4 inhibitor and may have a mild effect on the QTc interval. Special caution must be used if fluconazole is prescribed. If the participant is on TB treatment and fluconazole, ECG should be done every two weeks.
- f) If a participant requires an oral magnesium-containing substance e.g. magnesium trisilicate, this must be dosed two hours separate from the fluoroquinolone.

6. Treatment of participants

During BEAT Tuberculosis, participants who are enrolled will be randomized to either the Study Strategy or the Control Strategy.

Eligible participants will be randomized (1:1) to one of the two treatment arms using prepared lists stratified by site and HIV status and using blocks of varying sizes. The randomization lists will be

prepared in advance prior to consenting the first participant by a statistician. The randomization allocation will be done by the central data management team.

6.1. Study Strategy

All treatment in the Study Strategy is given orally for 24 weeks.

- a) Bedaquiline
- b) Linezolid
- c) Delamanid
- d) Clofazimine
- e) Levofloxacin

Table 1: Study Strategy doses

Product	Weight Group				
	16 - 23kg	23.1 - 29.9kg	30 - 33.9kg	34 - 50kg	>50kg
BDQ	¹ 200mg daily for two weeks; followed by 100mg three times weekly for weeks 3 - 24		400mg once daily for 14 days followed by 200mg three times weekly for weeks 3 - 24		
DLM	25mg twice daily for 24 weeks	50mg twice daily for 24 weeks		100mg twice daily for 8 weeks followed by 200 mg daily for 16 weeks	
² LNZ	180 - 210mg (crush 1 tab and mix in 10ml water, administer 3-3.5ml. Discard rest)	300mg daily	450mg daily	600mg daily	
³ LVX	375 - 500mg daily	500mg once daily		750mg daily	1000mg daily
CFZ	100mg three times a week or 50mg daily	100mg daily			

¹Only in participants ≥6 years old (lower dose from 15 - 29 kg; higher dose from >29 kg)

²10 - 12 mg/kg once daily in >15kg / 20mg per ml susp or 600mg

³15 - 20 mg/kg once daily

As per standard practice, at the time of treatment initiation, a sputum sample will be sent for ascertainment of fluoroquinolone sensitivity.

- If the sample shows fluoroquinolone sensitivity by LPA, then CFZ will be stopped.
- If the sample shows fluoroquinolone resistance by LPA, then LVX will be stopped.
- If the LPA is indeterminate or missing, both LVX and CFZ will be continued for the duration of the treatment period.
- If fluoroquinolone sensitivity is determined prior to the start of treatment, CFZ will not be started.
- If fluoroquinolone resistance is determined prior to the start of treatment, LVX will not be started.
- If fluoroquinolone sensitivity is determined by genotype, then CFZ will be stopped. Additionally, the genotypic result will be confirmed by phenotype as per the national testing guidelines and treatment modified as required, if there is a discrepancy. Discuss with the PI or Clinical Medical Monitors.

6.2. Control Strategy

The Control Strategy is the South African Standard of care for RR-TB. This will be based on the most up to date, approved SA NTP guidance. Should this guidance change during the course of the study, the Control Strategy will also change. The site/s must follow the latest approved SA NTP guidelines as the Control Strategy.*

**This amendment in the protocol was submitted as a Clarification Memorandum, on 21 January 2020 to both SAHPRA and Wits HREC.*

All treatment in the Control Strategy is given orally.

The regimen duration of the intensive phase can be extended if the participant is smear positive at week 16.

- a) Bedaquiline
- b) Linezolid
- c) Isoniazid_{high dose}
- d) Levofloxacin
- e) Ethambutol
- f) Pyrazinamide
- g) Clofazimine

Table 2: Control Strategy doses

Product	Weight Group				
	16 - 23kg	23.1 - 29.9kg	30 - 33.9kg	34 - 50kg	More than 50kg
BDQ	¹ 200mg daily for two weeks; followed by 100mg three times weekly for weeks 3 - 24		400mg once daily for 14 days followed by 200mg three times per week for weeks 3 - 24		
LNZ	180 - 210mg (crush 1 tab and mix in 10ml water, administer 3-3.5ml. Discard rest)	300mg daily	450mg daily	600mg daily	
²INH_{high} dose	300mg daily	400mg daily			600mg daily
LVX	375 - 500mg daily	500mg once daily		750mg daily	1000mg daily
³E	400mg daily	600mg daily	800mg daily		1200mg daily
⁴Z	750mg daily	1000mg daily	1250mg daily	1500mg daily	2000mg daily
CFZ	100mg three times a week or 50mg daily	100mg daily			

¹Only in participants ≥6 years old (lower dose from 15 - 29kg; higher dose from >29kg)

²10 - 15mg / kg once daily

³15 - 25mg / kg once daily

⁴30 - 40mg / kg once daily

As per standard practice, at the time of treatment initiation, a sputum sample will be sent for ascertainment of fluoroquinolone sensitivity.

- If fluoroquinolone sensitivity is confirmed, the regimen will be continued unchanged.
- If fluoroquinolone resistance is confirmed, the regimen will be modified as per the latest NTP guidelines.
- If the fluoroquinolone resistance is known prior to treatment initiation, an individualized regimen will be given.
- If fluoroquinolone sensitivity is confirmed by genotype, the regimen will remain unchanged. Additionally, the genotypic result will be confirmed by phenotype as per the national testing guidelines and treatment modified as required, if there is a discrepancy. Discuss with the PI or Clinical Medical Monitors.

6.3. Additional sensitivity testing to be performed in both treatment strategies

Study specific laboratory testing will be performed at the WHO Supranational TB Reference Laboratory in Johannesburg. Reference testing will be performed on isolates shipped from the regional NHLS TB culture laboratory where routine primary cultures are performed. Study specific phenotypic drug resistance (pDST) will be performed on all participants at baseline for the following additional drugs, which is in addition to what is routinely tested: Bedaquiline, Clofazimine, Linezolid, Delamanid. Isolates will be stored for all post baseline culture positive samples and pDST performed at the end of the study. Additional whole genome sequencing will be performed on culture positive baseline samples showing phenotypic resistance to any of the tested drugs, 10% of baseline susceptible isolates and any post baseline isolates showing resistance. The whole genome sequencing will be performed at the end of the study.

The BACTEC™ MGIT™ 960 DST method will be used as previously described for phenotypic drug susceptibility testing. Testing will be performed at the WHO recommended critical concentration for the specific drug.

The EpiCentre TBExist software (Becton Dickinson, USA) will be used for interpretation and the incubation period extended from the recommended 13 to 28 days, adjusted for slow growing drug resistant isolates.

Whole genome sequencing will be performed using the MiSeq (Illumina, UK) platform. Library preparation will use the Nextera-XT library preparation kit (Illumina, UK) and sequencing performed using the 2 × 300 bp MiSeq cartridge v.3 (Illumina, UK) with a target of 30×-50× paired coverage (~80–100X coverage). The sequence data (FASTQ files) generated from the Illumina instrument will be

analysed using CLC Genomics Workbench 8.5.1 software to detect resistance-associated variants in the genes of interest for the relevant drug. Reference mapping against the annotated reference genome H37Rv (NC00962.3) and the quality-based variant analysis tools will be applied for the analysis.

Should BDQ or LNZ resistance be detected, the participant will be removed from trial medication and continued on study and a rescue regimen will be suggested by the National Clinical Advisory Committee. Medications for this will be obtained from the provincial department of health.

6.4. In-patient and ambulatory treatment

Inpatient treatment is not mandatory, but participants may be hospitalized at the initiation of RR-TB treatment for a short period of time to ensure that they can tolerate the regimen. It may also be advisable for specific groups and for very ill participants, for instance during the initiation of treatment or when adverse events occur during treatment. All attempts should be made to have Directly Observed Therapy (DOT) throughout the whole treatment course and should be administered seven days per week. Ambulatory DOT services will be "community-based" in which one of more treatment supporters selected by the participant at their screening visit, will sign for the participant's drug intake daily. It will be preferable for the treatment supporters to accompany the participant to the screening and follow-up visits and liaise with the clinical staff.

6.5. Management of dosing

6.5.1. Missed doses

Participants who miss doses either directed by the investigator or due to self-non-adherence should be encouraged to make up these doses at the end of treatment. If the participant vomits up to half an hour after taking treatment, the dose may be repeated only once.

Participants must receive 14 days of Bedaquiline at 400mg. This can occur prior to enrollment on the study. Therefore, if a participant has already received BDQ prior to randomization then the total days (including pre-randomization BDQ) at 400mg, must not exceed 14.

6.5.1.1. Missed doses: Study Strategy

- If a participant has missed 7 days or more of medication over the course of the 6 months of treatment, the total number of days missed have to be replaced.
- If a participant missed less than 7 days of medications over the course of the 6 months, no missed doses have to be replaced.

- If a participant has missed doses of LNZ due to an adverse event, the LNZ will not be replaced at the end of the study. LNZ can be reintroduced or replaced with an alternative before the end of the study.

6.5.1.2. Missed doses: Control Strategy

- The national guidelines will be used for the approach to missed doses of participants on the control strategy.
- If a participant has 3 negative sputum cultures, a month apart, in the preceding 6 months, no missed doses will be replaced.
- If the participant does not have 3 negative cultures (as per (2) above) by the time their 9/18 months of treatment are completed, their treatment will continue until they have 3 negative cultures as (2) above.

6.5.2. Overdose

Overdose of anti-tuberculosis medicines while on trial will be assessed by the investigator to determine whether the overdose was as a result of (i.e. suicidal ideation), or led to, an adverse event. In this case it will be recorded as an adverse event. If it does not lead to an adverse event, it will not be recorded as an AE but will be noted in the participant's source documentation.

6.6. Schedule of events

6.6.1. Screening Visit

The screening visit may occur over a number of days up to 30 days prior to treatment assignment. If a participant fails screening, a full re-screen (all screening procedures must be repeated) may occur at a later date. Rescreening should only occur for those exclusion criteria that are potentially reversible.

The following information will be collected and procedures performed:

- a) Written Informed Consent or Assent as applicable
- b) Demographic Data: Full name, date of birth, age, gender, ethnicity, education level
- c) Prior medical and surgical history including history of previous TB episodes and outcomes, and HIV treatment history, smoking, illicit drug and alcohol use. Medical history includes conditions that occurred 3 months prior to screening, inclusive of those conditions that are ongoing at screening
- d) Two sputum specimens
 - i) Smear microscopy for AFB
 - ii) DR-TB Reflex test consisting of 1st and 2nd line LPA and culture

- e) Any available Drug Sensitivity Testing for TB including genotypic and phenotypic testing
- f) Triplicate 12-lead ECGs separated by at least 5 minutes. *(the ECG should be done before vital signs and any lab assessments)
- g) HIV testing according to the National Testing Algorithm. If a participant has a documented HIV positive test or is currently on ARVs, a repeat test does not have to be performed.
- h) Concomitant Medications for the prior 30 days
- i) Full Physical Examination including height, weight and vital signs
- j) Targeted neurologic examination
- k) Ophthalmic Examination (Ophthalmologic Medical History and Visual acuity)
- l) Blood tests:
 - i) Hematology: FBC with a differential white cell count and platelets
 - ii) Liver Function Tests: Bilirubin (total and direct), albumin, ALT
 - iii) Chemistry: Potassium, creatinine and urea
 - iv) Urine Pregnancy Test (women of childbearing potential only, whether they are sexually active or not)
 - v) CD4+ counts (in HIV infected participants, who have not had a CD4 count done in the last 3 months)
 - vi) HIV Viral load (in HIV infected participants on treatment, who have not had a viral load done within the last 3 months)
- m) Chest X-ray within three months of screening
- n) Eligibility Assessment

* All ECGs should be done with participant at rest, in triplicate, 5-10 minutes apart.

QT interval has diurnal variation, therefore ECGs should be done at approximately the same time of day throughout the study as far as possible. Ideally approximately 4-6 hours post-dose, and before lunch (approximate T_{max} of study TB drugs). However, there is no need to exclude or reschedule ECGs when they are collected at different times of the day from a previous visit.

6.6.2. Randomization

The following information will be collected and procedures performed pre-dosing:

- a) Eligibility Assessment
- b) Urine Pregnancy Test (women of childbearing potential only)
- c) 12-lead ECG in triplicate

- d) Vital Signs, including weight
- e) Brief Physical Examination
- f) Early Morning Sputum Collection
- g) Concomitant Medication(s)/Other Treatment(s)
- h) Adverse Events
- i) Administration of assigned medication. **Please note:** if the participant is already on BDQ at the time of randomization, complete 14 days of loading dose or continue on dosing schedule if on 200mg three times weekly. Record any TB medicines prior to randomization in the TB medicines log. The day of randomization is considered the first day of trial treatment.

6.6.3. Follow-up visits (on treatment)

The following information will be collected and procedures performed:

- a) 12-lead ECG in triplicate
- b) Vital signs, including weight
- c) Physical Examination as needed
- d) Laboratory Safety Assessments
- e) Sputum Collection: An early morning specimen is preferable. However, a spot specimen is also acceptable
- f) Concomitant Medication(s)/Other Treatment(s)
- g) Adverse Events
- h) Administration of assigned medication
- i) Intensive sampling PK will be done in 30 participants in both treatment strategies, provided the participant is taking clofazimine at the time of intensive sampling. This will take place at the week 4 visit, at the following time points: pre-dose, 2, 4, 6, 8, 10, and 24 hours post-dose. Participants must consent to this procedure separately. In these 30 intensively sampled participants, ECGs will be done in triplicate at each PK sampling time point.
- j) Pre-dose sparse sampling for all drugs for all participants (study and control strategies) will be done at weeks 4, 12, and 24.
- k) Triangle ECG measurement in participants at weeks 2, 4, 12 and 24. Participants must consent to this procedure.
- l) Dried blood spot samples at week 4. Participants must consent to this procedure.
- m) Free trough drug concentration analysis in 20 participants on study strategy weekly for first 8 weeks of treatment. Participants must consent to this procedure.

6.6.4. Post end of treatment visits

Please note: these visits will take place monthly for the first 3 months, followed by 3 monthly visits until end of study is reached. All participants must attend the end of study visit (week 76).

The following information will be collected and procedures performed:

- a) Vital signs, including weight
- b) Sputum Collection: An early morning specimen is preferable. However, a spot specimen is also acceptable

In line with the national policy, these visits can be conducted by the research nurse. If there is more than 10% weight loss, and/or a participant has signs and symptoms of TB, refer to the investigator. If the participant has any ongoing grade 3 or 4 adverse events or serious adverse events, the participant must be reviewed by the investigator.

6.6.5. Procedures not assigned to a specific study visit

a) Trough clofazimine assay

To be performed between 2 weeks and 4 months after treatment completion or between 2 weeks and 4 months after CFZ has been stopped, to coincide with a scheduled study visit for all participants. 5ml of blood will be taken for this sample.

b) Pharmacogenetic sample

A maximum of 10ml of blood will be taken at one of the scheduled study visits for participants who consent to this separately.

6.6.6. Procedures to be performed for pregnant women

- a) A full anomalies scan should be conducted between week 16 and 20 or when the participant presents if the pregnancy is more advanced.

Table 3: Schedule of Events: On treatment

BEAT Tuberculosis Schedule of Events: On treatment

Window period	N/A	N/A	+/- 3 days					+/- 14 days														
Evaluation	Screening	Randomization	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76
Signed informed consent	X																					
Demography	X																					
Medical & Treatment History	X	X																				
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV status ¹	X										As clinically indicated											
Inclusion & exclusion criteria	X	X																				
Signs/Symptoms & Diagnoses	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial medications dispensing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs including weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Exam ²	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Hematology ³	X		X	X	X	X	X	X	X	X												
Full Liver Function Tests ⁴	X			As clinically indicated																		
ALT ⁵			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry ⁶	X		X		X	X	As clinically indicated															
Targeted neurological examination ⁷	X				X	X	X	X	X	X	X	X	X	X	X	X						
12 lead ECG in triplicate ⁸	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Triangle ECG measurement ⁹			X	X		X			X													
Pregnancy Testing ¹⁰	X	X		As clinically indicated																		
Chest X-ray	X			As clinically indicated																		
HIV Viral Load (if HIV+) ¹¹	X								X													
CD4 count (if HIV+) ¹²	X								X													
Sputum AFB Smear & Culture In Liquid Media ¹³	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Susceptibility Testing (DST)	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intensive PK (30 participants) ¹⁴				X																		
Dried Blood Spot sample (20 participants) ¹⁵				X																		
Sparse PK sampling ¹⁶				X		X			X													
Free trough drug concentration analysis ¹⁷			X	X	X																	
Total blood volumes in ml (excl. intensive PK volume and DBS sample)	25	0	15	23	20	28	20	20	28	30	15	15	15	15	15	15	15	15	15	15	15	15

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- ¹ Using the National HIV testing algorithm. If a participant has a documented HIV positive test or is currently on ARVs, a repeat test does not have to be performed.
- ² Visual Acuity using the Snellen chart. Performed at each visit when the participant is on LNZ
- ³ Full Blood count with Haemoglobin, White cell, platelets and differential. Performed at each visit when the participant is on LNZ. A maximum of 5ml (1 tube) of blood will be drawn per visit
- ⁴ Total protein, Albumin, Bilirubin (conjugated and unconjugated), ALT. A maximum of 5ml (1 tube) of blood will be drawn per visit
- ⁵ ALT to be done at all visits while the participant is on TB treatment. If ALT >3xULN, to do full LFT panel. A maximum of 5ml (1 tube) of blood will be drawn per visit
- ⁶ Potassium, Urea Creatinine. A maximum of 5ml (1 tube) of blood will be drawn per visit
- ⁷ Targeted neurological examination including fine touch, reflexes and vibration sense
- ⁸ Investigator to read all ECG's and act according to cardiac safety guidelines (section 8.4). In addition, ECG's at weeks 4, 12 and 24 will be centrally read by a cardiology consultant
- ⁹ Additional ECG readings using the triangle device at weeks 2, 4, 12 and 24 in participants who consent to this. These ECG readings will not be used for patient management purposes.
- ¹⁰ Urine BHCG; if positive for serum BHCG
- ¹¹ A maximum of 5ml (1 tube) of blood will be drawn for HIV Viral Load
- ¹² A maximum of 5ml (1 tube) of blood will be drawn for CD4 Count
- ¹³ All positive isolates from screening onwards must be stored for later whole genome sequencing
- ¹⁴ For participants in both treatment strategies, provided the participant is taking clofazimine at the time of intensive sampling. Pre-dose, 2, 4, 6, 8, 10, and 24 hours post-dose. In these 30 intensively sample participants, ECGs will be done in triplicate at each PK sampling time point. A maximum of 30ml (6 tubes) of blood will be drawn in this PK visit. Perform on BDQ administration days. Participants need to sign a separate informed consent in order to take part in this
- ¹⁵ Additional samples taken for DBS validation in participants who consent to this procedure. Blood will be sampled for DBS at the same time-points as plasma from 20 participants who are scheduled for intensive sampling at 7 time-points over 24 hours (pre-dose, 2, 4, 6, 8, 10, and 24 hours post-dose). 50 microlitres of blood will be needed for this procedure
- ¹⁶ Pre-dose sparse sampling for all drugs for all participants (control and study strategies) will be done at weeks 4, 12, and 24. A maximum of 8ml (2 tubes) of blood will be drawn per PK visit. Perform on BDQ administration days
- ¹⁷ Additional PK performed in 20 participants randomized to the Study Strategy who consent to this procedure. Performed once a week for the **first 8 weeks of treatment**

Table 4: Schedule of Events: Off-treatment (post end of treatment visits)

BEAT Tuberculosis Schedule of Events: Off-treatment (post end of treatment visits)									
These off-treatment visits can begin at any time point, starting 1 month from the date that the participant completed treatment. These visits will take place monthly for the first 3 months, followed by 3 monthly visits until end of study is reached. All participants must attend the end of study visit (week 76 / 19 months).									
Window period	+/- 14 days								
Evaluation	*Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 19 / week 76
Signs/Symptoms & Diagnoses	X	X	X	X	X	X	X	X	X
Vital signs including weight	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Sputum AFB Smear & Culture in Liquid Media [^]	X	X	X	X	X	X	X	X	X
<i>*Month 1 is calculated as 4 weeks after the participant completed treatment.</i> <i>E.g. Participant completed treatment on 1 April 2020. Month 1 off-treatment visit will therefore be scheduled for 1 May 2020.</i>									

[^]All positive isolates from screening onwards must be stored for later whole genome sequencing

6.6.7. Ascertainment of fluoroquinolone sensitivity

As per the SANTP, at the time of diagnosis of RR-TB, a reflex DR-TB LPA is sent to the laboratory. The timing of the receipt of these results for both the first- and second-line probe assays is dependent on the sample: smear positive vs. smear negative. In some cases, this may be available prior to treatment initiation. In the Study Strategy, the use of CFZ or LVX will be determined as below. If the assay is inconclusive or indeterminate, then the test is repeated on the culture specimen.

Table 5: Action on ascertainment of fluoroquinolone sensitivity

	Study Strategy	Control Strategy
Fluoroquinolone sensitive Please note: If there is fluoroquinolone sensitivity by genotype, CFZ will be stopped. Additionally, the genotypic result will be confirmed by phenotype	Stop CFZ	No Change

<i>as per the national testing guidelines and treatment modified as required, if there is a discrepancy. Discuss with the PI or Clinical Medical Monitors.</i>		
Fluoroquinolone resistant	Stop LVX	Follow the current SANTP
Fluoroquinolone indeterminate or result not received	Continue CFZ and LVX for the duration of treatment	No Change

6.6.8. Instructions for PK samples

EDTA blood for drug assays will be centrifuged on site and plasma will be stored at minus 80° Celsius until shipping to the Division of Clinical Pharmacology, University of Cape Town. Validated drug assays will be performed in batches using liquid chromatography tandem mass spectrometry. Free drug concentrations will be determined by ultracentrifugation. Participant plasma will not be used for any additional purposes other than understanding TB drug pharmacokinetics. Residual plasma remaining after the drug concentrations are performed will be destroyed within five years of study completion. All concurrent medications, which may affect plasma drug concentration by the way of drug-drug interactions will be recorded.

6.6.9. Discontinuation of the treatment

Treatment may be discontinued in some situations although investigators should contact the Clinical Medical Monitors prior to changes:

The most common situations in which the regimen may be discontinued include:

- Pregnancy during treatment: For participants who become pregnant during treatment, it may be advisable to modify the treatment regimen. A decision regarding continuation or discontinuation of the regimen should be made after a review by the National Clinical Access Committee and discussion with the participant.
- Withdrawal of consent.
- Severe toxicity: One or more drugs may need to be suspended permanently due to severe toxicity. In such cases, the Clinical Medical Monitors of the trial should review the medical history carefully to determine how the regimen should be modified.

- Treatment failure: If clinical and bacteriological responses to treatment are poor at 12 weeks, a change in the treatment regimen should be considered. An extended DST should be done if still culture positive at week 12, whether or not the regimen is changed, in order to inform future management decisions.

Investigators should inform the Clinical Medical Monitors of changes in doses, or withdrawal of medicines in the allotted strategy. Treatment substitutions may be discussed.

All participants that discontinue treatment should be encouraged to remain in follow-up unless they explicitly withdraw consent from further follow-up.

7. Pharmacy plan

Study sites will obtain all anti-tuberculosis drugs through the South African National TB Program.

7.1. Drugs in the Study Strategy

Table 5: Source, Brand Name, and Composition of Study Drugs

Manufacturer	Brand Name, Dosage	Composition
Janssen Therapeutics	Sirturo™ 100 mg	bedaquiline 100 mg
Novartis	Lamprene™ 50 mg, 100 mg	clofazimine 50 mg, 100 mg
Otsuka	Deltyba™ 50 mg	delamanid 50 mg
Pfizer or generic as provided by the SANTP	Zyvox™ 600 mg or generic	linezolid 600 mg
Levofloxacin (As supplied by the SANTP)	(generic)	levofloxacin 250 mg, 500 mg

Table 6: Storage requirements for study drugs

Drug	Temperature Storage Requirements	Other Requirements
Bedaquiline	Store below 30°C	Store in the original container or package to protect from light
Clofazimine	Store below 25°C	Protect from moisture
Delamanid	Store below 25°C	Store in the original container or package to protect from light and moisture
Linezolid	Store at or below 25°C	Protect from light. Keep bottles tightly closed to protect from moisture.
Levofloxacin	Store below 25°C	Store in well-closed containers

7.2. Drugs in the Control Strategy

The study will assist the TB Program in obtaining these drugs and maintaining supply of control arm drugs for the study.

Storage of control arm agents is the responsibility of the study pharmacist at the site.

7.3. Accountability for the Study Drugs

The study pharmacist will acknowledge receipt of and keep an inventory of all study drugs. The study pharmacist or an investigator with a valid dispensing license has the responsibility to assure that study drugs are dispensed to participants in compliance with the protocol. Procedures will be detailed in the Pharmacy Plan.

8. Management of toxicity and specific conditions

8.1. HIV infection

Participants who are known to be HIV infected, or who are found to be HIV infected at trial screening, will be recruited into the study and follow the routine study procedures, provided they fulfil all other study eligibility criteria.

Newly diagnosed HIV positive participants will be given appropriate counselling about the medical consequences of their diagnosis and about the need to take responsible precautions to reduce the risk of infecting others. They will be referred to appropriate medical and social HIV treatment services. Wherever possible, participants in the BEAT Tuberculosis trial who are co-infected with HIV will be managed in a joint treatment clinic to ensure close co-ordination of management of the two conditions, and to ensure that appropriate decisions can be made concerning the management of drug interactions and side effects.

There are a number of drug-drug interactions with BDQ and the commonly used antiretroviral, efavirenz. For the HIV infected participant, which comprises up to 70% of DR-TB patients in South Africa, the alternatives for efavirenz include nevirapine, rilpivirine and lopinavir/r. The new Integrase Inhibitor, dolutegravir (DTG) is rarely the perpetrator of drug-drug interactions and would be the safest option to combine with the BEAT Tuberculosis regimen. The incorporation of DTG into the South African Antiretroviral program is imminent. Dolutegravir as a single drug or part of a fixed dose combination will be purchased for all HIV infected participants for the duration of the trial regimen until it is available from the national program.

8.1.1. Permissible ART

For HIV infected participants, to avoid potentiating known key toxicities of LNZ (neuropathy and myelosuppression), and efavirenz (EFV lowers BDQ levels), the following regimens are recommended:

- For persons above 30kg diagnosed with DR-TB who are treatment naïve, or who have defaulted ART and are currently not on ART:

TDF*/ FTC and DTG

- For persons below 30kg, appropriate therapy may include LPVr. These cases should be discussed with the PI.
- For persons already on ART, perform viral load and CD4 cell count at screening and change ART as per guideline outlined below:

Table 7: Guidance for modification of ART regimens during treatment for RR/MDR-TB

Current ART Regimen	Proposed ART regimen	
	VL < 400	VL > 400
TDF * or ABC/ FTC/ EFV	TDF*/ FTC and DTG	Review previous VL/ history of treatment interruptions to determine if switch to second line ART is needed
TDF or ABC/ FTC/ NVP	TDF*/ FTC and DTG	Review previous VL/ history of treatment interruptions to determine if switch to second line ART is needed
TDF* or ABC or AZT/ FTC and LPV/ rit (or DTG)	Change AZT to TDF* Keep the rest of the regimen unchanged	Review and address reason for increased VL Resistance testing as per national guidelines

**ABC is used instead of TDF if there is renal impairment, or if child is <30kg.*

Participants who are on efavirenz should be changed to the appropriate new regimen prior to randomization.

Females of childbearing potential should be counselled about the potential teratogenicity of DTG and advised as per the South African National Department of Health HIV guidelines to use contraception.

8.2. Management of Linezolid Toxicities

The expected LNZ toxicities of peripheral neuropathy and myelosuppression are common, but generally manageable.

While adverse events tend to occur more commonly with higher doses, they usually improve or resolve after interruption of treatment, with re-challenge at half the dose after improvement of the symptoms. Immediate dose reduction without interruption is also an option for mild to moderate adverse events.

The following guidelines are intended to guide investigators in managing linezolid specific toxicities. Decisions must be made in the context of the overall health status of the participant. Discuss with the Clinical Medical Monitor if there is uncertainty. Efforts should be made for participants to complete at least 8 weeks of LNZ 600mg/day before discontinuing LNZ altogether.

8.2.1. Myelosuppression

Platelets and absolute neutrophil counts are variable, and results should be repeated (within 3 days) before interrupting LNZ. Exclude other causes as far as possible, i.e. concomitant medications, known infective processes.

Interrupt LNZ if:

- Confirmed Absolute Neutrophil Count (ANC) – grade 3 or higher
- Confirmed platelets – grade 3 or higher

Haemoglobin levels do not have the same variability. If the haemoglobin is below 8.0g/dL, LNZ must be interrupted and haemoglobin repeated at least weekly. LNZ may be restarted when the Hb is more than 8.0g/dL.

Re-challenge LNZ once counts have improved. If no or little evidence of improvement within 1-2 weeks, continue investigating for other causes.

8.2.2. Peripheral Neuropathy

Peripheral neuropathy may be more common when participants have other conditions or treatment that may also cause peripheral neuropathy, notably diabetes mellitus, HIV, medicines including the thymidine analogues in HIV treatment, and terizidone and INH in TB treatment. It is more commonly seen after several months of treatment.

The more commonly seen progression of symptoms is as follows: participant complains of coldness or numbness of the distal feet, which tends to progress to pins and needles, and sometimes a burning sensation. Some participants complain of a cramping sensation. These symptoms tend to move proximally with time. Objectively the investigator may note an antalgic gait and toe-walking, hyperesthesia, and reduced vibration sense at the first metatarsal joint.

The decision to interrupt the LNZ dose is usually made in consultation with the participant, as participants have differing levels of tolerance for this adverse event.

Generally, once peripheral neuropathy is judged to interfere significantly with walking or sleeping, and there is pain, either pins and needles or burning, the LNZ dose should be interrupted and re-challenged at half dose after the participant experiences improvement in symptoms. If there is no vibration sense at the toe, or symptoms are said to spread to the level of the knee or higher also interrupt LNZ.

Since this adverse event is believed to be related to mitochondrial toxicity, it is possible that symptoms will continue to worsen before they subjectively improve. Interruptions often span several weeks. If significant enough, LNZ may be permanently discontinued. Contact Clinical Medical Monitors if uncertain.

Analgesia is usually ineffective, with opioids leading to dependence after extended periods. Some participants find gabapentin/pregabalin helpful.

8.2.3. Optic Neuritis

Investigators should have a high index of suspicion for this adverse event, and participants should be counselled to inform the site if any visual changes are noted. Fortunately, optic neuritis from LNZ seems to be reversible if detected early. A drop in distance visual acuity of two or more lines or new visual symptoms requires further investigation and interruption of LNZ. Exclude other causes, i.e. participant not wearing glasses/contact lenses, migraine, etc. If optic neuritis is likely or confirmed LNZ should not be re-challenged.

8.2.4. Lactic Acidosis

Lactic acidosis should be suspected if participants report nausea and/or vomiting, tiredness, or other symptoms of lactic acidosis. Exclude more common causes of the symptoms. If suspected, investigate further and manage appropriately. If confirmed interrupt LNZ and other possible causative medicines, e.g. antiretroviral treatment, until improved.

8.3. Liver toxicity

Many anti-TB drugs can cause alterations in liver function tests. Participants entering this trial will have active TB. Elevation in liver function tests is not unexpected. Concomitant illnesses, including HIV infection, and other medications, such as ART, including DTG, may also alter these laboratory parameters. Therefore, changes in liver function enzymes or ALT should be evaluated within the clinical context of the abnormalities. All participants who have new Grade ≥ 3 elevation of ALT should be evaluated for hepatitis A, B and C virus infection and have a full LFT and an INR checked.

For participants with normal or Grade 1 LFTs at entry who develop asymptomatic or symptomatic Grade 3 elevations during study treatment, study TB drugs and DTG, where applicable should be interrupted until levels and symptoms are Grade ≤ 2 , at which time therapy may be reintroduced.

For participants entering the study with a Grade 2 elevation, they will be allowed to continue on study drugs unless they are symptomatic or the investigators feel it is unsafe for the participant to continue the medication.

If Grade 3 toxicity develops after re-introduction of the study medications and the Grade 3 toxicity does not resolve within 14 days, then the participant may be discontinued from study medications and expert advice will be sought. The participant will continue to be followed on study, on appropriate therapy.. All medications may be restarted if the laboratory abnormalities were thought secondary to a concomitant illness. Study TB drugs (but not DTG) can be restarted if there has been documented acute viral hepatitis and the ALT or bilirubin take longer than 14 days to reach Grade ≤ 2 toxicity.

Study TB drugs and study ART will be interrupted if any of the following liver chemistry criteria are met:

- ALT $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN (>35% direct bilirubin; bilirubin fractionation required)
- ALT $\geq 3 \times$ ULN with symptoms of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
- Grade 4 elevation of ALT or direct bilirubin

In consultation with the Clinical Medical Monitors, careful assessments should be done to rule out the use of alcohol, non-study medication-related toxicity, or viral hepatitis (including viral hepatitis complicated by immune reconstitution inflammatory syndrome) as the cause for any liver toxicity that warrants permanent study drug discontinuation based on the liver stopping criteria specified above.

Evaluations to be considered (but are not required) include:

- Viral hepatitis serology including: Hepatitis A IgM antibody; Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (IgM)
- Syphilis screening
- Drugs of abuse screen including alcohol
- Liver imaging to evaluate liver disease

Reintroduction of TB and ART drugs can be discussed with the Clinical Medical Monitors.

8.4. Cardiac safety guidelines

Participants in this trial will be receiving at least three agents (BDQ + DLM and CFZ) that have the potential to prolong the QTcF interval. Grading will be based on the average of triplicate ECGs at each visit.

The following should be adhered to:

- Grading by clinical symptoms should be based on the investigator's opinion that the symptom is possibly/probably/definitely related to study medications.

Grading will be as follows:

Table 8: Grading of QTc

Grade 1	Grade 2	Grade 3	Grade 4
		Absolute QTcF >500 ms	Life-threatening consequence, e.g., torsades de pointes or other associated serious ventricular dysrhythmia.
Any one of the following clinical symptoms (one event, without clear evidence of non-cardiac etiology): • Syncope • Chest pain	Recurrence/ongoing clinical symptoms (without clear evidence of non-cardiac etiology): • Syncope • Chest pain • Palpitations	Recurrence/ongoing clinical symptoms – with evidence of ventricular tachycardia* • Syncope • Chest pain • Palpitations • Dizziness	

*Note that the presence of ventricular tachycardia (VT) is the adverse outcome to be avoided/identified; the symptoms are surrogates for “possible” VT, but if VT is demonstrated, then participant’s Study Strategy will be permanently discontinued irrespective of QTcF or symptoms.

*Prior safety monitoring included change in QTcF from baseline. The ACTG 5343 study was a study conducted combining BDQ and DLM and it showed that QTcF increases when BDQ and DLM are co-prescribed, are no more than additive.^{lxx} Measures of QtcF change from baseline have not shown to be related to risk of cardiac arrhythmia. Many participants have differences from baseline of more than 60ms, but QtcF still within normal limits. In stable participants with QtcF less than or equal to 480, but change from baseline of more than 60ms, it is reasonable to repeat ECGs every 2 weeks, with more frequent monitoring at investigator discretion.

Management will be as follows:

- The immediate clinical management of participants should be based on the site’s interpretation of the ECGs, unless a report from the central readers of ECGs is available.
- Electrolytes include at least: Potassium, Magnesium and Calcium. Also test TSH if participant is at risk of hypothyroidism.

Table 9: Management of QtcF increase

ECG determined or clinical cardiac toxicity		
Severity	Study drug use	Follow up and management
Grade 3 (ECG)	Hold regimen	• Participant will be hospitalized for monitoring until the abnormality returns to Grade ≤ 2. • Correction of electrolytes where necessary. • Repeat ECG following repletion of electrolytes, and if QTcF reading is Grade ≤ 2, study TB regimen may be restarted, at the discretion of the investigator. • If Grade 3 finding remains, study TB drugs will be permanently discontinued.
Grade 3 or 4 (cardiac		• Participant will be hospitalized and discontinued permanently from study TB regimen.

clinical criteria)	Permanently discontinue regimen	• The participant will be referred to the SA NTP for treatment of their DR-TB according to local standards of care. • The participant will continue to be followed on study, off study drugs.
Grade 4 (ECG)		

9. Safety reporting

9.1. Definitions

Adverse Event:

Any untoward medical occurrence that may present during treatment with a medicine/intervention but which does not necessarily have a causal relationship with this treatment

Adverse Drug Reaction or Adverse Reaction:

A response to a medicine/intervention which is noxious and unintended.

The phrase 'response' means that the causal relationship between the medicinal product/intervention and the adverse event is at least a reasonable possibility.

Unexpected Adverse Reaction:

One in which the nature, specificity, severity and outcome is not consistent with the applicable product information (i.e. with the approved package inserts for registered products, or the investigator's brochure or other product information for unregistered products).

Serious Adverse Event or Serious Adverse Drug Reaction:

Any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability / incapacity, or
- is a congenital anomaly / birth defect
- is a medically significant / important event or reaction

9.2. Adverse Event Reporting

Symptoms or conditions that occur prior to randomization will be recorded in the participant's medical history as pre-existing conditions. All new or worsening symptoms or conditions that occur following randomization will be considered AEs and will be recorded on the AE CRF. Only Grade 3 and 4 will be reported in the CRF. AEs that are ongoing at the time of study exit will be followed up for up to 30 days after study exit and then, if not resolved, will be referred to a health care provider for further follow-up. After this period sites must report serious, unexpected, clinical suspected adverse drug reactions if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

Study staff will document in source documents and the appropriate CRF AEs reported by or observed in enrolled participants. Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. The relationship of all AEs to study product will be assessed as either related or not related.

Study participants will be provided a 24-hour telephone number and contact information and instructed to contact the study clinician to report any AEs they may experience. For life-threatening events, they will also be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where the study clinician is based.

9.3. Grading of Adverse Events

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017 must be used and is available on the DAIDS RSC Web site at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>

Table 10: Relatedness of AEs

Relatedness Rating		Definition
Not Related	Unrelated	An adverse event, which is not related to the use of the drug.
Unlikely	Unrelated	An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s) or concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible	Related	An adverse event, which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s) or concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.
Probable	Related	An adverse event, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by dechallenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	Related	An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

9.4. Safety Reporting requirements and timelines

Please refer to the approved, most up-to-date BEAT Tuberculosis Clinical Medical Monitoring Plan for instructions on the medical and safety oversight of trial participants, including safety reporting to:

- Wits Human Research Ethics Committee (HREC)
- South African Health Products Regulatory Authority (SAHPRA)
- Other applicable review bodies

9.5. Notable events

In addition, the following should be reported to the Clinical Medical Monitors as notable events:

- All Grade 3 and 4 cardiac events
- All treatment emergent Grade 3 or 4 liver toxicity
- If one or more drugs are suspended permanently due to severe toxicity
- All pregnancies occurring in the female participants while enrolled on the trial either on treatment or in follow up

All notable events must be reported to the Clinical Medical Monitors within 72 hours of site awareness.

9.6. Protocol deviation definitions and reporting

Protocol deviations are classified into five grades as follows:

- Grade 1: No impact on data quality or patient safety
- Grade 2: Minor impact on data quality
- Grade 3: Minor impact on patient safety
- Grade 4: Major impact on data quality or patient safety
- Grade 5: Leading to patient/(s) death

Please refer to: Ghooi, Ravindra Bhaskar et al. "Assessment and classification of protocol deviations." Perspectives in clinical research vol. 7,3 (2016): 132-6. doi:10.4103/2229-3485.184817

Please refer to the most up to date clinical medical monitoring plan for more guidance on protocol deviations. Deviations should be reported to the regulatory authorities in accordance with the policies and procedures of these review bodies.

All protocol deviations will be submitted to the Data Monitoring Committee (DMC) which will be reviewed at the 6 monthly meetings. If the DMC review results in a change in the grade, this decision will be communicated to the applicable regulatory authorities.

10 Statistical considerations

10.1 Sample size calculation

The primary objective of the trial is to evaluate the efficacy and safety of the Study Strategy, specifically to demonstrate that the Studystrategy has non-inferior efficacy to the Control Strategy.

The table below shows the power that would be available to demonstrate non-inferiority with a total sample size of 400 (200 in each arm), using a 10% margin of non-inferiority and two-sided 5% significance level. A 10% margin is considered an appropriate reduction in efficacy given the benefits of the shorter regimen and the streamlined treatment strategy, and is also consistent with recent phase III MDR-TB trials that have used 10% (STREAM Stage 1 and 2) or 12% (endTB and endTB-Q) margins of non-inferiority.

Since this is a pragmatic trial with broad eligibility criteria including almost all those diagnosed with RR-TB by GeneXpert, the primary analysis will include all randomized participants and there will be no exclusions and therefore no need to account for a lost to follow-up or 'not assessable' number in the sample size calculations (all those without cure will be considered as 'not cured', see definitions of primary efficacy outcome above).

Table 11: Power with a total sample size of 400

Proportion cured in Control Strategy	Absolute increase in proportion cured in intervention strategy		
	0.0	0.02	0.05
0.60	53.6%	69.4%	87.4%
0.65	55.7%	71.9%	89.4%
0.70	58.9%	75.3%	91.9%
0.75	63.5%	80.0%	94.7%
0.80	70.0%	85.8%	97.4%

The proportion of patients with cure was approximately 80% in both arms on the DLM study 213 and also on both the long regimen and short regimen in the STREAM Stage 1 trial.

We would expect poorer outcomes on the Control Strategy in this trial due to the wider eligibility criteria. Nevertheless, it is reasonable to assume a higher proportion of cures on the Study Strategy due to the shorter duration resulting in fewer on treatment losses to follow-up and the expected modest increase in efficacy.

A total sample size of 400 participants gives 87.3% power to show non-inferiority assuming a proportion cure of 0.60 in the Control Strategy and 0.65 in the study strategy (an absolute increase of 0.05) or 89.4% assuming a proportion cure of 0.65 in the Control Strategy and 0.7 in the Study Strategy.

10.2 Interim analyses

There will be no formal interim analyses of the data, but the Data Monitoring Committee (DMC) will review efficacy and safety data every six months after commencement of recruitment or as required. The DMC will also consider failure rates, and give attention to mortality data; reviewing numbers and cause of failure/death by treatment arm. Recommendations to stop the trial prematurely will be based only on safety considerations; therefore no type I error correction will be done for the primary analysis. Further details of the role and function of the DMC is given in the DMC charter

10.3 Preliminary analysis plan for primary endpoints

All participants included in the analysis will be analyzed in the treatment group to which they were originally assigned.

Detailed analysis plans for the primary and secondary analyses will be developed and approved prior to database lock. These will include details of a number of sensitivity analyses.

In general, the primary efficacy analysis will be based on the intention to treat analysis (ITT) population, including all participants randomized into the study. Since this is a strategy trial, there will be no exclusions from this analysis, all participants will be classified according to the primary outcome classification above.

For the primary analysis, the difference in proportion of participants with a successful outcome at the end of treatment and at the end of follow up at 76 weeks after randomization between the study and control strategies with 95% confidence intervals will be estimated. The analysis will be stratified by the randomization stratification factors. Non-inferiority will be shown if the upper bound of the 95% confidence interval of the difference in proportion of successful outcomes between control and study strategies is less than the 10% margin of noninferiority.

The proportion of participants with a primary safety outcome (see above for definition) will be estimated, and the difference in proportion will also be calculated with 95% confidence intervals.

If treatment is modified or extended for participants allocated to either strategy, they may still be on treatment at the final follow-up visit 76 weeks after randomization. In this situation, for the primary efficacy outcome classification, the end of treatment outcome will be defined at this time-point (or the last participant visit while on treatment) and the end of follow-up outcome will be considered to be the same as the end of treatment outcome.

10.4 Preliminary analysis plan for secondary endpoints

An important secondary endpoint is the composite efficacy / safety endpoint. Participants will be considered to have a successful endpoint in this analysis if they have a successful primary efficacy endpoint and have not had a grade 3 or more adverse event (the primary safety endpoint).

The difference in proportion of participants with a successful outcome (for this endpoint between the study and control strategies with 95% confidence intervals will be estimated. The analysis will be stratified by the randomization stratification factors. The objective is to demonstrate superiority of the study strategy in this endpoint.

Further details of analyses for secondary endpoints will be provided in the statistical analysis plan.

10.5 Sub-group and sensitivity analyses

The primary analysis will be repeated in sub-groups defined by each of the following variables:

- HIV status
- Whether the mycobacteria are sensitive to fluoroquinolones at baseline
- Cavitation
- Site

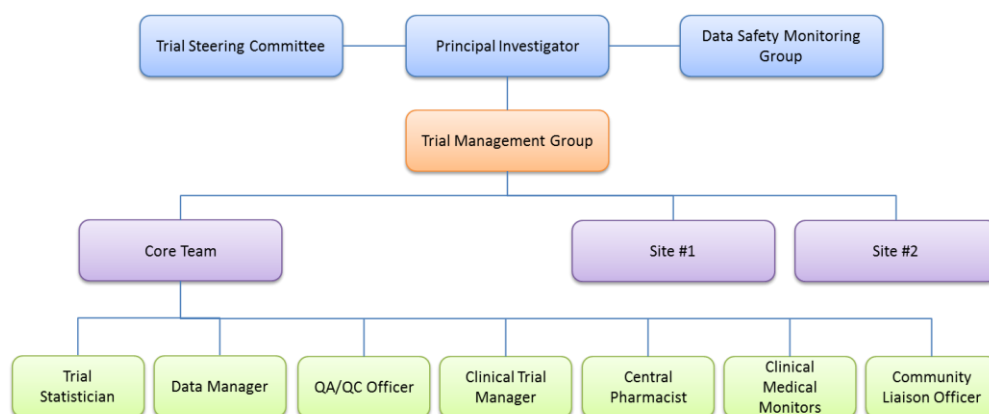
A sensitivity analysis will be conducted whereby the primary analysis will be repeated where lost to follow-up after the end of treatment will be classified as unsuccessful rather than successful.

Further sub-group analyses and sensitivity analyses will be described in the statistical analysis plan.

11 Trial management committees

11.1 Trial Management Group (TMG)

BEAT tuberculosis' implementation structure will consist of a Trial Management Group (TMG) that will be headed by the PI. The core group will be based in Johannesburg.



The Principal Investigator will lead the trial management group (TMG) consisting of a clinical trial manager, trial statistician, data manager, QA/QC officers, Clinical Medical Monitors, central pharmacist and community liaison officer.

11.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall strategic oversight for the BEAT Tuberculosis study on behalf of the PI and USAID. The TSC will ensure that the BEAT Tuberculosis activity is conducted to the rigorous standard set out by the South African Department of Health Guidelines for Good Clinical Practice (GCP). The TSC will provide advice to the PI on all aspects of the BEAT Tuberculosis activity. It will concentrate on progress of the trial/project, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question. The TSC should agree on proposals for substantial protocol amendments and provide advice to the sponsor and funder

regarding approvals of such amendments. Although there may be periods when more frequent meetings are necessary, the TSC should meet at least annually. Terms of Reference (TOR) have been drafted and members have agreed to participate.

12 Data Monitoring Committee (DMC)

This is an independent group of experts that will advise the BEAT Tuberculosis TSC and TMG. The members of the DMC will serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DMC is to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and make recommendations to BEAT Tuberculosis TSC and TMG concerning the continuation, modification of inclusion criteria, or termination of the trial. Further details of roles and responsibilities are provided in the DMC charter.

12.1 Record and Data Management

12.1.1 Source Documents

Source documents are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents will include, but are not limited to, progress notes, in-patient hospital records, electronic data, screening logs, and recorded data from automated instruments.

All source documents pertaining to this trial will be maintained by the Investigators. The Investigator has to permit trial related monitoring, audits, Wits Human Research Ethics Committee (HREC) review and South African Health Products Regulatory Authority (SAHPRA) regulatory inspections providing authorized personnel direct access to source documents, including documents required to confirm inclusion/exclusion and relevant in-patient records while participants are on trial treatment

12.1.2 Central Data Management

Data Management will be centralized within the PHRU Data Management Centre, and responsibilities include: coordinating and managing the CRF development process, designing and validating the study database, developing a Data Quality Management Plan and implementing central data quality management. Data quality will be monitored with metrics being communicated to both the site and the protocol team. Quality control reports and queries routinely will be generated and distributed to the study sites for verification and resolution.

Data exports for interim and final analyses and safety reporting will be provided as required by the protocol team.

12.1.3 Data Storage

Study records will be kept in participant specific binders at the site. The binders will be stored by each clinic in a secure and hazard free data storage environment, with double lock. Access will be restricted to authorized study personnel.

Database files will be password-protected and access to the files will be limited to authorized study staff members only. All data will be backed up at regular intervals, and backups will be stored in secure areas with limited access.

12.1.4 Data collection

CRFs will be completed on all participants who sign informed consent. For screening failure participants, a CRF page will be completed with the reason for failure. For participants who are withdrawn prematurely, all the visits the participants attended need to be completed

12.1.5 Case Report Forms (CRFs)

CRFs will not be used as source for this study. Participants will not be identified by name on any CRFs. Participants will be identified by a unique study number provided by the Data Management Center (DMC) upon randomization.

12.1.6 CRF Development

CRFs will be adapted for use in DataFax using Adobe FrameMaker. CRFs will be version controlled. A copy of the blank CRFs will be filed in the Data Management Study File (DMSF). Each new CRF version must be approved by the Principal Investigator, Statistician, Data Manager and Quality Assurance Reviewer. The CRF Approval Form must be signed and filed in the DMSF, together with blank copies of the new CRF(s).

12.1.7 Participant Confidentiality

No personal participant information will be collected on any CRF developed for this study in order to protect the participants' privacy.

12.1.8 Quality control and Quality assurance

The QA/QC officers from the Beat Tuberculosis Core team will visit participating clinical research sites to review the individual subject records. This will include consent forms, enrollment procedures including eligibility criteria, CRFs, supporting data, laboratory specimen records, and medical records

(physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study subjects, adherence with the protocol, and accuracy and completeness of records. This will include accurate recording and reporting of Adverse Events. The QA/QC officers will also inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management. Additional activities or study elements may be monitored as needed.

The site investigator will make study documents (e.g., consent forms, drug accountability records) and pertinent hospital or clinic records readily available for inspection by QA/QC officers, the local IRB/EC, other regulatory bodies, and the industry supporter or designee for confirmation of the study data.

Each site will have a written plan for local quality control including data quality management

13 Ethics and regulatory

This research will be carried out in accordance with International GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

The protocol and required trial related documents will be reviewed by the Wits HREC. The trial will not start until the HREC has approved the protocol, written informed consent, any written information to be provided to the participant or any modification thereof, plus any other trial related documents required for review.

13.1 Regulatory Authorities

SAHPRA will receive the protocol, amendments, reports on SAEs, and the Integrated Clinical Trial Report. Written approval will be obtained from the Regulatory Authorities prior to commencement of the trial and implementation of e.g. amendments as applicable.

13.2 Informed Consent

Written informed consent will be obtained from all participants (or legally acceptable representative) before any trial-related procedures (including any screening or pre-treatment procedures) are performed. Informed consent will be taken by the investigators or designees as per the site standard operating procedures. The informed consent document will be translated from English into the local languages spoken in the area of the clinical sites. For participants who are unable to read at the level of Standard 8, an independent witness will be present at the time of the discussion. This independent witness could be a family member, friend or a staff member from the clinic but not employed by the research unit but acceptable to the participant. Investigators may discuss the availability of the trial and the opportunity for entry with a potential participant without first obtaining consent. However,

informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

Written assent will be obtained from all participants who are minors (less than 18 years of age), confirming their willingness to participate in the trial. In addition to this, the accompanying parent or legal guardian must also provide consent for the child to take part. The original signed informed consent form will be kept with the trial records and a copy of signed informed consent form will be provided to the participant or the participant's legally authorized representative. Another copy of the signed informed consent form and a source document identifying the trial and recording the dates of participation will be placed in the participant's medical record.

The monitor will inspect the original completed consent form(s) for all participants.

13.2.1 Confidentiality

All site staff, the Sponsor, and any sponsor representatives will preserve the confidentiality of all participants taking part in the trial, in accordance with International GCP, applicable local legislation/regulations. Subject to the requirement for source data verification by the trial personnel by reference to the participant's notes, confidentiality of all participant identities will be maintained. Unique identifiers will be used on the CRF and in all trial correspondence, as permitted. The written informed consent will contain a clause granting permission for review of the participants' source data by the sponsor or designees.

14 Publication policy

The results of the study will be presented at national and international meetings and in peer reviewed journals irrespective of the results.

15 Protocol Amendment policy

Protocol amendments as needed will be presented to and approved by the TSC then submitted to the SAHPRA and the Wits HREC for approval.

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