Protocol Title: endTB-Q (Evaluating Newly Approved Drugs in Combination Regimens for Multidrug-Resistant TB with Fluoroquinolone Resistance)
Sponsor: Médecins Sans Frontières (Doctors Without Borders) – France
Principal Investigators: Carole Mitnick, Sc.D. and Lorenzo Guglielmetti, M.D.
Site Principal Investigator: [*Insert PI Name*]
Research Center: [*Insert Research Center Name*]

Participant Name (please print): _____

Study Subject ID: _____

About this consent/assent form

You are being asked to participate in a study, called endTB-Q. This research consent/assent form is written to help you understand this study and decide whether to participate. A member of our study team will talk to you about taking part in this study. There may be words that you do not understand or information that is unclear or confusing. Please ask us questions so we can help you understand better. You may take some time to think about and discuss your participation with others. Being in the study is completely up to you; you do not have to be in the study if you do not want to. After you have had time to ask questions and think about your participation, we will ask you to sign the consent/assent form if you agree to participate. We will give you a signed copy of this research consent/assent form to keep.

Even after signing this form, you can decide not to be in this study.

If you are not able to sign the consent/assent form, but you would like to participate, you can ask someone you know to sign for you and you can make a thumbprint to show that you understand the study and would like to take part.

Introduction

You have been asked to join this study called endTB-Q clinical trial because you have a type of tuberculosis (TB) that can't be treated with drugs that are commonly used to treat TB, rifampin and fluoroquinolones. This is known as multi-drug resistant tuberculosis (MDR-TB) with fluoroquinolone (FQ) resistance. Researchers want to know what combinations of drugs work well for people who have MDR-TB with FQ resistance. We do not know which combination of drugs is the best. The new combination of drugs used in this study is called "experimental"; all the drugs have been used before but we do not know how well they work together.

Around 350 people with MDR-TB with FQ resistance in 7 countries will participate in this study. About [*number to be locally adapted*] people will take part at [*Research Center Name*].

This study has been approved by the [*Research Center Ethics Committee*] [*and the applicable national regulatory authority*].

Médecins Sans Frontières (Doctors Without Borders) – France is the sponsor of this study.

Why is this study being done?

Current treatment for MDR-TB with FQ resistance has 5-9 drugs taken every day for 20 to 24 months. During at least six months, treatment includes a daily shot. This treatment may cause many mild and some serious side effects, for example: feeling sick to the stomach, throwing up, hearing loss, numbness/tingling in fingers and toes, kidney damage, mental illness/feeling sad,

etc. Two new drugs (delamanid and bedaquiline) have recently become available. New treatments with these drugs may be shorter and/or simpler (no injection). Such treatments must be tested to see if they are safe and work well for people with multidrug-resistant TB with FQ resistance. The endTB-Q study will compare new shorter, injection-free treatments to the current treatment for MDR-TB with FQ resistance.

How long will I be in this study?

You will be in this study for 1.5-2 years (73 to 104 weeks). During this time, we will ask you to make 26 to 30 study visits to [*Research Center Name*].

What will happen in this study?

If you choose to be in this study, we will ask you to sign a consent/assent form before you start the study. If you are currently taking any medicines that can't be taken with your study drugs, you may need to stop these medicines before you can start taking the study drugs. Your doctor may give you new drugs instead of your current medicines. If this makes you feel bad, please tell the study doctor. If your medicines cannot be replaced by other treatment or need to be stopped for more than 2 weeks before taking study drugs, you may not be able to be in this study.

At the beginning of the study, you will be assigned by chance (like rolling dice) to one of the 2 treatment groups described below. Two patients out of 3 will get the experimental treatment. One out of 3 will get the regular treatment for MDR-TB with FQ resistance. Nobody can choose your study treatment group.

If you are assigned to the experimental treatment, you will get 4 study drugs that will be taken by mouth. You will be assigned to take the study drugs for 24 weeks (6 months) or 39 weeks (9 months). The duration of the experimental treatment you will receive will depend on the severity of your TB. This will be based on exam results before you start the study treatment and on exams performed during the first weeks of study treatment.

The experimental treatment includes the MDR-TB drug linezolid. The amount of linezolid you receive will be changed after about 4 months of treatment or even earlier if you are experiencing some particular side effects. We are looking at two ways to lower the total dose of linezolid: reduce the amount given every day or give it less often (3 times/week). This study will help us to know if one way is better than the other. The way you take less linezolid will be assigned to you by chance (like rolling dice): about half of participants receiving the experimental treatment will receive the daily dose and about half will receive the 3 times/week dose. Nobody can choose how your linezolid dose will be reduced.

If you are assigned to the control treatment, you will get the treatment used for MDR-TB with FQ resistance in your country according to guidelines from World Health Organization. You will receive study drugs by mouth and maybe by needle shots. The treatment will last for about 20 to 24 months.

Your study doctor will tell you how many pills of each drug you will have to take. Study staff will teach you how, when and where you should take your study drugs and for how long. You must follow these instructions carefully.

You will also have scheduled study visits (described below).

If you miss doses or a study visit, a study worker may call you or go to your home to check if you are well. He/she might discuss with you ways to help you take all your study drugs and go to all your study visits. *[to be adapted locally based on the site set-up]*

With your agreement, the study doctor will inform your regular doctor or other medical doctors who may be treating you, of your participation in the study.

You will go to the [*Research site name*] for study visits until at least 73 weeks (17 months) and possibly as long as 104 weeks (24 months) after you start your study treatment. The exact time you spend in the study will depend on the overall progress of the study. If you are still on treatment at the end of the study, we will help you talk to the regular TB doctors to make sure you can finish your treatment.

Visit procedures

All participants have the same visits and the same procedures. All procedures are part of normal care for people with MDR-TB with FQ resistance. In the study, we do them more often to see how you are doing, learn about any side effects, and to understand how the treatment is working. What happens at each visit is explained here:

Visit before starting treatment

At this visit, we will:

- Answer all your questions and get your consent/assent to be in the study.
- Ask about your job and schooling, smoking or alcohol use. *[to be moved to screening consent/assent if applicable]*.
- Ask about any changes in your medical history or medicines since the screening visit, perform a brief exam and ask you about TB symptoms and daily activities.
- The study doctor might change some of the medicines you are already taking and will recommend birth control so you/your partner can avoid pregnancy while taking study treatment.
- Check your vision, hearing, movement and feeling in toes, mental health status.
- If you are woman and can get pregnant, collect about ½ tablespoon of blood for a pregnancy test. This test will be repeated if the study drugs are started a few days after this blood draw.
- Do an electrocardiogram to check if your heart is working normally.
- Unless recent results are available, we might also:
    - Collect up to 2 tablespoons of blood to test for viruses like hepatitis B and C, which affect your liver, and HIV, which affects your body's ability to fight infection. These might affect your treatment for TB. All test results will remain confidential. You have the right to refuse these tests. Refusing a test will not affect your participation in the study or any access to usual treatments that do not depend on knowledge of the test result. If the test result(s) is (are) positive, you will be referred to appropriate care. If you have HIV infection, we will test CD4 count and HIV viral load to see if the disease is well controlled.
    - Collect ½ tablespoon of blood for laboratory testing.
    - Ask you to cough up sputum (phlegm). This will be used to test whether the TB bacteria can be treated with regular drugs and/or drugs in the study treatment. This is called testing for drug resistance.
    - Perform a chest X-ray.

Follow-up Visits (Week 1 to Week 73/Week 104)

After you start taking the study drugs, you will return to [*Research site name*] for your follow-up visits every week during the first 3 months, then approximately every month until the end of your study participation. Each visit takes about 1 ½ hours including waiting time.

At each visit, we will:

- Take your medical history; perform a brief exam; ask about TB symptoms, how you are feeling, whether you are taking your study drugs correctly, and which other medicines you are taking; and answer all your questions. The study doctor may change some of your prescriptions if you are taking medicines that can have interactions with drugs in your TB regimen.
- If you are a woman who can get pregnant, we will ask you about your last menstrual period and use of birth control. The study doctor might do a pregnancy test.
- The study doctor will recommend birth control so you/your partner can avoid pregnancy while taking study drugs.

Times of visits and study activities at each visit are in the table below:

Visit	Medical exam and interview[1]	1 tbsp. Blood Collection (for adverse events)	½ tbsp. Blood Collection for tests for people with HIV[2]	½ tbsp. Blood Collection for Blood Sugar Level[3]	Sputum Collection	Test of your heart[4]	Chest X-Ray	Check vision, hearing, movement and feeling in toes	Mental Health assessment	ECOG Performance status[5]	Pregnancy test [6]
Week 1	X					X					(X)
Week 2	X				X	X					(X)
Week 3	X					X					(X)
Month 1	X	X			X	X		X			(X)
Weeks 5, 6, and 7	X					X					(X)
Month 2	X	X			X	X	X	X			(X)
Weeks 9, 10, and 11	X					X					(X)
Month 3	X	X			X	X		X			(X)
Months 4 and 5	X	X			X	X		X			(X)
Month 6 (Week 24)	X	X	(X)	(X)	X	X	X	X		X	(X)
Months 6.5, 7, and 8	X	X			X	X		X			(X)
Month 9 (Week 39)	X	X			X	X	X	X		X	(X)
Month 10	X	X			X	X		X			(X)
Month 11	X	X	(X)	(X)	X	X		X			(X)
Month 12	X				X	X					(X)
Months 13.5 and 15	X				X						(X)
Month 17 (Week 73)	X		(X)	(X)	X	X	X	X	X	X	(X)
Months 19, 20, and 22[7]	(X)				(X)						(X)
Month 24[7]	(X)	(X)			(X)		(X)	(X)	(X)	(X)	(X)

[1]Medical exam and interview includes: talking about your medical history, discussing any (change in) medicines you're taking, physical exam; asking about TB symptoms and about taking your treatment.
[2]CD4 and viral load counts: these are tests that explain how well controlled disease is.
[3]If patient had abnormal blood sugar level at baseline.
[4]This is called an electrocardiogram and will tell if there is anything abnormal about the way your heart is working.
[5]Your doctor or nurse will ask you questions about which of your activities you can do and whether you need help.
[6]For women who might be pregnant.
[7]Exams after Month 17 will be done only if your study follow-up is still on-going.

If you have other diseases, for example hepatitis C, we might collect the exam results that your doctor orders according to clinical routine practice.

If needed, your study doctor might call you for additional examinations.

Stopping or leaving the study early

If you decide you want to stop being in the study, you should tell us. We will ask you to have a study visit and will make sure that you leave the study safely. We will talk to you about follow-up care you might need.

The study doctor might also decide to take you out of the study early. This may happen because:

- You become pregnant.
- The study doctor thinks it is best for you to stop taking the study drug(s).

- You can't make the required study visits.
- We stop the study.

If this happens, the study doctor will explain why. We will ask you to come in for a study visit as described above. We will also help arrange other care you might need. And, depending on when you stop, we may ask you to make one or two more visits.

At this/these visit(s), we will do the following:

Visit	Medical exam and interview[1]	2 tbsp. Blood Collection (for adverse events)	½ tbsp. Blood Collection for tests for people with HIV[2]	½ tbsp. Blood Collection for Blood Sugar Level[3]	Sputum Collection	Test of your heart[4]	Chest X-Ray	Check vision, hearing, movement and feeling in toes	Mental Health assessment	ECOG Performance status[5]	Pregnancy test [6]
Early termination	X	X			X	X	(X)	X	X	X	(X)
Week 39 (Month 9)	X		(X)	(X)	X		(X)			X	
Week 73 (Month 17)*	X		(X)	(X)	X		(X)			X	

[1]Medical exam and interview includes: talking about your medical history, discussing any (change in) medicines you're taking, physical exam; asking about TB symptoms and about taking your treatment.
[2]CD4 and viral load counts: these are tests that explain how well controlled disease is.
[3]If patient had abnormal blood sugar level at baseline.
[4]This is called an electrocardiogram and will tell if there is anything abnormal about the way your heart is working.
[5]Your doctor or nurse will ask you questions about which of your activities you can do and whether you need help.
[6]For women who might be pregnant.

*If you leave the study early, your last visit will be at or before the Week 73 follow-up visit.

What will happen to me after the end of the study?

Once you complete your participation in the study, any follow-up of your TB will be done by your regular doctor.

If you still have side effects when you end the study, your study doctor may stay in touch with you until the side effect gets better or stops getting worse. Your study doctor may also contact you if you experience a new side effect.

You may refuse to be contacted and do not have to provide any information if you don't want to.

Managing your Samples and Health Information in the Study

To keep all your information private, we will label all your samples and health information with a code instead of your name. The study team will keep a key that connects your name to the code. The study doctor will keep the key to the code in a password-protected computer and/or locked file.

In a special lab in Belgium, sputum samples and TB bugs from your sputum might be tested to see if drugs work against the bug and to see if the bug is the same as the one that was in your sputum at the beginning of the study.

Will anything bad happen to me from being in this study?

Risks of Taking Study Drugs:

You will take several MDR-TB drugs when you are in this study. The drugs used in the control are the standard MDR-TB medicines used in your country according to international guidelines from the World Health Organization. Experimental treatments will use the following 4 drugs: bedaquiline, delamanid, clofazimine and linezolid.

Medicines for MDR-TB have different side effects. Your study doctor will tell you the most common side effects that you may have while taking study treatment and you will be given a paper ("leaflet") that describes the main side effects. There may be other risks that are not known yet. We will do frequent clinical, laboratory and other examinations in order to find and promptly treat possible side effects. And, your doctor will explain in detail when you should get in touch with him/her.

As with any drug, an **allergic reaction** can happen. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. Sometimes allergic reactions can be more serious, and even result in death.

Some of the drugs may have an unknown, harmful effect on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant. Because of these unknown risks, women cannot start this study if they are known to be pregnant, trying to become pregnant, or unwilling or unable to stop breastfeeding an infant. To protect against these risks, for women who are able to get pregnant, we will require negative pregnancy tests before starting the study drugs. For women who are able to get pregnant, and men who are able to father a child, we will require use of 2 forms of birth control if you are sexually active while taking your study drugs (and possibly after). Acceptable female birth control methods for use in this study are hormonal, barrier methods, and intrauterine device (IUD). Acceptable male birth control methods for use in this study are condoms with spermicide. Your study doctor will explain these to you so you understand the options available.

For female participants, if you miss a period, or think you might be pregnant during the study, you must tell the study doctor right away. If you become pregnant, your treatment might be changed and you might stop taking part in the study.

Male participants do not have to stop taking the study drugs or stop taking part in the study if their partner becomes pregnant. You should let us know immediately if your partner becomes pregnant.

In both cases, the study doctor will ask for permission to collect information about the outcome of your (partner's) pregnancy and the condition of your newborn.

Risks of Taking the Study Drugs with Other Medicines

Some drugs are not safe to be taken with the study medicines, or may not work when taken with the study medicines. Please tell and consult with your study doctor if, at any time during the study, your doctor prescribes or you begin using any other medications.

For your safety during this study, talk to your study doctor BEFORE you take any:

- new medicines prescribed by another doctor;
- other medicines sold over-the-counter without a prescription;
- dietary or herbal supplements.

Risks of Blood Draws

You may have a bruise (a black and blue mark) or pain where we take the blood samples. There is also a small risk of infection, light-headedness, and/or fainting.

What are the possible benefits from being in this study?

By participating in the study, your treatment may be all-oral and shorter than the current treatment recommended for MDR-TB with FQ resistance. We do not know if these shorter treatments work better than the currently available standard treatment. Some patients will need their treatment to be changed; if you participate in the study, your doctor will have more information about how best to change your treatment. The study doctors can also take care of your side effects sooner and better by having extra tests in the study.

You will receive more treatment support in the study than you would outside the study. Others with MDR-TB with FQ resistance may benefit in the future from what we learn in this study**.**

What other treatments or procedures are available for my condition?

You do not have to be in this study to get treatment for MDR-TB with FQ resistance. Other treatment is available in your country through [*local TB care provider/entity*]. This treatment is similar to that in the control arm in the study. Talk with the study doctor if you have questions about the other treatment.

Can I still receive TB treatment if I do not take part in this study?

Yes. Taking part in this study is completely up to you. You can decide not to take part. You will receive treatment through [*local TB care provider/entity*] if you do not take part in this study. You will not lose any benefits you have the right to receive. Treatment outside the study is also free of charge.

What should I do if I want to stop being in the study?

If you decide to stop being in the study, we will make sure that you stop the study safely. We will talk to you about follow-up care you might need, and you will be encouraged to come back at least for one additional study visit.

And, we will tell you if we learn any new information that could make you change your mind and choose to leave the study.

Information collected while you are in the study will be used to help answer study questions. When you leave the study, your information may still be used for the study. If you do not want this information to be used, and you want it to be destroyed, please contact your study doctor or the email address endTB.clinicaltrial@paris.msf.org.

Will I be paid to be in this study?

You will not be paid to be in this study. We will pay transportation costs for study visits. You will also receive [*local arrangement for monthly food supplements*] when you take part in the study. In sum, you will be reimbursed [*local currency*] _____ for transportation for the baseline visit, [*local currency*] _____ for each follow-up visit, for any unscheduled visits, and [*local currency*] _____ for your final visit.

What will I have to pay for if I am in this study?

You will not have to pay to be in this study. You also will not have to pay for the study drugs, or for any study-related procedures and visits.

What happens if I am injured as a result of taking part in this study?

If you suffer injury as a direct result of participation in this study, the sponsor has made insurance arrangements to pay for any injury you may suffer. If this happens, please inform your doctor and seek medical attention right away. The sponsor will ensure that you receive appropriate medical treatment.

The sponsor will not pay to treat a medical condition or disease you had before joining this study or expenses for injury, treatment, or hospitalization that are not the result of your participation in the study.

In an emergency, the sponsor has made plans to pay for a specialist visit, related treatment, and/or a hospital stay. For non-urgent situations, the sponsor may pay for your visit to see a specialist. The study team will review your situation and decide whether the sponsor will pay for the resulting treatment if your condition is not the result of your participation in the study. You do not waive any of your legal rights by signing this consent/assent form.

Who can I speak to if I have questions, concerns or complaints?

If you have questions about this study, you can contact [*PI Name and title*] at [*PI telephone number*]. You can also call [*Clinical Investigator*] at [*CI number*] with questions about this study. If you have questions about the scheduling of appointments or study visits, call [*Study Coordinator*] at [*SC number*].

For medical emergencies outside business hours, please contact **[*Must include 24/7 phone number of licensed site physician investigator here*].**

If you want to speak with someone not directly involved in this study, please contact the [*Research Center IRB*] office. You can call them at [*Research Center IRB number*].

If I take part in this study, how will you protect my privacy?

We are careful to protect the identity of people in this study to the extent permitted by law. We will also keep your information secure and confidential. Study information kept on a computer will be password-protected, and paper files will be stored in a locked office at [*Research site*]. Your study records will be kept at the clinic/hospital for [*XX*] years [*to be adapted locally*] following the study completion. As needed to monitor the study quality, your records may be looked at by institutions responsible for quality and privacy, such as the sponsor, Ethics Committee and other Authorities.

For the study, we will store some non-medical information about you, such as your date of birth and city of residence. You can ask us to access, modify, complete, update, or delete this information. If you have any complaints about the protection of your data, you could contact your local/national Data Protection Authority [*Name and contact to be adapted locally*].

The information collected for this study will be used:

- For the purpose of this study: the sponsor, the study doctor, or other doctors involved in the study may share reports on the study with scientific groups. After the study ends, you may see your records, and you may be told the study results.
- To make new recommendations about treatment of MDR-TB with resistance to FQ: your coded information may be used and shared with other institutions, during and after completion of the study, notably with the World Health Organization.

In all cases your identity will never be disclosed.

If your coded information will be sent electronically to other researchers or institutions, it will be encrypted (scrambled so it cannot be read by unconcerned people) and will be protected according to European Economic Area standards.

endTB-Q Research Informed Consent/Assent and Authorization

We are asking you to be in this study because you have a multidrug-resistant tuberculosis (MDR-TB) with fluoroquinolone (FQ) resistance, and you are:

☐ at least 18 years old. We seek your **consent** to participate in this study.

☐ between 15 and 17 years old (minor). We seek your **assent** to participate in this study. Because you are younger than 18 years of age, we will also ask your parent(s) or someone else who takes care of you (legal guardian) to give permission for you to take part in the study, by signing a parental consent. We will need permission from both you and your parent(s)/legal guardian before you can take part in this study. If you decide not to participate, nobody else can make you participate. Your parents or legal guardian may be informed of results of study procedures [*to be adapted locally*].

You completed the screening process for this study and are eligible to take part, or you completed the screening process for another study (endTB) and were found to be eligible for this study (endTB-Q). In the second case, you agree that your data and personal information collected during endTB screening will be used for the endTB-Q study.

Your signature on this document means the following:

I have read this consent/assent form. This study has been explained to me, including risks and possible benefits, other possible treatments or procedures, and other important things about the study. I have had the opportunity to ask questions. I understand the information given to me. I recognize that my participation is voluntary and that I can refuse or end my participation at any time, without any loss of benefits that I would otherwise have. I recognize that by signing this document, I do not lose any of my legal rights as a patient. I will receive a complete, signed, dated copy of this research consent/assent form.

By signing below, I agree to take part in this study.

_____ _____
Signature or thumbprint of participant Date (DD/MMM/YYYY) and Time

_____
Name of participant, printed in capital letters

_____ _____
If applicable, Signature of witness Date (DD/MMM/YYYY) and Time

_____
Name of witness, printed in capital letters

Study representative who obtained informed consent/assent:

I have explained this study to the participant and have answered all of his/her questions. He/she understands the information described in this document and accepts voluntary participation in the study.

_____ _____
Signature of study representative Date (DD/MMM/YYYY) and Time

_____
Name of study representative, printed in capital letters

endTB-Q Research Adult Consent/Assent Informed Consent Form Addendum Health Information Future Use

Your health information collected during the study can be useful for other research in TB. We are asking permission to store your health information for future use in research on better treatment and diagnosis of TB, for up to 20 years after the study ends. The endTB-Q study sponsor will control access to this information and will share it only for research on better TB treatment or diagnosis. We do not know yet what these studies will be but they will be on better TB treatment or diagnosis (including resistance). Your coded health information will be handled according to the European regulation for the protection of personal data.

Your health information contains a code instead of your name. To further protect your privacy, we will change this code before your information is shared for other research.

Your health information will not be sold for profit.

You can be in the endTB-Q study if you do not agree to store your information for future use.

Any use of your coded health information in your country or in other countries for other research will be reviewed by an Ethics Committee in your country.

Results from this future TB research can be made public. Your identity will never be shared. No one will share individual findings with you or anyone else about you or your health.

Even after signing this consent/assent addendum for future use of health information, you have the right to change your mind. Anytime during the storage period of your health information, you can contact your study doctor or send an email to endTB.clinicaltrial@paris.msf.org to request any information regarding the use, storage and location of your coded health information and/or its destruction.

Informed Consent/Assent and Authorization - Health Information Future Use

We are asking to use your health information because you gave your consent/assent for endTB-Q study and you are:

☐ at least 18 years old. We seek your **consent** to store your health information for future use.

☐ between 15 and 17 years old (minor). We seek your **assent** to store your health information for future use. Because you are younger than 18 years of age, we will also ask your parent(s) or someone else who takes care of you (legal guardian) to give permission, by signing a parental consent. We will need permission from both you and your parent(s) or legal guardian. If you decide not to participate, nobody else can make you participate.

Your signature on this document means the following:

I have read this consent/assent form. The purpose of the future use of my health information has been explained to me.

I understand that this future use is separate from my participation in the endTB-Q study and my decision to allow future use of this information will not affect my participation in endTB-Q.

I have had the opportunity to ask questions. I understand the information given to me. I recognize that my participation is voluntary and that I can refuse or end the storage of my health information for future use at any time, without any loss of benefits that I would otherwise have.

I agree to have my health information stored for future use: ☐ Yes ☐ No

I recognize that by signing this document, I do not lose any of my legal rights as a patient. I will receive a complete, signed, dated copy of this future use of health information consent/assent form.

_____ _____
Signature or thumbprint of participant Date (DD/MMM/YYYY) and Time

_____
Name of participant, printed in capital letters

_____ _____
If applicable, Signature of witness Date (DD/MMM/YYYY) and Time

_____
Name of witness, printed in capital letters

Study representative who obtained informed consent/assent:
I have explained the future use of health information to the participant and have answered all of his/her questions. He/she understands the information described in this document and accepts voluntary participation.

_____ _____
Signature of study representative Date (DD/MMM/YYYY) and Time

_____
Name of study representative, printed in capital letters