MRC/UVRI and LSHTM Uganda Research Unit

University of California
San Francisco

Informed Consent Form to be a Research Subject

Study title: ALTER - Adjunctive Linezolid for the Treatment of tubERculous meningitis

This is a medical research study. One of the study doctors—Dr. Freddie Mukasa Kibengo (Masaka Regional Referral Hospital/MRC/UVRI & LSHTM Uganda Research Unit), Dr. Fiona Cresswell (MRC/UVRI & LSHTM Uganda Research Unit), or Dr. Felicia Chow (University of California, San Francisco, UCSF)—or another member of the research study team will explain the study.

For participants: You are being invited to participate in a medical research study because you have or are suspected to have tuberculous (TB) meningitis, which is a serious infection of the brain. Medical research studies include only people who choose to take part. Please take your time to decide whether you wish to participate. You may discuss with your family and friends and with your health care team. Please read this information sheet carefully. If you are unable to read, the study staff will go through it with you, but please feel free to ask if you have any questions. If you agree to take part in this study, you will sign 2 copies of this document. One copy is for you to keep and the other will be kept in the clinic's files. If you do not want to keep a copy, we will keep it for you.

For next of kin/caregivers (in the event that the participant is unable to provide consent): You are being asked to consent for the patient who has or is suspected to have tuberculous (TB) meningitis, which is a serious infection of the brain, and is unable to make decisions or provide consent for a medical research study at this time. Medical research studies include only people who choose to take part, or in the event that a participant cannot provide consent, whose caregivers consent to participation. Please take your time to decide whether to provide consent for the patient. You may discuss with other family members and friends and with the health care team. Please read this information sheet carefully, which is directed at the participant. If you are unable to read, the study staff will go through it with you, but please feel free to ask if you have any questions. If you agree for the patient to take part in this study, you will sign 2 copies of this document. One copy is for you to keep and the other will be kept in the clinic's files. If you do not want to keep a copy, we will keep it for you. **The patient will be asked to**

give their consent as soon as they regain consciousness or capacity and will be free to continue participation or leave the study.

Why is this study being done?
TB meningitis is a serious, life-threatening infection of the brain. We are conducting a study to determine if a medication called linezolid, which has been shown to work against tuberculosis affecting the lungs, can help treat TB meningitis by reducing the risk of death and improving outcomes for people who have the infection. Specifically, we are interested in learning how linezolid affects other medications used to treat TB meningitis, including high dose rifampicin, and whether linezolid is well-tolerated in patients with TB meningitis.

Why am I being asked to volunteer in this study?
You have been asked to participate in the study because you have or are suspected to have TB meningitis.

Who is paying for this study?
Dr. Felicia Chow received a grant from the United States National Institutes of Health Fogarty International Center to pay for the study.

How many people will take part in this study?
We plan to enroll about 60 participants with TB meningitis or suspected TB meningitis.

Where will I be seen for this study?
All study visits will take place at Masaka Regional Referral Hospital in Masaka, Uganda.

How long will I be in this study?
This study will take place over about 10 visits during a 24-week period. For the initial approximately two weeks of the study, you will be admitted to Masaka Regional Referral Hospital. While you are admitted to the hospital, the study visits will occur in the hospital. If you are well enough to be discharged, follow up visits will occur in the clinic. The first study visit, which will take place in the hospital, will require about 1.5 hours of time. Follow up visits, which will be in the hospital or in the clinic, will last anywhere from 30 minutes to 1 hour.

What will happen if I take part in this research study?
You will receive either a standard dose of oral rifampicin (10 mg/kg/day) or high dose oral rifampicin (35 mg/kg/day). The dose you receive will be determined randomly using a computer. This means you will have an equal chance of receiving either dose. The computer will also randomly determine if you will receive linezolid 1200 mg daily or no linezolid. In addition to high or standard dose rifampicin and linezolid or no linezolid, you will also receive the other 3 standard medications used to treat TB meningitis. If you are in a group receiving linezolid, you will receive it for only 1 month, after which it will be stopped. If you are in a group receiving high dose rifampicin, you will receive it for only 1 month, after which it will be reduced to standard dose. After 2 months, you will continue to receive the two medications typically used to treat TB meningitis, standard dose

rifampicin and isoniazid. This treatment will continue for 10 more months, as per national treatment guidelines for TB meningitis in Uganda.

Study treatment

	Group 1	**Group 2**	**Group 3**	**Group 4**
Weeks 1 to 4	High dose rifampicin (35 mg/kg/day) + Isoniazid + Pyrazinamide + Ethambutol + Linezolid	Standard dose rifampicin (10 mg/kg/day) + Isoniazid + Pyrazinamide + Ethambutol + Linezolid	High dose rifampicin (35 mg/kg/day) + Isoniazid + Pyrazinamide + Ethambutol	Standard dose rifampicin (10 mg/kg/day) + Isoniazid + Pyrazinamide + Ethambutol
Weeks 5 to 8	All groups receive standard dose rifampicin (10 mg/kg/day) + isoniazid + pyrazinamide + ethambutol			
Week 9 to Month 12	All groups receive standard dose rifampicin (10 mg/kg/day) + isoniazid			

Procedures

1. Lumbar puncture: To determine that you are eligible for the study, the doctors have already performed a lumbar puncture, also known as a spinal tap, during which they removed a sample of the fluid surrounding your brain and spinal cord using a needle inserted into your lower back. As part of the study, we will repeat the lumbar puncture at Day 2, Day 14, and possibly at Day 28, depending on if you are still hospitalized and/or willing to undergo another lumbar puncture. The reason for the repeat lumbar puncture is to determine if the medications used to treat the TB meningitis are reaching the fluid around your brain and if the infection is improving. For each lumbar puncture, no more than 10 milliliters of spinal fluid will be removed for the study. Additional spinal fluid may be collected for clinical care (e.g., to help with diagnosis or treatment of your infection).

2. Blood draw, history and physical exam: In addition to the lumbar punctures, we will draw blood regularly over the first month of the study and then every few weeks after that. Up to a maximum of 10 milliliters of blood will be drawn at each study visit, in addition to blood that may be drawn as needed for clinical care (e.g., to help treat your infection or monitor your response to treatment). If you are seen for a sick visit or for early study withdrawal, blood may be drawn at those visits, not to exceed 10 milliliters per visit. A blood draw will consist of having a small needle inserted into a vein, most commonly in your arm, to remove blood. You will also be seen by a medical doctor or nurse at your study visits to go over how you have been doing and what symptoms you have had, discuss your medications, and for a physical exam, including a neurologic and eye exam. This will allow us to closely monitor if you are having any symptoms related to the medications you are receiving for TB meningitis or complications related to the infection itself.

3. Neurocognitive testing: Further into your treatment for TB meningitis, if you are able, we will perform neurocognitive testing, which is a series of pen and paper tests that look at your memory, attention, and other brain activities, along with your mood. These tests take about 1 hour to complete. In addition, we will ask questions to understand if you have any difficulty with movement or thinking related to the infection and whether this affects your day-to-day life.

What follow up will take place in the study?
Because TB meningitis is a serious illness, you will remain in the hospital for at least the first 2 weeks of medical treatment for close monitoring. During this time, you will have repeat lumbar punctures, as detailed above, and blood draws. We will be closely monitoring your blood counts and how your liver is working to determine if any changes to your TB meningitis treatment are required. When your doctors determine you can be discharged after the first two weeks of therapy, you will be required to return to clinic at Weeks 3, 4, 8, 12, 18 and 24 after beginning treatment. The study will take place over 24 weeks. If you are unable to travel to clinic, a research study team member may come to your home with your permission. We also request permission for the research team to contact you by phone if needed.

During the study, if you require specialty care (e.g., from a doctor that specializes in brain or eye health) that is not available at Masaka Regional Referral Hospital, or if you need an imaging procedure such as a brain scan, we will endeavor to refer you for this care if safe and logistically doable and will cover the cost. After the study ends, you will continue to be cared for by the medical team at the TB clinics as per the guidelines of the National TB Programme. Before your care is transitioned to the TB clinics, the study doctors will communicate with the TB clinic medical team.

Can I stop being in the study?
Yes. You can decide to stop participating in the study at any time. Participation in this study is voluntary, meaning it is completely your choice, and you can stop participation at any time or refuse to participate without penalty or loss of any benefits to which you are entitled. Tell the study staff if you are thinking about stopping or decide to stop. They will tell you how to stop your participation safely. If you withdraw from the study, you can continue to receive your standard TB medications free from the hospital or at the TB clinic. The study doctor may also stop your participation in this study at any time if they believe it is in your best interest to stop, if you are not able to comply with the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

Linezolid: We do not know for sure whether linezolid will be helpful for treating TB meningitis. You may experience unwanted symptoms or side effects related to taking linezolid. Linezolid can cause a decrease in your blood cell counts or symptoms such as nausea, vomiting, or diarrhea. Linezolid can also cause damage to your nerves (e.g., nerves of the arms and legs or in the eye) resulting in numbness and tingling in your

hands and feet or blurred vision, although these symptoms are uncommon when you only take linezolid for one month. The side effects of linezolid are usually mild and go away on their own or after stopping the medication. However, as with any medication, severe negative reactions can occur, and certain symptoms, such as those affecting the nerves, may be permanent.

High dose rifampicin: We do not know for sure whether high dose rifampicin will be helpful for treating TB meningitis. As a result, there is a risk with high dose rifampicin that you may receive more rifampicin than is beneficial and that a higher dose may have more side effects. Rifampicin causes harmless red discolouration of the bodily fluids (e.g. urine), can cause rash, flu-like symptoms, and liver damage. The side effects of rifampicin are usually mild and go away on their own or after stopping the medication. However, as with any medication, severe negative reactions can occur.

Everyone taking part in the study will be watched carefully for any side effects. You should talk to your study doctor about any side effects that you experience while taking part in the study.

Phlebotomy: Risks of blood draw include temporary discomfort, bruising, and, rarely, infection. Occasionally, some individuals may feel light-headed or briefly lose consciousness after seeing their blood drawn.

Lumbar puncture: Risks of lumbar puncture include bruising, bleeding around the puncture site, and rarely infection or fluid leak causing a headache. Having a lumbar puncture has the same risks for you whether you have the lumbar puncture in this study or in standard clinical care. A lumbar puncture was required to determine your eligibility for this study, and it is recommended that you receive at least 2 and possibly 3 additional lumbar punctures to check if the infection is improving and if the medication is reaching the spinal fluid. This is probably more than you would receive during standard hospital care. It is routine practice for the doctors to ask for your consent on each occasion that spinal fluid is taken.

Neurocognitive testing: For the neurocognitive testing, you may experience fatigue or frustration in trying to complete the tests. You can take a break and/or stop the testing at any time. Some of the questions on the depression questionnaire may make you feel uneasy or embarrassed. You can choose to skip or stop answering any questions that make you uncomfortable.

Randomization: We know from prior studies that rifampicin is an important drug in the treatment of TB meningitis but that only a small amount reaches the spinal fluid at currently recommended dosing. Giving a higher dose may help more rifampicin reach the spinal fluid to more effectively kill the germ that causes tuberculosis. We also know that linezolid is helpful in treating tuberculosis in other parts of the body, including the lungs, and that it reaches the spinal fluid easily and may help to more effectively kill the germs that cause tuberculosis. We will not have a better idea of whether higher dose rifampicin

or linezolid are helpful in treating TB meningitis until after the study is completed. However, because a computer will randomly decide if you are part of the group that receives high or standard dose rifampicin and linezolid or no linezolid, you have an equal chance of receiving the standard treatment for TB meningitis, which would include standard dose rifampicin and no linezolid, as the higher dose rifampicin and linezolid. If we find that high dose rifampicin and/or linezolid were beneficial in treating TB meningitis, it is possible that you may have received neither medication as part of the trial.

Risk to unborn child and plans for pregnant or breast-feeding women: It is not known if the drug or drug combinations in this study harm unborn babies. Pregnant or breast-feeding women will be excluded from the study. Participants are strongly advised not to become pregnant or father a child while on study treatment. If you are sexually active and able to become pregnant or father a child, we strongly recommend that you use a barrier form of contraception (e.g., condoms) to prevent pregnancy, as hormonal contraceptives (e.g., oestrogen-containing pills) may not be effective while on study medications. You must have a pregnancy test before you enter this study to document whether you are pregnant. If you become pregnant, think you may be pregnant, or have fathered a child at any time during the study, tell the study staff right away. If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends).

Other risks: If you decide to stop participating in the study, you will not be charged for any care received that was paid for by the study during the time that you were in the study. You may need to cover some of the cost of your medical care and hospital stay beginning only from when you leave the study, although your bed and medications to treat TB will continue to be free as is the usual practice at Masaka Regional Referral Hospital.

As always, the study procedures may have side effects or risks that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study. For more information about risks and negative side effects, ask your study doctor.

Are there benefits to taking part in the study?
We know that linezolid and high dose rifampicin both reach higher levels in the spinal fluid where the tuberculosis infection is concentrated in TB meningitis. However, because we do not know for sure if treatment of TB meningitis with linezolid or high dose rifampicin will lead to improved survival or outcomes, there may not be any direct benefit to you from participating in this study. As part of the study, you will receive more intensive monitoring than you would likely receive in routine TB care and this may result in earlier detection and treatment of complications.

What other choices do I have if I do not take part in this study?
You are free to choose not to participate in this study, and may withdraw from it at any time without any penalty or loss of your legal rights. If you decide not to participate, you

will receive the standard 12-month treatment for TB meningitis from the hospital medical team, which will likely include some blood draws and potentially a repeat lumbar puncture.

Will my taking part in the study and my medical information be kept confidential?
Yes. Your participation in the study, all personal information collected about you, and all laboratory test results will be confidential. Only you and the study doctors and staff will know your study ID. The study doctors and staff at participating hospitals and the University of California, San Francisco will have access to information about you but they will not release any identifying information about you to other researchers. The research study staff will protect your personal health information as described in this consent form. Your records may be reviewed by the University, the study sponsor, study monitors, auditors, Research Ethics Committee or other government regulatory authorities to assure the accuracy and quality of the records and the correct conduct of the research study. Any information about you that leaves the clinic/hospital will have your name, address, and other personal identifying information removed.

With your consent, the study doctor may share medical information about you if you need care from a doctor outside the study. If information from this study is published or presented at scientific meetings, your name and other personal identifying information will not be used.

Spinal fluid and blood collected during the study may be sent for storage and analysis outside of Uganda to UCSF or another university that we are collaborating with in the U.S. In preparation for shipping, specimens will be labeled with a study ID number and the date of collection. No other identifying information will be included.

What will happen to any samples I give?
The blood samples and spinal fluid taken during your hospital stay will be analysed in Uganda or at a university with which we are collaborating to measure the levels of linezolid and other drugs. All samples will labeled with a study ID number and there will be no way that you can be identified from these samples. We will also discuss the option of giving additional consent for long-term storage of samples for approved future research. If you have provided storage consent for future research, the samples will be stored at the MRC/UVRI & LSHTM Uganda Research Unit laboratories at Masaka. If you have declined to give additional storage consent for future research your samples for will be destroyed at the conclusion of this study. Storage consent for future research can be given at any time before the samples are destroyed.

What are the costs of taking part in this study?
You will not be charged for any part of participating in the study. If you decide to stop participating in the study, you may need to cover the cost of your medical care and hospital stay beginning only from when you leave the study.

Will I be paid for taking part in this study?
You will be reimbursed up to 30,000 Ugandan shillings for transportation expenses, along

with your time and effort, for each clinic study visit. While you are hospitalized, which will be for the first 2 weeks of treatment at a minimum, you will be compensated 10,000 Ugandan shillings per day to cover meals that are not provided by the hospital.

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor or a member of the research study team if you have concerns about the study or feel you have been injured because of taking part in this study. If you wish to file a formal complaint, you can do this via the study doctors at the MRC/UVRI & LSHTM Uganda Research Unit or to the Chairman of the Uganda Virus Research Ethics Committee – UVRI REC (see details below).

Treatment and Compensation for Injury
If you are injured as a result of being in this study, MRC/UVRI & LSHTM Uganda Research Unit together with the study will give you the necessary treatment for your injuries without charge. You will be told where you can get additional treatment for your injuries. There may be monetary compensation for injuries that are related to participation in the study.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you. Leaving the study will not affect the standard care that you will receive for treatment of TB meningitis. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can contact Dr Freddie Mukasa Kibengo (MRC/UVRI & LSHTM Uganda Research Unit clinic on Plot 2-5 Ntikko Road, Masaka town) on telephone number 0752 731 735 or talk to your study doctor or a member of the research study team about any questions or medical concerns or issues related to study procedures that you have about this study.

For questions about your rights while taking part in this study, you may contact:
Dr. Tom Lutalo, the Chairman of the Uganda Virus Research Institute Research Ethics Committee (UVRI REC) on telephone number 0414 320 776 at the UVRI, Entebbe.

Name of Participant	Signature/Thumbprint (with witness)	Date

Name of Next of Kin or Caregiver *(if required)*	Signature	Date
Name of person obtaining consent	Signature	Date
Principal Investigator or Site PI or designee	Signature	Date

The participant is illiterate and thumbprint used. As a witness, I confirm that all the information about the study was given and the participant consented to taking part.

Name of Impartial Witness *(if thumbprint used)*	Signature	Date