

**PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT (FOR PARTICIPANTS WHO
ARE 18 YEARS OF AGE OR OLDER)**

STUDY NUMBER: BEAT Tuberculosis (Building Evidence for Advancing new Treatment for Tuberculosis)

STUDY TITLE: 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)

SPONSOR: USAID (United States Agency for International Development)

PRINCIPAL INVESTIGATOR: Dr Francesca Conradie

INSTITUTION: Isango Lethemba TB Research Unit

DAYTIME AND AFTER HOURS TELEPHONE NUMBER(S): _____

To the potential participant: This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

1. Introduction

Good day, my name is _____. I am a _____ at the Isango Lethemba TB Research Unit. I would like to invite you to consider participating in a research study, called BEAT Tuberculosis (Building Evidence for Advancing new Treatment for Tuberculosis), to look at a new combination of tuberculosis (TB) medicines.

You are being asked to take part in this research study because you are infected with TB in your lungs. This strain of TB is resistant to at least one of the TB medicines, called rifampicin, that is currently used for treating TB. This study is sponsored by USAID (United States Agency for International Development). The doctor in charge of this study at this site is Dr Francesca Conradie. Before you decide if you want to be a part of this study, we want you to know about the study.

- a) Before agreeing to participate in this study, it is important that you read and understand the following explanation of the purpose of the study, the study procedures, benefits, risks, discomforts, and precautions as well as the alternative procedures that are available to you, and your right to withdraw from the study at any time.
- b) This information leaflet is to help you to decide if you would like to participate. You need to understand what is involved before you agree to take part in this study.
- c) If you have any questions, do not hesitate to ask a study staff member.

- d) You should not agree to take part unless you are satisfied about all of the procedures involved.
- e) You may not participate in another investigational medicine research study, nor take any other investigational medicine during your participation in this study.
- f) You should not have participated in an investigational medicine research study within the past 28 days.
- g) Please be open with the study team regarding your health history, since you may otherwise harm yourself by participating in this study.
- h) If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.
- i) If you have a personal doctor, please discuss with or inform him/her of your possible participation in this study. If you wish, the study team can also notify your personal doctor in this regard.

2. The purpose of this study

You have been diagnosed with rifampicin resistant tuberculosis (RR-TB). Currently in South Africa, this type of TB is being treated with 7 medicines called bedaquiline (BDQ), linezolid (LNZ), isoniazid (INH), levofloxacin (LVX), ethambutol (EMB), pyrazinamide (PZA) and clofazimine (CFZ), and the treatment duration is usually for a total of 40 - 48 weeks, but the treatment can be as long as 76 weeks. This is called the South African Standard of Care Regimen based on recommendations from the World Health Organization (WHO).

The purpose of this study is to determine if a new combination of 5 medicines called bedaquiline (BDQ), delamanid (DLM), linezolid (LNZ), with levofloxacin (LVX) and/or clofazimine (CFZ), taken together for 24 weeks, will treat and cure your type of TB. This is called the Study Strategy. The study will also look at the safety of these medicines and if this new combination of medicines works as well as the standard of care in treating your TB.

This study will compare the Study Strategy with the South African Standard of Care Regimen, also known as the Control Strategy, and you will be randomly assigned to one of these two strategies.

3. Length of the study and number of participants

- The study will be performed at 2 sites in Port Elizabeth in South Africa.
- Approximately 400 participants will participate in this study, across both study sites.
- The participants will be 6 years of age or older.
- The total amount of time required for your participation in this study will be a maximum of about 76 weeks.
- You will be asked to visit the research unit a minimum of 16 times during the study, this depends on which treatment strategy you are randomized to and when you complete your treatment.

4. Procedures

If you agree to take part in this study, you will first be asked questions and be examined to see if you qualify for this study.

Before receiving your first dose of medicine, you will be randomly assigned on a 1:1 ratio (purely by chance, like flipping a coin) to receive one of the two possible treatment strategies. This study is open label, which means that everyone, including you and your study doctor will know what medicines you will receive and how long you will receive them for. All the medicines in both strategies are tablets that need to be swallowed.

The study is divided into 3 parts:

Part	Name	Length	Reason
1	Screening	Up to 30 days	During this time, the study doctor is checking if you meet the requirements and if it is safe for you to be part of the study. This may be several visits in a period of up to 30 days. If you do not meet all of the requirements when you are screened, you may have the opportunity to be screened again at a later time if the study doctor thinks you would be able to meet the requirements then.
2	Treatment	40 weeks, which could be extended to 48 weeks or up to 76 weeks (Control Strategy) Or 24 weeks, which could be extended to 36 weeks (Study Strategy)	You will receive medicine depending on the treatment strategy you have been randomized to. If the study doctor determines that you need to pause your treatment for any reason, then your treatment may extend longer than the prescribed length of time. If your TB has not improved after 16 weeks of treatment, your study doctor may also decide to extend your treatment.
3	Follow Up	36 weeks or less (Control Strategy) Or 52 weeks or less (Study Strategy)	After you finish taking the medicines, and to make sure that your TB has not come back, your study doctor will check on your health until the week 76 visit. During this time, you may not be taking the medicine from this trial but you will visit the hospital at least 5 times if you are on the Control Strategy and 7 times if you are on the Study Strategy.

One of the two treatment regimens is the **South African Standard of Care Regimen or Control Strategy**, which is made up of the following medicines, taken for a total of about 40 - 48 weeks:

- Bedaquiline
- Linezolid
- Isoniazid
- Levofloxacin
- Ethambutol
- Pyrazinamide
- Clofazimine

The duration of this regimen is usually 40 weeks, however depending on laboratory results and your clinical condition, the treatment can be extended to 48 weeks or 76 weeks with extra medication added, depending on how severe your TB is.

Control strategy doses

Product	Weight Group				
	16 - 23kg	23.1 - 29.9kg	30 - 33.9kg	34 - 50kg	More than 50kg
BDQ	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	
INH_{high dose}	300mg daily	400mg daily			600mg daily
LVX	375 - 500mg daily	500mg once daily		750mg daily	1000mg daily
E	400mg daily	600mg daily	800mg daily		1200mg daily
Z	750mg daily	1000mg daily	1250mg daily	1500mg daily	2000mg daily
CFZ	100mg three times a week or 50mg daily	100mg daily			

If you are randomized to the Control Strategy, at the time that you start your medicines (at the randomization visit), a sputum sample will be sent to the laboratory to test whether your strategy will stay the same or if it will be changed as per the most up-to-date approved South African National TB Programme Guidelines. This decision will be made at approximately 4 weeks after you start your medicines, when the laboratory results become available. The tests that are performed on your sputum sample tell us if the type of TB that you have is resistant or sensitive to second-line medicines. This is routine practice for the treatment of DR-TB in South Africa.

The other treatment regimen is the **Study Strategy**, which is made up of the following medicines:

- Bedaquiline
- Linezolid
- Delamanid
- Clofazimine
- Levofloxacin

The duration of this strategy is 24 weeks, however depending on laboratory results and your clinical condition, the treatment can be extended to 36 weeks.

Study strategy doses

Product	Weight Group				
	16 - 23kg	23.1 - 29.9kg	30 - 33.9kg	34 - 50kg	>50kg
BDQ	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	

LNZ	180 - 210mg (crush 1 tab and mix in 10ml water, administer 3-3.5ml. Discard rest)	300mg daily	450mg daily	600mg daily	
LVX	375 - 500mg daily	500mg once daily		750mg daily	1000mg daily
CFZ	100mg three times a week or 50mg daily	100mg daily			

If you are randomized to the Study Strategy, at the time that you start your medicines (at the randomization visit), a sputum sample will be sent to the laboratory to test whether you should stay on the medicines as they are or have one of the medicines (either clofazimine or levofloxacin) stopped. This decision will be made at approximately 4 weeks after you start your medicines, when the laboratory results become available. The tests that are performed on your sputum sample tell us if the type of TB that you have is resistant or sensitive to second-line medicines.

For both strategies, you will be given the medicines at each visit during the treatment period and asked to bring back all empty packets and unused medicines to your next visit.

Below is a **list of the visits** and what will happen at each visit during the study, for both treatment strategies. Depending on your response to the medicines and study procedures, there may be some changes to the treatment visits and procedures, and how long you stay in the study.

	Up to 30 days	Treatment Visits: Study Strategy								*Post-Treatment Follow-up Visits														
		Treatment Visits: Control Strategy												*Post-Treatment Follow-up Visits										
^Procedure	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																							
Inclusion & exclusion criteria	X	X																						
Chest X-ray	X	As clinically indicated																						
Pregnancy Testing	X	X	As clinically indicated																					
Medical & Treatment History	X	X																						
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood tests	X		X	X	X	X	X	X	X	X	X	As clinically indicated												
ECG	X		X	X	X	X	X	X	X	X	X	X	X	X										
Triangle ECG measurement			X	X		X			X															
Eye Exam (screening and if you are taking LN2)	X		X		X	X	X	X	X	X	X	X	X	X	X									
Nerve Exam	X				X	X	X	X	X	X	X	X	X	X	X	X								
Sputum Collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		
HIV testing	X									As clinically indicated														
HIV Viral Load & CD4 count (if you are HIV positive)	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 medication		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		
Adherence Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Intensive PK sampling				X																				
Dried Blood Spot sample				X																				
Sparse PK sampling				X		X			X															

* Monthly visits post-treatment for the first 3 months, followed by 3 monthly visits until week 76 is reached. All participants must attend the end of study visit (week 76). In line with the national policy, you will see the study nurse during these visits, unless the study nurse would like you to also see the study doctor.

^ The pharmacogenetic sample and trough clofazimine assay have not been listed in the table above as these procedures are not assigned to a specific study visit.

Procedures explained

Signed informed consent:

Signed Informed Consent which includes consenting to HIV testing, if applicable.

Demography:

This is personal information you will be asked for including your full name, date of birth, age, gender, ethnicity and education level.

Inclusion & exclusion criteria:

This is a process of checking that you meet the study requirements and to make sure it is safe for you to take part.

Chest X-ray:

This is a photograph of your lungs.

Pregnancy testing:

- If you are a woman who is able to have children, your urine will be tested to see if you are pregnant, whether or not you are sexually active.
- If you know you are pregnant at the screening visit, your urine will still be tested to confirm the pregnancy. If your urine test shows you are pregnant, you will be given the choice to take part in the study, and if you agree to take part, you must sign a separate consent form: the PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT FOR PARTICIPANTS WHO ARE PREGNANT (>18 YEARS).
- If you are not pregnant at the screening visit but you think you may be pregnant at any time during the study, please tell the study staff right away. The study staff will talk to you about your choices. Please note that you If you are planning to become pregnant during the study, you may not take part in the study.
- If you become pregnant while taking your treatment, you will be given the choice to stay on the study and if you agree to this, you must sign a separate consent form: the PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT FOR PARTICIPANTS WHO ARE PREGNANT (>18 YEARS). If you choose not to stay on the study, then you will be withdrawn from the study and referred to the National TB Programme where you will continue your healthcare. All aspects of healthcare related to your pregnancy and infant will be your responsibility.
- We would like to know the outcome of the pregnancy. If the outcome of the pregnancy is not known by the time of the last scheduled study visit (Week 76), or you have withdrawn yourself from the study, then the study staff will arrange to contact you for information about the outcome of the pregnancy. We would also like access to your medical records and those of your baby, from the time you became pregnant and for a minimum of six weeks after the baby is born.
- If you are HIV infected, you will be offered a new medicine called dolutegravir. This medicine has been associated with problems to unborn babies. While you are taking this medicine, you are advised to use safe contraception. If you suspect you may be pregnant, please come to the research unit immediately.

Medical & treatment History:

You will be asked about your medical (including alcohol use) and surgical history. You will also be asked about your HIV treatment history (if applicable).

Physical examination:

This will happen at every visit and it is an assessment of your body to check for signs of disease. It includes height (only at screening), weight and a measurement of your blood pressure, heart rate, breathing rate and body temperature.

Blood tests:

Blood will be taken from you by inserting a small needle into a vein in your arm. The blood will be tested to check if you are healthy and that the medicines are not doing you any harm. A total of about 390mL (milliliters) (78 teaspoons) of blood will be collected over the whole study, or about 20mL (4 teaspoons) at each study visit. It is possible that more blood will be taken if a side effect occurs.

ECG:

A test that is done by placing 12 sensors (like stickers) to your chest, arms and legs to check how your heart is working. This is a painless test and will not cause discomfort to you.

Triangle ECG sub-study (optional):

At the week 2, 4, 12 and 24 study visit, you will receive a 30-second ECG using the Triangle device, if you consent to this extra procedure. Participants will need to read and sign a separate informed consent form if they would like to take part in this sub-study.

Eye examination (at the visits where you are taking linezolid):

At the screening visit, this involves the medical history to do with your eyes as well as a vision check. If you are taking linezolid as part of your trial medicine, the study staff will check your vision by asking you to read the letters or symbols off a chart.

Nerve examination:

You will be asked to answer some questions about whether you experience any feelings such as a painful burning, stinging, tingling, a sensation of pins and needles or numbness in your feet and/or legs. The doctor will test your legs to see what your reflexes are like and if you feel vibrations.

Sputum collection:

At every study visit you will be asked to cough up sputum (phlegm) into a small cup. The sputum is used to check that you have TB, the type of TB you have, how many TB bacteria you have and what medicines will work on the TB bacteria. Tests on the sputum will also show us if the medicines you are taking are treating your TB.

If any of the sputum results show TB germs at the randomization visit or any visit afterwards, these will be stored, with your consent, and sent to a central laboratory to see if it is the same or a different TB bacteria to the one you were originally infected with.

HIV testing:

- The study staff will review medical records to see whether you are HIV-infected. If the medical records are not clear, the study staff will test you for HIV using an approved test, and if positive, confirmed with a second test.
- You will be counselled on HIV before the blood tests are taken and again once the results are given to you.
- Most HIV-positive (HIV+) participants will receive the antiretroviral (ARV) called dolutegravir (DTG) which will be given for the duration of your TB treatment. If you are HIV positive, and already on antiretrovirals (ARVs), you will be switched to DTG at the randomization visit. DTG is being used in this study because it will be the safest option to combine with the TB medicines. This medicine, DTG, is not safe in pregnancy so you will need to use safe contraception for as long as you are taking it.

HIV viral load (if HIV+):

If you are infected with HIV, we will measure the amount of HIV virus in your blood, only if you have not had a viral load done within the last 3 months. This is routine in HIV care.

CD4 count (if HIV+):

If you are infected with HIV, and have not had a CD4 count done in the last 3 months, we will measure your CD4 cell count (a kind of cell that fights infection). This is routine in HIV care.

Signs/symptoms, diagnoses:

At every visit the study staff will document any symptoms or diagnoses that you may experience at the study visit or since your last visit.

Trial medication:

At the randomization visit, and every visit thereafter, all of the medicines in your trial regimen including the doses will be documented.

Adverse events:

You will be asked if you have had any medical problems since your last visit.

Adherence assessment:

We would like you to choose at least one treatment supporter at your screening visit. This can be a relative, friend or even a nurse at the clinic. This person (or people) will sign for when you take your medicine every day. If possible, we would like to see this person (treatment supporter) when you come to the clinic and receive your medication for the first time and thereafter when asked to come in due to any adherence problems you may have.

Intensive pharmacokinetic (PK) sampling (optional):

At the week 4 visit, blood will be drawn 7 times over 24 hours and will only be done in 30 participants in both treatment strategies, who are 18 years of age or older and who must be taking clofazimine at the time of the sampling. Participants will need to sign a separate informed consent if they would like to take part in this additional procedure.

Dried blood spot sample (optional):

If you have consented separately to the intensive PK sampling which takes place at the week 4 visit, and you agree to take part in the dried blood spot procedure, a small amount of blood (50 microlitres) will be taken at the same time-points as plasma during the intensive sampling. We want to see if the dried blood spot method is as accurate as the pharmacokinetic (PK) sampling method for four of the anti-TB medicines: bedaquiline, levofloxacin, linezolid and clofazimine.

If you would like to take part in this extra procedure, you will need to give extra consent and only 20 participants will take part.

Sparse pharmacokinetic (PK) sampling:

Blood will be taken at weeks 4, 12 and 24 to check what happens to the medicines once you swallow it. This is for all participants, in both treatment strategies. Please do not take the morning dose of any of your medicines at these 3 visits. Bring all of your study medication to the research unit. The study staff need to give you the doses at a very specific time-only after your blood has been taken. It is important that when the blood is taken, that you do not have any medicines in your blood stream from that morning. Blood will be taken from you by inserting a small needle into a vein in your arm. About 8 milliliters (2 teaspoons) of blood will be taken from you for this test.

Pharmacogenetic sample (optional):

A maximum of 10ml of blood will be taken at one of the scheduled study visits but preferably as early on in the study as possible. The aim of this is to collect an additional blood sample to examine how differences in genes influence how participants respond to the TB medicines. Participants will need to sign a separate informed consent if they would like to take part in this additional procedure.

Trough clofazimine assay:

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

5. Will any of these study procedures result in discomfort or inconvenience?

Venipunctures (i.e. drawing blood) are normally done as part of routine medical care and present a slight risk of discomfort. Drawing blood may result in faintness, inflammation of the vein, pain, bruising or bleeding at the puncture site. A small blood clot may form at the site of the needle tube used for the PK sample collection, or there may be swelling in the area. There is also a slight possibility of infection. Your protection is that experienced personnel perform the procedures under sterile conditions.

A chest X-ray is a commonly used diagnostic procedure that exposes you to a small amount of radiation. Although all radiation is cumulative over your lifetime, small doses from X-rays should not create a significant risk to your health.

6. Risks of the study medicine

TB is a serious illness that can be fatal. The combinations of medicines used to treat TB have rarely been associated with serious side effects including death.

This is a list of the common risks or side effects of taking the medicines in both strategies:

Liver problems	May be associated with nausea and vomiting, stomach pain, fever, yellow eyes and dark urine. Liver problems may also be suggested by blood tests, which will be done regularly. In rare cases, liver problems can be serious and can lead to death.	Bedaquiline, linezolid, levofloxacin, isoniazid, pyrazinamide
Headache	Pain in the head	Bedaquiline, linezolid, levofloxacin, Isoniazid, pyrazinamide
Stomach problems	Pain in the abdominal area, nausea, vomiting or diarrhea	Bedaquiline, linezolid, delamanid, levofloxacin, Isoniazid, pyrazinamide
Joint pains	Sore and stiff joints	Bedaquiline, pyrazinamide

Aside from these common side effects, some of the medicines also have other side effects:

Bedaquiline: There may be a chance of a change in the heart rhythm or the way that the heart beats. This can be serious. We will be doing frequent checks of your heart by doing ECGs. If your doctor finds a problem, bedaquiline may be stopped or other corrective actions taken. This medicine also takes a long time to leave your body. It is often a year before it is entirely removed from your body.

Delamanid: Very few side effects.

Linezolid: This medicine can cause painful and numb feet, also called peripheral neuropathy. Your doctor will check the feeling in your feet at every visit while you are taking. If a problem develops, the linezolid dose may be halved or it may be stopped. In addition, linezolid can also cause a problem with your eyesight, called optic neuritis. Your doctor will check your eyesight at every visit. If you notice a change in your ability to see clearly, please come back to the clinic. Linezolid can

damage your bone marrow and stop it producing red blood cells, white blood cells and platelets. This is called myelosuppression. Your doctor will do regular blood tests to pick this up. If this side effect develops, your doctor will either stop your linezolid or halve the dose.

Isoniazid: In high doses can cause painful and numb feet, also called peripheral neuropathy. Your doctor will check the feeling in your feet at every visit while you are taking it. In addition, your doctor will give you a vitamin called pyridoxine to help prevent this.

Clofazimine: This medicine causes darkening of the skin. This usually happens after a month of treatment and it does go away once the treatment is stopped.

The other medicines that you will be given are all registered in South Africa and have been used for many years. Regular checkups are done to look out for any other side effects.

7. Unforeseen risks

The combination of medicines in the Study Strategy is new and investigational and there may be other risks or side effects which are unforeseen or unknown. You should immediately contact a study staff member if any side effects occur throughout your participation in this study.

8. Benefits

- There is a good chance that your TB may get better because you are in this study, but we cannot guarantee this. Therefore, you may not benefit from this study.
- However, the information that we get from the study can help in making future decisions about the treatments for TB, and in the long run it will likely help other TB patients.

9. Alternative treatment

This study compares two different treatment strategies or ways of treating TB. The one is the Study Strategy which is a new combination of approved medicines. These medicines were chosen based on other research work and because they have not been used a lot in the community. This means that it is not likely there will be any resistance. The other strategy is the country's standard of care treatment which you would normally receive from your clinic to treat the type of TB that you have, if you were not taking part in this study. This way of treating TB is based on agreement by specialists both in South Africa and overseas.

10. Benefits and risks of standard alternative treatment

If you choose to not be a participant on this study, you will continue to get treatment as per standard of care within South Africa from the TB program. This will include some of the study medicines.

11. Are there any warnings or restrictions concerning my participation in this study?

- If you are planning to become pregnant during the study period, you may not take part in the study.
- If you are a female, of reproductive potential (defined as having reached her first menstrual cycle and not having undergone a documented sterilization procedure such as hysterectomy, bilateral oophorectomy, or salpingectomy), and engaging in sexual activity that could lead to pregnancy, you must agree to avoid pregnancy and be willing to use effective contraception: either an intrauterine contraceptive device (IUCD) or a hormonal method for the duration of

the treatment regimen and for three months thereafter. It is required that the method would have had to be started at or before the time of randomization.

- You must also read and sign the Supplementary Informed Consent for Women of Childbearing Potential (this is for females of childbearing potential).

Why would the doctor take me off this study early?

The study doctor may need to take you off the study early without your permission if:

- The study is cancelled by USAID, local regulatory authorities or the site's Research Ethics Committee. An ethics committee is a committee that watches over the safety and rights of research participants.
- A data monitoring committee (DMC) recommends that the study be stopped early. A DMC is an outside group of experts that monitors the study.
- You are not able to attend the study visits as required by the study.
- You are not able to take the medicines as required by the study.

The study doctor may also need to take you off the treatment regimen without your permission if:

- Continuing the study medicines may be harmful to you.
- You need a treatment that is not allowed to be taken while on the study medicine.

What if I am not able to come to the appointments?

It is very important that you attend all of the study visits that are described. If you do not think that you will be able to attend all of these visits, then you may not want to participate in this study. However, if you think that you can attend all of the appointments but then find out later that you cannot, we would like your permission to continue to contact you. We would contact you by telephone as necessary (about five times) and ask questions about your health and wellbeing. These contacts would continue until your participation in the study would have ended if you had continued (76 weeks after randomization).

12. Interactions

It is important that you let a staff member know of any medicines (both prescriptions and over-the-counter medicines), herbal or traditional medicines, alcohol or other substances that you are currently taking. These medicines are not allowed during the treatment period.

During this study, you should not take these medicines:

- a) The systemic use of moderate and strong CYP3A4 inhibitors (including : amiodarone, erythromycin, , miconazole, diltiazem, verapamil, conivaptan, clarithromycin, telithromycin, nefazodone, itraconazole and 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 medicine 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 (registration required).
- d) Selective serotonin reuptake inhibitors (SSRIs) as co-administration with linezolid increases the risk for the serotonin syndrome.

This list is long but it is important that you know which medicines you are not allowed to take. If you do go to a different clinic, please show this list to any doctor or nurse you may see so they do not give you any medicine on the list.

13. Rights as a participant in this study

Your participation in this study is entirely voluntary and you can decide not to participate, or stop at any time, without stating any reason. Your withdrawal will not affect your right to access other medical care.

Withdrawal

- You may discuss potentially withdrawing yourself from the study with any clinical study personnel (e.g. nurse or doctor). You will be treated the same no matter what you decide. Your withdrawal will not affect your access to other medical care.
- You can be withdrawn from the study if it is considered to be in your best interest. If your participation is ended early, you may be asked to return for study-ending tests and procedures for your safety.
- If you did not give an accurate history or did not follow the guidelines of the study and the regulations of the study facility, you may be withdrawn from the study at any time.

Discontinuation of study treatment

You must inform a member of the study team if you would like to stop taking any of your medicines. We will supervise any discontinuation with your health as first priority.

New findings

You will be informed about any new information from this or other studies that may affect your health, your welfare or willingness to stay in this study. If you want the results of the study, please let the study staff know.

Pregnancy

If you are pregnant or breastfeeding, you may take part in this study if you sign a separate consent form- the PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT FOR PARTICIPANTS WHO ARE PREGNANT (>18 YEARS). We would like to collect more information on pregnant women as there is very little research on the best way to treat pregnant women with drug resistant TB. In the current standard of care, pregnant women are given the same anti-TB medicines as a non-pregnant women. It is therefore important to learn more about how these medicines work during pregnancy.

However, if you are not pregnant but planning to become pregnant during the study period, you may not take part in the study. The reason for this is that it is not advisable to fall pregnant if you have a serious illness such as drug resistant TB.

If you become pregnant while taking your treatment, you will be given the choice to stay on the study and if you agree to this, you must sign a separate consent form: the PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT FOR PARTICIPANTS WHO ARE PREGNANT (>18 YEARS). If you choose not to stay on the study, then you will be withdrawn from the study and referred to the National TB Programme where you will continue your healthcare. All aspects of healthcare related to your pregnancy and infant will be your responsibility. We would like to access to your medical records and those of your baby, from the time you became pregnant and for a minimum of six weeks after the baby is born.

14. Emergency care and hospitalization

If you seek emergency care or if hospitalization is required at any time during the study or up to a year after taking the last dose of your medicines, please tell the treating doctor that you are enrolled in this research study and that a study team member must be informed.

15. Financial arrangements

- Taking part in this study will not lead to added costs to you.
- USAID will provide payment for all study procedures and reasonable medical expenses that you may incur as a direct result of this study as determined by USAID and the study team.
- Neither you nor your medical scheme will be expected to pay for any study medication, study related visit or study procedures.

16. Reimbursement for study participation

You will not be paid to participate in this study but your transport and, when necessary, refreshment costs will be reimbursed adequately, according to SAHPRA requirements. You will therefore be reimbursed R300 per study visit.

If your DOT (Directly Observed Therapy) supporter accompanies you during the randomization visit, as requested by the study staff, the DOT supporter will be reimbursed R300. The DOT supporter will also only be reimbursed R300 per study visit, if the study staff request him/her to accompany you during that specific study visit.

17. Insurance

The Clinical HIV Research Unit has taken out insurance in the event of study related injury or illness. A study-related injury or illness is one that occurs as a direct result from giving the study medicine or other study-specific procedures carried out in accordance with the protocol for this study.

ABPI STATEMENT ON COMPENSATION:

The Clinical HIV Research Unit, a Division of Wits Health Consortium, will provide compensation for reasonable medical expenses incurred as a result of study-related injury, illness, or death determined according to the guidelines laid down by the Association of the British Pharmaceutical Industry (ABPI Compensation Guidelines Version 2014), and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (second edition, 2006).

- You must notify the study team immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered.
- If a research-related injury occurs, you have not waived any of the legal rights which you otherwise would have as a participant in this study by signing this form.

Further detailed information on the payment of medical treatment and compensation due to injury can be obtained from the study team. The study team has a copy of the ABPI Guidelines (Version 2014) and the Insurance Certificate, should you wish to review them.

The insurance does not cover, and the Clinical HIV Research Unit, a Division of Wits Health Consortium, will not pay for:

- Medical treatment of other injuries or illnesses.
- Injury caused by non-observance of the protocol.

The study team is indemnified by the Clinical HIV Research Unit, a Division of Wits Health Consortium, conditional upon:

- Their compliance with the applicable requirements of the study protocol.
- Their compliance with the regulations of the South African Health Products Regulatory Authority and the University of the Witwatersrand, Human Research Ethics Committee (HREC).
- The handling and administration of the study medication in accordance with instructions and guidelines provided in the protocol, subsequent amendments and related documents.

- The indemnification is not intended to be and is not a substitute for their personal malpractice insurance.

Please note that if you have a medical aid you should enquire whether your medical aid company requires notification of your intention to participate in a clinical study.

http://www.abpi.org.uk/our-work/library/guidelines/Documents/compensation_guidelines_2014.pdf

18. Ethical approval

- This clinical study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (Wits HREC) and written approval has been granted by that committee.
- The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from a member of the study team should you wish to review it.
- This study is sponsored by USAID (United States Agency for International Development). Members of the study team do not have any financial or personal interests with this organization that may bias my actions.

19. Source of additional information

For the duration of the study, you will be under the care of **the study doctors**. If at any time between your visits, you feel that any of your symptoms are causing you any problems, or you have any questions during the study, please do not hesitate to contact the study doctor on _____.

The 24-hour telephone number through which you can reach an authorised study staff member is _____.

If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (Wits HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

20. South African Health Products Regulatory Authority (SAHPRA)

If you have questions about this trial, you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Chief Executive Officer
South African Health Products Regulatory Authority
Department of Health
Private Bag X828
PRETORIA
0001

E-mail: Boitumelo.Semete@sahpra.org.za
Tel: (012) 842 7629/26

21. Confidentiality

- All information obtained during the course of this study, including hospital records, personal data and research data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.
- This information will be reviewed by authorised representatives of USAID.
- The information might also be inspected by the National Health Research Ethics Council (NHREC), University of the Witwatersrand, Human Research Ethics Committee (Wits HREC), the South African Health Products Regulatory Authority (SAHPRA) and/or the United States Food and Drug Administration (FDA), as well as your personal doctor. Therefore, you hereby authorise the study doctor to release your medical records to USAID, its employees or agents, domestic and foreign regulatory health authorities, SAHPRA, NHREC and Wits HREC.
- These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study.
- Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence. You will be informed of any finding of importance to your health or continued participation in this study but this information will not be disclosed to any third party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the South African Department of Health exists. In this case, you will be informed of the study doctor's intent to disclose such information to the authorised state agency.

22. Personal doctor/specialist notification option

Please indicate below, whether you want the study team to notify your personal doctor or your specialist of your participation in this study. **Please tick one:**

☐ YES, I want the study doctor to inform my personal doctor / specialist of my participation in this study.

☐ NO, I do not want the study doctor to inform my personal doctor / specialist of my participation in this study.

☐ I do not have a personal doctor / specialist.

Participant: Signature

Date

23. Participant questions

Did the participant raise any questions? **Please circle one:**

YES / NO

If YES, what were they:

PARTICIPANT INFORMED CONSENT SIGNATURE PAGE

I hereby confirm that I have been informed by the study doctor about the nature, conduct, benefits and risks of clinical study **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)

I declare that:

	Participant Initial and date
I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical study.	
I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.	
I consent to having an HIV test, if my HIV status cannot be confirmed.	
In view of the requirements of research, I agree that the data collected during this study can be processed in a computerized system by the study team.	
I also agree that any accumulated de-identified data can be compared with data from other trials.	
I may, at any stage, without prejudice, withdraw my consent and participation in the study.	
I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.	

PARTICIPANT:

Printed Name	Signature / Mark or Thumbprint	Date and Time
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PERSON OBTAINING INFORMED CONSENT :

DESIGNATION (if other than the study doctor): _____

I herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study

Printed Name	Signature	Date and Time
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STUDY DOCTOR:

Printed Name	Signature	Date and Time
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TRANSLATOR (if applicable):

Printed Name	Signature	Date and Time
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WITNESS (if applicable):

Printed Name	Signature	Date and Time
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SUPPLEMENTARY INFORMED CONSENT FOR FEMALES OF CHILDBEARING POTENTIAL

☐ **N/A** (Please tick if a participant is male)

☐ **N/A** (Please tick if a female participant is post-menopausal for >12 months)

☐ **N/A** (Please tick if female participant had a hysterectomy)

☐ **N/A** (Please tick if a female participant had an bilateral oophorectomy and/or salpingectomy)

- I understand that I will be receiving an investigational medicine and should not become pregnant while I am participating in this study.
- If I am sexually active, I must be using an effective method of contraception.
- A pregnancy test will be performed at the first study visit (screening visit) and at various intervals during the study. If the pregnancy test is positive at any point, I have the option to still take part in the study, provided I give separate informed consent.
- I understand that the safety of the study medicine during pregnancy has not been established and the use of this study medicine may involve risks to me or my unborn child, should I become pregnant while receiving this medicine.
- I will allow the study team access to my medical records from the time I may became pregnant and for a minimum of six weeks after the baby is born.
- The study doctor and/or a member of the study staff have discussed information on pregnancy prevention for women of childbearing potential with me.

I understand that I should immediately call a study doctor or a dedicated study staff member at phone number _____ **if:**

	Participant Initial and date
I am or I think I may be pregnant.	
I have missed my menstrual cycle or it is late, or I have a change in my usual menstrual cycle (for example, heavier bleeding during my menstrual cycle or bleeding between cycles).	
I have changed or plan to change my birth control method, or if I need to take any medication not given to me by the study doctor.	

I also confirm that:

	Participant Initial and date
This supplementary informed consent for females of childbearing potential has been explained to me to my satisfaction and in my home language.	
I have been given the chance to ask questions and they have been answered to my satisfaction.	

PARTICIPANT:

Printed Name	Signature / Mark or Thumbprint	Date and Time
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PERSON OBTAINING INFORMED CONSENT:

DESIGNATION (if other than the study doctor): _____

I herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study

Printed Name	Signature	Date and Time
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STUDY DOCTOR:

Printed Name	Signature	Date and Time
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TRANSLATOR (if applicable):

Printed Name	Signature	Date and Time
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WITNESS (if applicable):

Printed Name	Signature	Date and Time
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