Preparing for a clinical trial of interventions to maintain normal vaginal microbiota for preventing adverse reproductive health outcomes in Africa.

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<th>Study Code: VMB</th>
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<td>Participant Information Sheet: Screening</td>
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Rinda Ubuzima researchers are asking you to join a screening process to see if you meet the requirements to participate in a research study of interventions to keep the vagina healthy.

Bacteria are too small to see by the naked eye. They can be found everywhere in our surroundings, including in and on the human body. Most bacteria are harmless. Some bacteria are even necessary for human survival. For example, the bacteria in the gut help us break down our food. However, some bacteria cause disease. A person with fever usually has an infection by disease-causing bacteria, and requires drugs called antibiotics to treat the infection.

There are also bacteria in the vagina. These are called the vaginal microbiota or VMB. Most bacteria in the vagina are so-called ‘healthy bacteria’: they do not cause disease but help to kill ‘unhealthy bacteria’ such as the bacteria causing sexually transmitted infections (STIs) and urinary tract infections (UTI). Women with too many unhealthy bacteria in the vagina have a vaginal infection. The two most common vaginal infections are bacterial vaginosis (BV) and *Trichomonas vaginalis* (TV). These infections require an antibiotic to kill the unhealthy bacteria. However, the antibiotic does not always kill all the unhealthy bacteria and sometimes kills the healthy bacteria as well. Women who have taken an antibiotic to cure a vaginal infection may benefit from insertion of healthy bacteria in the vagina to restore the balance. This is called a probiotic.

In this VMB study, we will enrol HIV-negative, non-pregnant women aged 18-45 who suffer from vaginal infections, and particularly bacterial vaginosis (BV) and *Trichomonas vaginalis* (TV). Women often do not know that they have such infections but we can find out by examining the vagina and taking vaginal samples for testing in a laboratory. Women who have an infection will first receive metronidazole pills (which is an antibiotic) to cure the infection. This is how these infections are usually treated in Rwanda. Once cured, they will be allocated to one of four different study groups. The four groups are: 1. Counselling on what you yourself can do to prevent recurrence of vaginal infections (control group); 2. Counselling plus regular use of the antibiotic metronidazole (either a pill or a vaginal gel) for two months; 3. Counselling plus regular insertion of Ecologic Femi vaginal capsule...
(which is a probiotic) inside the vagina for two months; and 4. Counselling plus regular insertion of Gynophillus vaginal tablets (which is also a probiotic) inside the vagina for two month. The metronidazole pills are approved in Rwanda. All of the vaginal products have been tested and approved in Europe or the United States, but are not yet available in Rwanda. In the VMB study, we will determine whether these products are safe and acceptable to Rwandan women, and whether they can keep the vagina healthy.

Taking part in this screening process is entirely voluntary. We urge you to discuss any questions about this process with our staff members. If you decide to participate in this screening process, we will ask you to sign and date this consent form. We will then give you a copy of this form to keep.

1. **What is the name of this study?**
   ‘Preparing for a clinical trial of interventions to maintain normal vaginal microbiota (VMB) for preventing adverse reproductive health outcomes in Africa’, or ‘VMB trial’ for short.

2. **Who is doing this study?**
   Rinda Ubuzima in Kigali, Rwanda, and the University of Liverpool in Liverpool, the United Kingdom, are conducting the study.

3. **Why are we doing this study?**
   In this research study, we want to determine the safety of each of the three study products (one antibiotic and two probiotics) compared to the control group (counselling only), as well as the efficacy in reducing the recurrence of vaginal infections and the incidence of STIs and UTIs. We will also evaluate women’s acceptability and adherence to the study interventions, and the feasibility to conduct larger studies with the most promising products in Rwanda in the future.

4. **How can you join the study?**
   You are not being asked to join this study right now. You are being asked to be part of the screening process to see if you fulfil all the requirements to join. We will talk to you about what it means to be part of the study. If you meet the requirements and want to join, you will get a chance to join later.

   This document is called the Participant Information Sheet. It contains information to help you decide if you would like to join the screening process. If you decide to be screened, we will ask you to sign and date an Informed Consent Form. The Informed Consent Form says that you and I have discussed the information you need to know about the screening process. If you sign, it means that you agree to go through the screening process. It also means that you give permission for research centre staff to contact you. We will give you a copy of the Participant Information Sheet and the signed Informed Consent Form to keep.

   It is important to always remember the following things:
   - To be part of the screening process is your decision and not up to anyone else.
   - You may join the screening process and then change your mind and stop the process at any time.
5. Who will be screened?
The study will include 4 groups with a total of 60 women currently in good physical and mental health. The women must be 18 to 45 years old and HIV-negative and cannot be pregnant. Women are allowed to use condoms and contraceptive methods while participating. As explained above, this trial is for women who have vaginal infections. This is why we will only screen women at high risk of vaginal infections, defined as having had more than one sexual partner in the last 12 months OR having been treated for an STI and/or BV in the last 12 months. Women should not have undergone gynaecological surgery or invasive procedures in the last 3 months, and should not be participating in other health intervention study. Since not all women that we screen will meet all the requirements to join the study, we expect to screen at least 120 women.

6. How often do women have to visit the study clinic and for how long?
Women who test positive for pregnancy or HIV will only be seen at the study clinic once. For all other women, the screening process will require at least two study visits, but additional visits may be needed if you test positive for infections. We will aim to complete all screening visits within 6 weeks.

If you meet all requirements to join the study and decide to join, you would have to visit the study clinic for enrolment and again after 7 days, one month, two months, and 6 months. If you are allocated to a study product group, you would use the product from enrolment to the Month 2 visit.

7. What will you have to do when you qualify for the study and decide to join?
If you meet all requirements to join the study and decide to join, you will be placed into one of the four study groups. Group assignment will be by chance (like rolling a dice), which is called randomisation. Regardless of which group you are in, you will be given advice on which things you yourself can do to prevent vaginal infections. If you are in group 1, you will not receive any additional intervention (this is the control group). If you are in groups 2, 3 or 4, you will be asked to use a study product for two months, as explained above. How often you have to use the product varies for each product, from once every day for 5 days about once per month to 2-3 times per week throughout. Women who are joining the study will be given clear instructions about this at enrolment. You do not have to use any vaginal products during menses if you do not want to.

8. What will happen during the screening visit?
Upon arriving at the study clinic, you will be given a participant identification number. Next we will explain the study to you; this is usually done in a group with other potential participants. After the group session, you will be taken to a private room for an individual session. A study team member will answer your questions, and will determine whether you have understood the information about the study. She will also determine how well you can read to decide whether a witness should be present for the signing of the consent form. Finally, you will be asked to sign the screening informed consent form. The screening visit will take about 3 hours to complete.

After signing, you will undergo the following procedures:
- **Face-to-face interview** – A study team member will talk with you in private. You will be asked questions about yourself (including your sexual behaviour such as number of sexual partners and condom use, vaginal practices, circumcision status
and penile hygiene of your male partners) as well as medical questions.

- **Counselling** – Before you are tested for HIV, you will receive counselling about HIV, STIs and vaginal infections, how you can prevent them, and what it means to be tested. After the HIV test has been completed, you will receive the result and what it means. You will be given condoms free of charge.

- **Urine sample** – You will be asked to provide some urine, which will be tested immediately for pregnancy and urinary tract infection. If you are pregnant, you cannot join the study, and we will refer you to a health centre close to your home for antenatal care. If you want, you can still be tested for HIV at the study clinic.

- **Blood sample** – We will take 10 ml of blood (which is about 2 teaspoons) from your arm to test for HIV and other STIs. The blood will be tested for HIV immediately after collection using tests that are recommended by the Ministry of Health in Rwanda. If you are infected with HIV, you cannot join the study, and we will refer you to a health centre close to your home for treatment and care. The study clinic will not provide HIV treatment.

- **Vaginal examination in HIV-positive and/or pregnant women** – Even though you are not eligible to join the study, we will ask you to donate vaginal swabs for VMB testing. You will lie down on an examination table or squat, and either take the swabs yourself or have a study doctor take them. This does not require the insertion of a speculum and you will hardly feel it because the swabs have a soft tip (like cotton wool). If the doctor thinks that you may have a vaginal infection or STI, he will offer you a more thorough vaginal examination with diagnostic testing.

- **Vaginal examination in HIV-negative non-pregnant women** – While lying down on an examination table, the study doctor will insert a speculum, and will thoroughly examine inside. He will also take swabs (also with a soft tip like cotton wool) from your vagina and from the mouth of your uterus, and he will squirt about 2 teaspoons of clean fluid inside your vagina and suck it back up using a syringe. Some of these samples will be used for diagnostic testing and others for VMB research. Only one test (the wet mount) will be done immediately while you are at the clinic; this test will show whether you have a vaginal infection. The other tests will be done in local laboratories after you have left the clinic. These tests will show whether you have any of the following STIs: syphilis, genital herpes, Chlamydia, gonorrhoea, or TV.

- **Treatment** – If you were found to have a vaginal or urinary tract infection, you will receive treatment free of charge by the study team.

- **Scheduling of results visit** – You will be asked to return to the study clinic 1-2 weeks after the screening visit to obtain the STI test results. If you are found to have a curable STI that was not yet treated, you will receive treatment free of charge by the study team.

- **Rescreening** – We will offer enrolment to women who received metronidazole treatment for BV or TV at the screening or results visits but are free of STIs, UTI, and vaginal candidiasis. If we did not find any infections or just vaginal candidiasis during screening, you are not eligible. If we found an STI, UTI or vaginal candidiasis, you will receive treatment for those infections first, and you will be retested for vaginal infections after completion of that treatment. You may be rescreened up to 3 times.

9. **What happens if I meet all requirements to join the study?**

   If you still meet all the study requirements after the screening process, we will invite you to return to the study clinic for an enrolment visit. We will provide you with a different
Participant Information Sheet that explains the study in more detail. If you want to join, we will ask you to sign a new Informed Consent Form. However, you may freely refuse to join the study, even if you meet all the study requirements, and you may withdraw from the study at any time, even after having given informed consent.

10. What are my responsibilities in the study?
Your responsibilities as a study participant include the following:
- Provide truthful information about yourself
- Tell the study doctor about any problems you may have during the study
- Tell the study doctor about any medicine or vaginal products you use during the study
- Make an honest effort to attend study visits and use the study products as instructed, and if this is not possible or you do not want to, to tell the study team about it.

11. What are the potential risks or discomforts of this screening process?
- There are no serious risks associated with joining this screening process.
- You may feel discomfort from the blood sampling: you may feel dizzy or faint and you can develop a bruise or swelling (and very rarely, an infection) at the spot where the needle goes in your arm.
- You may become worried or anxious while waiting for your HIV test results or the test results for other infections. You may experience anger or distress if you learn you are HIV-positive or have another infection that is passed by sex. You may also experience problems with your partner(s).
- You may feel discomfort during the vaginal examination, especially insertion of the speculum. There is a very small risk of injury to the lining inside your vagina from the speculum. These injuries normally heal quickly.
- You may become embarrassed, worried, or anxious during the vaginal examination, or when discussing your sexual behaviours or health history.
- You could have problems with your partner(s) or family members if you tell them or if they find out that you have taken part in this screening.
- Though very unlikely, a breach of confidentiality is a potential risk.
- You may have to spend a significant amount of time at the study clinic, especially at the first screening visit, due to the large numbers of procedures that have to be done.

The study staff will do their best to help you deal with any uncomfortable feelings, problems or questions that you may have.

12. What are the potential benefits of this screening process?
At no cost to you, you will receive HIV counselling and testing, testing for pregnancy and UTI, condoms, and counselling on how to protect yourself from HIV and genital infections and how to use condoms. Some women will also receive a vaginal examination with testing for vaginal infections and STIs (all women who have signs or symptoms that warrant further investigation, and all HIV-negative non-pregnant women). You will receive treatment free of charge for vaginal infections, UTI, and curable STIs at the research centre. Conditions that cannot be treated at the research centre (including HIV and pregnancy) will be referred to local health centres close to your home. There is no treatment for genital herpes or human papillomavirus (HPV). Women with genital herpes will be educated about the infection and will be advised to use condoms when they experience an active herpes outbreak to prevent transmission to
others. If we identify funding to test samples for HPV (this test is not available in Rwanda), we will inform you of the result, and provide information on the link between HPV and cervical cancer, and how best to prevent HPV infections and cervical cancer.

13. What are my other options?
Your other option is not participate in the screening process. If you choose to do so, there will be no consequences for you.

14. Who will see my personal information?
All the information that you give us during the interviews and all laboratory test results will be kept confidential. At the beginning of the screening process, you will be assigned a participant identification number, and this number will be used on all study forms and samples instead of your name. Your name will only be written on the screening informed consent form and in the study participant identification register. These will be kept separately from the other study documents under lock and key. You have the right to ask the doctor for access to your records.

The people who do have access to all study documents are the study staff, study monitors, and personnel from regulatory bodies such as the Rwanda Ministry of Health, the Rwandan Institute of HIV/AIDS and other Diseases Prevention and Control (IHDPC), and the Rwandan National Ethics Committee. By signing the Informed Consent Form, you authorise this access to your records.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be included. The information from all participants will be merged, and only the pool of results will be used for publication or presentation.

15. What will happen with my samples?
Some of the samples will be used to identify and treat infections as mentioned above. Other samples will only be used for the VMB research. You will not receive the results of these research tests because: 1) They have no consequences for your health or medical care; 2) They are done outside of Rwanda, which means that it will take a long time before the results are available; and 3) We still have to find additional funding to be able to do some of the planned tests. Samples will be stored using your participant identification number and not your name.

We will ask you for permission to store your samples for the long term so that we can do these VMB research tests. If you agree, they will be used only for testing that is relevant to the VMB research that has been approved by the Ethics Committees. We will not do any testing on your genes. The informed consent form includes a space for you to give us permission to use your stored samples. If you do not sign, you will still be able to join the screening process, but we will destroy your samples after your study participation has ended.

16. What are the costs for participating?
There are no costs to you for taking part in the screening process. You will be given a total of three thousand Rwandan francs (3,000 RWF) for the screening process, to reimburse you for your transport costs and the time spent at the research centre.
17. **What if I get injured?**

You must tell the study staff immediately if you have any side effects or injuries while you are in the screening process. If you become ill or injured as a result of taking part in the screening process, you will receive medical treatment free of charge. The study staff will also tell you where you can get additional treatment, if needed.

If you are injured as a result of participating in the screening process or study, you will be compensated according to international guidelines and Rwandan legislation. For this, Rinda Ubuzima obtained a “no-fault” insurance from Phoenix of Rwanda Assurance company with policy number: P-KIG-15-201-PI-000008. If you have any questions regarding compensation, do not hesitate to ask the study doctor for more information. According to existing regulations, a disease which is diagnosed during the course of the screening process or the study, but is not caused by participation in the screening process or study, including a newly diagnosed HIV infection, is not covered by such insurance. Furthermore, Rinda Ubuzima or UoL are not responsible for any loss, injuries and/or damages that happened because:

- You used other medicine during the study without telling us
- You did not follow instructions given by the study doctor or nurse
- or negligence on your part.

18. **Voluntary participation**

Your participation in this process is voluntary and you have the right to not participate, or to decide not to continue with the screening at any time. Either choice will not affect your relationship with your doctor or your access to medical care. You are asked to sign two copies of this form: one copy will be kept at the research centre and a second copy will be given to you to take home. By signing, you do not give up any of your legal rights.

19. **Contact information for questions or concerns**

If you have any questions, you can contact the following people:

Principal Investigator: Dr Stephen Agaba  
Telephone number: +250 788 357 866  
Study Coordinator: Ms. Mireille Uwineza  
Telephone number: +250 788 593 158

This research study has been reviewed and approved by the Rwanda National Ethics Committee and the University of Liverpool Research Ethics Sub-committee for Physical Interventions to ensure that the rights and safety of all participants in the study are upheld and that the study is conducted according to strict guidelines.

If at any time you have any questions regarding your rights as a participant in a study, you may contact:

- Dr. Jean Baptiste Mazarati (Chairperson of Rwanda National Ethics Committee)  
  Telephone number: +250 788 309 807  
  OR
- Dr. Leatitia Nyirazinyoye (Secretary Rwanda National Ethics Committee)  
  Telephone number: +250 788 683 209.