Study Title: Optimizing the Dose of Flucytosine for the Treatment of Cryptococcal Meningitis.

The lead investigators of this research study are Dr. David Meya of the Infectious Diseases Institute (IDI) of Makerere University; Dr. Thomas McHale and Dr. David Boulware of the University of Minnesota USA.

Study Purpose

Cryptococcal meningitis or "Crypto" is a life-threatening fungal infection around the brain. Fortunately, this infection is very treatable with the correct medicine. However, flucytosine, one of the medicines currently used to treat cryptococcal meningitis, has serious side effects that can affect your kidneys and blood. In Uganda and other countries in Africa, this drug is not widely available and supplies are often low, making it difficult to consistently provide good treatment for crypto. For this reason, researchers have been searching for ways to improve access to flucytosine for patients and reduce side effects.

Researchers have done studies to determine the best dose for flucytosine. We are able to measure the levels of flucytosine that reach the brain. Based on these levels, we believe that lower doses of flucytosine may still be effective in treating crypto. We will also be giving you 2 additional medications to treat crypto meningitis that will be at standard recommended doses and have been shown to be effective even without flucytosine. Lower doses will allow more people to have access to the medicine and also may have fewer side effects.

The purpose of this study is to know whether this lower dose of flucytosine is a safe and effective treatment for people with cryptococcal meningitis. We hope to enroll around 50 people in this study in Uganda. In order to show that this medicine treats crypto at the dose under study, we will measure how quickly the crypto is cleared from your around brain. Researchers have used this measurement for decades to study how well medicines work for crypto.

Your participation in this study is voluntary. If you decide to participate in the study, you will receive a dose of 60 mg/kg of the medicine flucytosine, which is an experimental dose that is lower than the dose of 100 mg/kg that is currently recommended by international guidelines. If you decide not to participate in the study, care will still be provided according to the best standards of care available in the hospital. You confirm that the following has been explained to you, and you have had a chance to ask questions:

1. If you decide to participate in the study, you will receive the lower dose of the medicine flucytosine
2. It is unknown for sure whether lower doses of flucytosine will be effective in treating cryptococcal meningitis.
3. It is unknown for sure whether a lower dose of flucytosine will be safer than standard dosing.
4. You will also receive a second standard medicine for your infection, called IV amphotericin for either 1 dose (if liposomal) or 7 days (if deoxycholate). This is a standard medicine and is not experimental. You will receive a third standard medicine for your infection, called fluconazole. This is a standard medicine and is not experimental.
5. The IV amphotericin is a strong medicine with many side effects including fever, rigors and

chills. We will need to do blood tests to monitor this medicine's side effects. IV amphotericin is a standard, recommended medicine and is not experimental.

6. You will be required to take all of your medications faithfully.
7. The doctors will take fluid surrounding your spinal cord through a needle in your back, which is called a lumbar puncture. You will be required to receive at least 3 lumbar punctures, which we strongly recommend regardless of whether you decide to enrol in this study. These are important to check the pressure around the brain and to make sure the infection goes away. This is part of the best standard therapy.
8. After leaving the hospital you will be required to return for clinic visits every 2 to 4 weeks for 18 weeks. 18 weeks is the duration of the study. If you are unable to attend clinic because you are sick, let us know and we will help you get to clinic or come see you at home. If you miss your scheduled visit, a nurse will continue to call until we have reached you and a new visit can be scheduled. After 18 weeks, clinic will return to normal frequency as decided by you and your doctor.
9. At the end of 18 weeks, you will have the option to receive ongoing care through our clinic, continue receiving care through your own clinic, or establish care at a new clinic near your home. Study staff will assist in ensuring ongoing care at the end of the study period.
10. You may be contacted by phone or text message as a reminder of clinic appointments, to check how you are feeling, or how you are taking your medicines.
11. You will benefit from this study because you will receive more intensive medical care through a group of doctors and nurses that are experienced in treating meningitis. The test results will be used by doctors to make decisions for your health.
12. If you agree, some samples will be collected and stored for future research tests that are separate from this study. This may benefit future Ugandans and others around the world, but you will not benefit directly.
13. You can choose not to have your samples stored and still participate in this study. Tests will continue to be performed to assist doctors in taking care of you, but will not be stored.
14. Study doctors or a designated representative of the sponsor will review your medical records and tests from this hospital stay.
15. You will not be paid for participating in this study, but you will be given money to refund transport expenses up to 30,000 Uganda Shillings for each study related visit. You may also be compensated up to 50,000 Uganda Shillings if extra blood is drawn.
16. Any information that is collected about you shall be kept private, and your data will be used without your name, picture, or identity.
17. Agreeing to participate in this study is voluntary and you can withdraw from the study at any time if you so wish by telling the study doctors. If you withdraw from the study, you can continue to receive your crypto and HIV treatment at the hospital or clinic, at no cost.
18. You will not be giving up any of your legal rights by signing this consent form.
19. You are going to be given a copy of this form.

It is recommended by the national guidelines and your doctors that you continue to take

medicines for cryptococcal meningitis and to receive lumbar punctures while in hospital.

Risks

The study has the following risks:

Until this study is completed, there is no way of knowing for sure how effective lower dose flucytosine is for treating cryptococcal meningitis. For this reason, there is a risk that you could receive a medicine that is less effective than the standard dose of flucytosine. Lower doses of flucytosine have not been used in a lot of people. Side effects can occur, though we think they are less than those with standard doses of flucytosine. Common side effects are expected to include nausea, diarrhea, or vomiting. Most of the side effects are expected to be mild and go away with stopping the medicine. Severe unforeseen adverse reactions could occur but are expected to be less likely with this lower dose

A lumbar puncture (LP) is when a needle is inserted into the back to collect spinal fluid from a person with meningitis. It is the method doctors use to collect spinal fluid for laboratory analysis or to relieve headache that results from increased pressure around the brain. An LP is a part of the standard medical treatment for persons with cryptococcal meningitis, and is part of the therapy for this infection. Risks of lumbar puncture include possible bleeding around the puncture site, and rarely infection or fluid leak. Having an LP has the same risks for you whether you have the LP in this study or as part of standard clinical care. Repeated LPs are strongly recommended whether you choose to participate in the study or not.

A lumbar puncture is required for diagnosis, and it is recommended that you receive a total of at least 2 more LPs to relieve pressure around your brain, to help decrease the infection, and to ensure that the infection is gone at the end of therapy. These LPs will occur approximately every 2 days for the first week and at the completion of flucytosine therapy. If the pressure around your brain is high enough to be causing a headache, you will be recommended to have additional LPs to lower the pressure, which also makes your headaches better. This is the standard of care for cryptococcal meningitis and will be recommended regardless of whether or not you enrol in this study. We recognize that these LPs can be unpleasant, but the LPs are very important for your medical care to give you the best chance of surviving this serious infection.

This study requires that a small amount of blood be taken through a needle from a vein in your arm at several times during the study. Your doctors will do some tests on the blood to make sure your liver and kidney are working well, and to know if any severe problems happen. If there are problems found, your medicine may be decreased or stopped. This is about 30mL (6 teaspoons) more blood than would have been taken over the next 3 months than if you do not participate.

This small amount of extra blood taken should have no effect on you, since your body will have time to make new blood. It is possible that there may be a small amount of bleeding or bruising around the needle site. Infection at the needle site is also a very small possibility.

***Pregnancy*:**

Pregnant and breastfeeding women <u>cannot</u> enrol into the study. Pregnancy should be avoided when taking the recommended drugs for cryptococcal meningitis due to risks to the unborn child (fetus). This risk is not unique to the study. If you are sexually active, we recommend that you use at least two methods to prevent getting pregnant. If you later want to become pregnant or think

you may be pregnant, please notify the study doctor right away, so that some of your medicines may be changed.

Research Related Injury

If you experience problems related to crypto infection of the brain, HIV, or a new infection, treatment will be available, and you will not have to pay for it. If you experience other health problems, a referral to specialized care will be made, but this study cannot pay for health care, which is unrelated to the crypto infection. If you suffer bodily injury as a consequence of flucytosine therapy, there is insurance to compensate you through Lion Assurance Company, Ltd. P.O. Box 7658, Kampala.

Sample Storage

If you agree to participate in this study, we will collect some samples of your blood, urine, stool and spinal fluid for your medical care during the study. We would like to store these samples temporarily. These samples will be identified by a unique number, not your name or other personal information, so that others will not be able to identify you. Testing will be for research related to meningitis, the immune system, and to measure how much of the medicine gets into your blood. Some of the tests will be done locally in Uganda, and some will be done in the United States.

Extra Sample Collection

With your permission, we would also like to collect a small volume of extra blood (approximately 4 teaspoons or 20 mL) along with your other routine blood draws for research testing. This may require an additional blood collection that would not normally occur. This may be used to test the levels of flucytosine in your blood or may be used for research that studies the types of cells in your blood that fight infection. You will be compensated 50,000 Uganda shillings if extra blood is drawn. If you prefer not to have any extra blood draws, you may still participate in the study. Many research tests will be performed later and will not change your treatment, and thus you will not receive the test results.

Sample ownership and duration of storage

If you are willing to donate samples for future research, it means you are giving them to us. The samples will be under the responsibility of the researchers and may be shared with other researchers to assist with testing. You will not personally receive direct benefit from this future testing, but your contribution may help others in the future. They will not be sold. There is no limit on how long your samples will be stored. However, you can change your mind at any time without penalty and tell us to destroy the samples. If you prefer that we do not keep your samples after the study is completed, you may still participate in the study.

Confidentiality

Your study information will be kept private, but will be included in your medical records if relevant. Your name, picture of your face, or identity will not be shared or disclosed in any publications or presentations. Your records for the study may be reviewed by representatives of the University, and other government regulatory authorities to assure the accuracy and quality of the records and the correct conduct of the research study.

Study approval

Approval to conduct this research study has been granted by the Uganda National Council for Science and Technology (UNCST),Infectious Disease Institute Research and Ethics Committee, and University of Minnesota. The research study is funded by the National Institute of Health in the United States.

Contacts and Questions

You may ask any questions you have now. If you have questions later or any urgent health concerns, you are encouraged to contact:

- Dr. David Meya in **Kampala** on phone number XXXXXXXXX
- Dr. Conrad Muzoora in **Mbarara** on phone number XXXXXXXXXXX

You will be given a clinic appointment card with the doctors' phone numbers before you leave hospital.

In case of any questions regarding:

- Your welfare and rights as a research participant,
- Any questions or complaints not being answered by your study doctors
- You want to talk to someone besides the research team.

you should contact:

- Dr. David Patrick Kateete, the Chairman of the **Infectious Disease Institute Research Ethics Committee (IDIREC)** on telephone 0704879922 or 0393193144
- **Uganda National Council for Science and Technology (UNCST)**, Plot 3 Kimera Road; Ntinda, Kampala on telephone 0414-705-513.

If you have any questions about this research study, you can ask them now or contact the above doctors later. The study doctors will see you while in hospital.

For More Information

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by United States Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Sample Storage

☐ **I consent to the collection, testing and storage of my samples (blood, spinal fluid, stool and urine) for the purposes of this research. Samples will be stored indefinitely, unless I change my mind and ask for my samples to be destroyed. I also consent to have extra blood draws specifically for study purposes.**

☐ **I consent to the collection, testing and storage of my samples (blood, spinal fluid, stool and urine) for the purposes of this research only. This does not require additional blood draws, and all samples will be destroyed when the study is over.**

Informed consent

I hereby consent to participate in this research study called:

"Optimizing the Dose of Flucytosine for the Treatment of Cryptococcal Meningitis."

Name of Impartial witness **(If participant thumb print used)**	**Signature**	**Date**
Name of Participant	**Signature / thumbprint (with witness)**	**Date:**
Name of Surrogate	**Signature / thumbprint of surrogate**	**Date:**
Name of person obtaining consent	**Signature**	**Date**

The Participant signed with a thumb print. As a witness, I confirmed that all the information about the study as given and the participant consented to taking part.

Consent Reviewer (PI or Designee)	**Signature**	**Date**