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

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 women like you who are 18-45 years old, HIV-negative, not pregnant, and who suffer from vaginal infections, and particularly bacterial vaginosis (BV) and Trichomonas vaginalis (TV). As part of the screening process, you received metronidazole pills (which is an antibiotic) to cure the infection that you had. You have completed that treatment, and are now being invited to join the study. If you agree, and if you still fulfil all the requirements (we will recheck some of them during the enrolment visit), you 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 Gynophilus vaginal tablets (which is also a probiotic) inside the vagina for two months. 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 the study is entirely voluntary. We urge you to discuss any questions about the study with our staff members. If you decide to participate in the study, 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?**
   This document is called the Participant Information Sheet. It contains information to help you decide if you would like to join the study. If you decide to join, 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 study. If you sign, it means that you agree to join the study. 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 study is your decision and not up to anyone else.
   - You may join the study and then change your mind and stop at any time.

5. **Who will be in the study?**
   The study will include 4 groups with a total of 60 women currently in good physical and mental health. Only women who have received metronidazole pills to treat BV or TV infection during the screening process from the study team will be included. They must also be 18 to 45 years old, HIV-negative, not pregnant, and free of curable STIs, UTI, and vaginal candidiasis. Women are allowed to use condoms and contraceptive methods while participating. They should not have undergone gynaecological surgery or
invasive procedures in the last 3 months, should not have any medical conditions that might make study participation unsafe, and should not be participating in another health intervention study.

6. **How often do women have to visit the study clinic and for how long?**
   You have already completed the screening process. Today’s visit is called the enrolment visit. If you join the study today and still meet all study requirements (some of them will be rechecked today), you would have to visit the study clinic again after 7 days (Day 7 visit), one month (Month 1 visit), two months (Month 2 visit), and 6 months (Month 6 visit). If you are allocated to a study product group, you would use the product from enrolment to the Month 2 visit. Your study participation ends at the Month 6 visit.

7. **What will you have to do when you join and still qualify for the study?**
   If you decide to join and still meet all requirements for the study, you will be placed into one of the four study groups. There will be 15 women in each group. 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 4 days to once per day for 5 days followed by 3 times per week. If you join the study and are randomised, you will be given clear instructions on how and when to use the study products. You do not have to use vaginal products during menses if you do not want to. The first product insertion will be done at the study clinic under supervision of a study team member.

   A subgroup of three women in each study group (N=12) will be asked to self-collect vaginal samples at home every Monday, Wednesday, and Friday per week for the first four weeks after enrolment. This subgroup is called the frequent sampling group. These self-sampling procedures will be on top of the regular study procedures. Samples will either be collected by a study team member, or dropped off by you, at a time and place that is acceptable to you. The informed consent form includes a space for you to give us permission to ask you to join the self-sampling group. If you do not sign that space, you can still join the study, but we will not ask you to join the self-sampling group. If you do agree to self-sample and are selected, a study team member will teach you how to do this during the enrolment visit.

8. **What will happen during each study visit?**
   This section explains to you the different procedures that will be done at the study visits. Some of these are done at every visit and some at certain visits. Most visits will take about 3 hours to complete. You may have to come back to the research centre for additional visits if you have medical problems or concerns. Study staff will use the contact information that you provided to remind you of scheduled visits; this contact information will be updated at each visit. If you miss a visit, study staff will try to contact you again. They will only contact you in the ways that you have agreed on, and will not give any information about your study participation to your contact persons.

After you have signed the Informed Consent Form for Enrolment, the following will
When? | Procedure
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**Every visit** | 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. After you have started using the study products, you will also be asked about your experiences with these products.

**Every visit** | Counselling – You will receive counselling about HIV, STIs and vaginal infections, how you can prevent them, and what it means to be tested. At the Month 6 visit, you will receive another HIV test and the counselling related to the HIV test. You will be given condoms free of charge.

**Enrolment Month 6** | Urine sample – You will be asked to provide some urine, which will be tested immediately for pregnancy and UTI. If you are pregnant at the enrolment visit, you cannot join the study, and we will refer you to a health centre close to your home for antenatal care. If you find out that you are pregnant after you were allocated to a study group, you can complete the study. If you have a UTI, you will be treated and rescreened.

**Day 7, Month 1, Month 2** | Vaginal examination – While lying down on an examination table, the study doctor will insert a speculum, and will thoroughly examine inside. He will also take swabs (with a soft tip like cotton wool) from your vagina and will squirt about 2 teaspoons of clean fluid inside your vagina and suck it back up using a syringe. 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. We will also do other tests for vaginal infections in local laboratories after you have left the clinic. Some of the samples will be used for VMB research.

**Enrolment Month 6** | Vaginal examination – The vaginal examination and collection of samples will be the same as for the other visits, but in addition, samples will be taken from the mouth of your uterus for Chlamydia, gonorrhoea, and HPV testing (the latter if funds can be identified).

**Month 6** | 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, we will refer you to a health centre close to your home for treatment and care. The study clinic will not provide HIV treatment.

**Enrolment** | Randomisation, product instructions, and insertion of first dose – If you are still eligible after the urine testing and vaginal examination, you will be assigned to a study group. If you were assigned to one of the three vaginal product groups, study staff will give you detailed instructions about that product, and you will apply the first dose under their supervision. If you are selected to join the self-sampling group, you will also receive instructions on how to self-sample and handle the samples after collection.
Month 2 | **Terminate study product use** – You are now done with using the study products, but we would like to see you one more time at Month 6 to see if your vagina is still healthy after you stopped using the products and whether you have any new genital infections.

Every visit | **Treatment** – If you have a vaginal infection, curable STI or UTI you will receive treatment free of charge by the study team. If you have the infection at the enrolment visit, you will be treated first and rescreened for enrolment. If you have the infection after you were allocated to a study group, you will be treated and will be allowed to continue in the study. You can also continue to use the study products.

9. Are there any additional procedures during the study?
You may be invited to participate in a focus group discussion or in-depth interview to learn more about your knowledge about BV and its impact on women’s health plus talk to you about acceptability and adherence to the study products. If you decide to participate in a focus group discussion or interview, the procedures will first be explained to you. You will be given a separate consent form to sign. Participating in the focus group discussion and/or interview is voluntary. If you decide you do not want to participate, you can also still participate in the VMB trial.

10. What if you become pregnant during the study?
If become pregnant during the study after you had been allocated to a study group, you will be allowed to continue in the study and continue using the vaginal product (if applicable). The study team will stay in touch with you until delivery, and will record information about your pregnancy and delivery. You will also be referred to a health centre close to your home for antenatal care.

11. What are your 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 other 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.

12. What are the potential risks or discomforts of this study?
- There are no serious risks associated with joining the study.
- You may feel discomfort during the vaginal examination, especially insertion of the speculum, while using a vaginal product (if applicable), or while self-sampling (if applicable). There is a very small risk of injury to the lining inside your vagina from inserting the speculum, the metronidazole gel applicator, or swabs. These injuries normally heal quickly.
- You may become embarrassed, worried, or anxious during the vaginal examination, when inserting a vaginal product or swab in your vagina, 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 study.
• 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).
• 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 enrolment and Month 6 visits, 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.

13. What are the potential benefits of this study?
If you are allocated to a study product, you may experience better vaginal health because of the product. You will also receive regular vaginal examinations with testing for vaginal infections and STIs. 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. 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.

14. What are my other options?
Your other option is not to join the study. If you choose to do so, there will be no consequences for you.

15. How do I find out about the findings of the VMB trial?
You will be told of any new information learned during the course of the VMB trial that might cause you to change your mind about staying in the study. At the end of the VMB trial, you will be told when the study results may be available and how to learn about them.

16. 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 were 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 (IHDPDC), 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.

17. 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 study, but we will destroy your samples after your study participation has ended.

18. What are the costs for participating?
There are no costs to you for taking part in the screening process. You will be given three thousand Rwandan francs (3,000 RWF) for each scheduled study visit to reimburse you for your transport costs and time spent at the research centre.

19. 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 study. 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 study, you will be compensated according to international guidelines and Rwandan legislation. For this, Rinda Ubuza 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 study, but is not caused by participation in 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.

20. **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.

21. **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.