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Informed Consent

The FRESH LACTIN-V Trial

University of KwaZulu-Natal (UKZN)
University of California, San Francisco (UCSF)
Massachusetts General Hospital (MGH)
The Aurum Institute

Dear FRESH participant,

You are being invited to join a research study called **LACTIN-V** which is being conducted by FRESH investigators, Professor Thumbi Ndung'u (UKZN) and Drs. Krista Dong and Doug Kwon from the Ragon Institute (MGH). Collaborating investigators for this trial are: Dr. Vaneshree Govender (Aurum) and Dr. Craig Cohen and his associates at the Department of Obstetrics, Gynecology & Reproductive Sciences at UCSF.

Professor Ndung'u and Dr. Govender, as the Site Principal Investigators for the LACTIN-V study, are responsible for the conduct of this study.

LACTIN-V is a new product made from a live bacterium called *Lactobacillus crispatus*. *Lactobacillus crispatus* is a natural, healthy – or "good"- bacteria found in the vaginal tracts of women, which may be associated with a reduced risk of sexually transmitted infections (STIs) and HIV. The researchers want to test LACTIN-V to see if it can change a woman's ***microbiome*** (the combination of natural bacteria in her vagina) and shift it to a more "healthy", or protective *microbiome***.**

Joining the LACTIN-V study is completely voluntary. Your decision to enrol, or not, will not affect your participation at FRESH. If you choose to be in this study, you will be asked to use the study drug, LACTIN-V, or a *placebo* (looks like the study drug but has no drug in it) eleven times at the FRESH clinic or home. All LACTIN-V study visits will be on the same day as your regular FRESH visits. The LACTIN-V study will last for 10 weeks, will take place during 19 FRESH visits, and involve two additional pelvic exams.

The below consent form will explain details about the study and what you can expect should you choose to volunteer. Please ask any questions that you may have while we review this information together.

Thank you for your consideration,
The LACTIN-V Trial Investigators

I. What is the LACTIN-V Study?

The Challenge. Young, sexually active women, like you, are vulnerable to a condition called Bacterial Vaginosis (BV). BV is a common condition, characterized by low levels of *Lactobacillus* (a natural, healthy bacteria) and higher inflammation (your body's immune response to other bacteria) in your vaginal tract. BV is associated with an increased risk of getting sexually transmitted infections (STI) and HIV. There is treatment for BV, but even with treatment, BV often reoccurs.

There is evidence that a woman's "microbiome" – which is the combination of ***natural bacteria*** that live in a woman's vaginal tract, may help protect her from getting STIs or HIV, if her microbiome includes a "good" bacteria called "Lactobacillus".

The Aim. The aim of this study is to test a new drug called LACTIN-V which contains Lactobacillus, to see whether it can change a woman's microbiome (the combination of bacteria in her vaginal tract) and shift it to a more "healthy" or protective ***microbiome by increasing the presence of Lactobacillus*.** It should be understood that this study is not testing LACTIN-V as a prevention treatment for STIs and HIV. For this study, we only want to learn whether LACTIN-V is effective at altering the makeup of a woman's vaginal microbiome, by increasing the amount of Lactobacillus there.

What is LACTIN-V made of? The **LACTIN-V** product is made from a live bacterium called ***Lactobacillus crispatus***. *Lactobacillus crispatus* is one of the good kinds of bacteria found in the vaginal tracts of women who have a healthy *microbiome*--the type that is associated with lower inflammation and possibly, reduced risk of STIs and HIV.

Is it safe? There have already been 3 studies in the United States that tested **LACTIN-V** in over 250 women. These studies showed **LACTIN-V t**o be safe and easy to use. The FRESH LACTIN-V trial will allow us to learn whether LACTIN-V is safe and easy to use by South African women. We will also learn whether taking **LACTIN-V** will cause the good bacteria, *Lactobacillus crispatus*, to become a part of your microbiome.

Why am I being asked to join LACTIN-V?
You are being invited to join LACTIN-V because you meet the following enrolment eligibility requirements:

(1) You are enrolled at FRESH
(2) The results of your first pelvic exam at FRESH showed you have no STIs, but that you have Bacterial Vaginosis (BV). BV is a common condition characterized by low levels of *Lactobacillus* (a natural, healthy bacteria) and higher inflammation (your body's immune response to other bacteria) in your vaginal tract.
(3) You have been on Depo-Provera or Nur-isterate injections for at least 1 month
(4) You either have regular periods –or– you have no menstrual bleeding due to the Depo-Provera
(5) You are age 18-23 years
(6) You are not pregnant
(7) You are HIV-negative
(8) You do not have a serious or chronic illness, considered to be incompatible with study participation by the study doctor or investigators.

Who pays for the study? The sponsor, UCSF, has agreed to pay for all costs associated with this research study. The LACTIN-V study is funded by the United States National Institutes of Health, National Institute of Child Health and Human Development.

II. The Link between FRESH and the LACTIN-V Study

Only FRESH participants may enrol in the LACTIN-V study. The LACTIN-V study will be conducted at the FRESH clinic and you will participate for 10weeks. During these 10weeks you will continue to attend FRESH classes and have your finger pricked for HIV testing. All LACTIN-V study visits will take place on the same day as your FRESH visits, but as a LACTIN-V participant there will be some additional procedures performed (physical and pelvic exams, questionnaires and lab tests). At the end of the 10 weeks when you finish the LACTIN-V study, you will continue participating in the FRESH study.

If you test HIV-positive during your participation in the LACTIN-V study, you will receive HIV care, including immediate antiretroviral (ARV) treatment, from the FRESH Study, and continue at FRESH according to the regular FRESH study protocol. You may not, however, continue to take LACTIN-V. Only HIV-negative persons will be allowed to use LACTIN-V.

III. What happens if you join the LACTIN-V Study?

1. We tell you about the study today
2. You can ask any questions you want
3. If you decide to join today, you will sign an **Informed Consent Form**
4. We will give you a printed copy of your signed Consent Form to keep.
5. You will be assigned a study number (different from your FRESH Participant Identification [PID] number)
6. ***Paperwork***. You will fill out some basic forms: Demographics (e.g., age, race, education), medical, pregnancy and sexual risk history, etc. You will be asked some new questions and some of the same questions you were asked when you joined FRESH.
7. ***Treatment for low levels of vaginal lactobacilli (natural bacteria).*** Today you will start an antibiotic drug called **Metronidazole** to treat your Bacterial Vaginosis. You will take a tablet of Metronidazole twice per day for 7 days. You must take every dose exactly as directed. We will send you reminders to help you remember not to miss any doses. Only those who finish the 7-days of Metronidazole will be allowed to continue in the study and to start taking the Study Product.

Week 0	○ **Monday**	**Dose 1 and 2 Metronidazole - given at FRESH**
	○ **Tuesday***	**Dose 3 and 4 Metronidazole**
	○ **Wednesday***	**Dose 5 and 6 Metronidazole**
	○ **Thursday**	**Dose 7 and 8 Metronidazole - given at FRESH**
	○ **Friday***	**Dose 9 and 10 Metronidazole**
	○ **Saturday**	**Dose 11 and 12 Metronidazole**
	○ **Sunday**	**Dose 13 and 14 Metronidazole**

NOTE*: If you are in a Tuesday/Friday group, you will dose on Tuesday and Friday at FRESH. During the first week, you will start on a Tuesday and finish on Monday.*

8. ***Randomization and Placebo drugs***. We will enrol eligible women from FRESH to participate in the LACTIN-V study until 60 women have been "randomized" to receive either LACTIN-V or a "placebo" drug in a pre-filled vaginal applicator. "Randomization" means that you will be assigned, by chance, like a roll of a dice, to receive LACTIN-V or a "placebo" drug. The "placebo" drug is a powder that looks just like LACTIN-V but contains no active medicine. Participants will have a 2 out of 3 chance of getting LACTIN-V, which means you will have a 1 out of 3 chance of getting the 'placebo' drug. This study will be "blinded" which means we will not know which Study Product you are getting (not you, and not anyone at the FRESH clinic will know, until after the study is completed). The reason studies give a "placebo" or an inactive drug, is to find out whether the changes caused by the active drug (LACTIN-V) are really from that drug.

9. ***Dosing the Study Product***. You will receive a total of 11 doses of Study Product (LACTIN-V or placebo) over a 4-week period. During the 1st week, you will use the product every day for 5 days; during the 2 days you are here at FRESH, the nurse will assist with your dosing, and on the 3 days you do not come to FRESH, you will dose yourself with the product. During weeks 2, 3 and 4, you will only receive the Study Product on the 2 days you are at FRESH. A nurse will assist you with all doses you take at FRESH.

Week 1	○ **Monday**	**Dose 1 given at FRESH** (assisted by a nurse)
	○ **Tuesday***	**Dose 2** –-- > ****you dose at home***
	○ **Wednesday***	**Dose 3** –-- >****you dose at home***
	○ **Thursday**	**Dose 4 given at FRESH** (assisted by a nurse)
	○ **Friday***	**Dose 5** –-- > ****you dose at home***
Week 2	○ **Monday**	**Dose 6 given at FRESH** (assisted by a nurse)
	○ **Thursday**	**Dose 7 given at FRESH** (assisted by a nurse)
Week 3	○ **Monday**	**Dose 8 given at FRESH** (assisted by a nurse)
	○ **Thursday**	**Dose 9 given at FRESH** (assisted by a nurse)
Week 4	○ **Monday**	**Dose 10 given at FRESH** (assisted by a nurse)
	○ **Thursday**	**Dose 11 given at FRESH** (assisted by a nurse)

NOTE*: If you are in a Tuesday/Friday group, you will dose on Tuesday and Friday at FRESH. During the first week, you will start on a Tuesday and finish on Saturday.*

10. Study Visits & Study Procedures

- All LACTIN-V study visits will be on the same day as your FRESH visits.
- If you enrol in the LACTIN-V study, you will have 2 additional pelvic exams on Day 8 and Day 36 (mucosal sampling), over and above your regular FRESH pelvic exam on Day 64. These pelvic exams will take place on study week 1 ('Randomization Visit) and study week 5 (Follow-up Visit) and week 9 (Final Visit).

11. Avoiding Sex, Using Condoms and Other Products

- You will be asked to **avoid sex** during the 12 hours after you use the Study Product. This includes penile/vaginal sex, oral/vaginal sex, and penile/anal sex.
- You will be asked to **avoid sex** on the day before you have a gynaecological exam. This includes penile/vaginal sex, oral/vaginal sex, and penile/anal sex.
- During the 10 weeks of the study, we will give you the kind of condoms that have no spermicide (chemicals that help stop sperm/pregnancy), to be sure it does not prevent the Study Product from working.
- Throughout the 10 weeks of the study, you will be asked not to insert any substances or devices into your vagina. This means no tampons and no other vaginally inserted products (e.g. traditional muthi, douching from a shop, lubricants, drying agents or sexual stimulants).

IV. Study Visits for the LACTIN-V

TODAY (Week 0) → "**Enrolment Visit**" (Mon or Tue)
This visit will take about 1 hour longer than your usual FRESH clinic visit. You will learn about the study and sign a Consent Form confirming your desire to enrol in the study. You will fill

paperwork (Demographics, contact details, medical history, sexual behaviour) and the following:

- ***Physical Exam.*** This is a routine examination including listening to your heart and lungs and taking vital signs.
- ***Urine sample***: You will provide a urine sample so we can check for a urinary tract infection (UTI) and pregnancy. If you have a UTI you will be referred for treatment. If you become pregnant during the study the Study Product will be discontinued, but you will continue with your visits.
- ***Antibiotic Treatment.*** You will start a 7-day course of the antibiotic drug called **Metronidazole**, which you will drink twice per day to treat the Bacterial Vaginosis that was detected during your first FRESH mucosal exam. You will take the first dose of Metronidazole here at FRESH and your 2nd dose tonight. You will be dispensed a 2-day supply of Metronidazole to take at home, which you will take twice per day. On Thursday (or Friday) when you return for your regular visit to FRESH, you will be dispensed additional Metronidazole for that day, and to take at home that night and the following day. It is critical that you take every dose, twice per day, so the BV will be cleared. We will send you reminders to help you remember to drink your tablets.

  **NOTE: As far as possible, completion of the 7-days of Metronidazole, all 14 doses, is required for you to remain enrolled in the LACTIN-V study.*

  What happens if I drink alcohol while taking Metronidazole?
  Drinking alcohol within three days of taking Metronidazole can cause additional unwanted side effects (full list of side effects, below, in Table 3, page 7) below). The most common is face flushing (warmth and redness), but other possible effects include: abdominal pain (cramps), and nausea and vomiting. **Please avoid drinking alcohol while taking Metronidazole, and for the three days after the last dose of Metronidazole.**

NEXT WEEK (Week 1) → **"Randomization Visit**" (Mon or Tue)
This visit will be the Study Product Start and take about 45-minutes longer than your usual FRESH visit.

- You will again have a physical exam, urine test for a urinary tract infection (UTI) and pregnancy, provide information on sexual risk behavior and the following:
- ***Pelvic examination*:** The pelvic exam will be the same as the "mucosal" exams you have at FRESH. The study nurse and/or a doctor will perform an exam of your genital area and insert a speculum to examine your vaginal tract. During the exam the nurse will "wash' your vagina with sterile water and collect samples with soft cotton swabs and a syringe to collect the fluid. (*NOTE: If at the pelvic-mucosal exam we find you have a new infection, you might be disenrolled from the LACTIN-V study.)*
- ***Study Product**:* You will start Study Product this week. Your first dose of Study Product, contained in a pre-filled vaginal applicator, will be used at the clinic with the assistance of a nurse. Before you leave the clinic, the nurse must give you a two-day supply of Study Product (1 dose per day) for you to take home. At home, you will use the Study Product on your own, before bedtime. On your next visit to FRESH (Thurs or Fri), the nurse will assist with your 4th dose and give you one dose to use the next day - at home, before bedtime.
- ***Reporting Side effects**.* You will be asked to pay close attention to your body once you start the Study Product and record any changes or concerns about your vaginal discharge including the amount, consistency or color and if you notice any bad smell. Also notice whether you have any vaginal pain or discomfort during

administration or in between doses. If this occurs or you have any questions, you can send a WhatsApp or SMS a please-call-me to the study hotline and you will get a call back. You will also have a chance to report your concerns during every LACTIN-V study visit. The study investigators will determine whether the side effects are mild or more serious, and whether you can continue using the Study Product or not.

ROUTINE CHECK-IN → **Week 1 through 4**

- All LACTIN-V study visits will be on the same day as your regular FRESH visits (Mon/Thurs or Tue/Fri).
- During the Study Product dosing period (weeks 1 to 4), the product will be given with the help of a nurse.
- You will be asked to report any side effects.
- You will be asked questions about sexual activity and menstrual cycle.

FOLLOW-UP VISIT → **Week 5**

This visit will take about 30-minutes longer than your usual FRESH visit.

- A medical and sexual activity survey will be completed.
- A physical and pelvic ('mucosal') exam with sample collection will be conducted.
- A urine sample may be collected.
- You will be asked to report any side effects
- You will provide feedback on your experience while receiving the Study Product ("Acceptability Questionnaire").

ROUTINE CHECK-IN → **Week 5-8**

- All LACTIN-V study visits will be on the same day as your regular FRESH visits (Mon/Thurs or Tue/Fri).
- You will be asked to report any side effects.
- You will be asked questions about sexual activity and menstrual cycle.

FINAL VISIT and/or EARLY STUDY DISCONTINUATION → **Week 9**

This visit will take about 30-minutes longer than your usual FRESH visit.

- At the completion of the LACTIN-V study there will be a "Final Visit".
- If for any reason you discontinue taking the Study Product before the end of the treatment period, you will be booked for your "Final Visit" right away.
- At the "Final Visit" you will complete:
  - A final medical and sexual activity survey
  - A final physical and pelvic ('mucosal') exam with sample collection.
  - A final urine sample may be collected.
- Reasons for Early Study Discontinuation may include:
  - You opt to discontinue participation for any reason
  - You are unable/unwilling to follow the study requirements
  - You experience a serious adverse event (side effect) that make it unsafe to continue
  - The investigators stop or cancel the study for any reason
  - The investigators believe your ongoing participation is causing you unacceptable risk for any reason.

UNSCHEDULED VISITS

- If you have any problems or questions during the study, you may call the study nurse or counselor. You can use WhatsApp, or send a please-call-me SMS, or make a voice call.
- Examples of problems you might have include: lost or damaged Study Product during week 1, discomfort or pain, discolored or abnormal discharge.

V. Risks and Benefits

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1. Risks: Previous research studies with LACTIN-V have shown it to be well-tolerated and safe, but there may be side effects we have not seen in previous studies. Participants in the LACTIN-V study will be watched closely and will have access to the study team in the event you experience any problems or side effects.

   The risk of serious side effects from using LACTIN-V are unlikely as it has been shown to be safe in several other studies and because it is made from bacteria that normally live in a healthy vagina.

   There is little to no risk of the bacteria in LACTIN-V being absorbed into your body and getting into your blood, resulting in a blood infection called "***bactaeremia***". Of over 400 women who have used LACTIN-V, none of the women developed bactaeremia. Similarly, studies of LACTIN-V in animals have not resulted in any cases of bactaeremia.

   The specific risks associated with LACTIN-V are listed below in Tables 1-4. We will review these risks together. Please ask about anything you don't understand, before agreeing to participate in this study.

Table 1. Possible Drug Side Effects (LACTIN-V)

Common

Vaginal Discharge

Uncommon

- *Gastrointestinal symptoms:* abdominal (stomach area) pain, constipation, diarrhea, nausea, vomiting
- *Urinary symptoms:* needing to urinate urgently, needing to urinate at night and pain with urination
- *Vaginal, genital or menstrual symptoms:* genital itching, bleeding between menstrual periods, delayed menstrual periods, vaginal odor, vaginal burning sensation, vaginal irritation, vaginal bleeding and vaginal dryness, genital swelling, rash, vaginal candidiasis (yeast infection)
- *Other symptoms:* lower back pain

Unknown Frequency

- Contact dermatitis (a red, itch rash caused by a substance that touches your skin)

Rare, but serious

- *Allergy:* A possible risk of using the LACTIN-V product or the placebo product is an allergic reaction. It is possible to have an allergic reaction to one of the ingredients (*Lactobacillus crispatus* and the preservative powder). In rare cases, if not properly treated, an allergic reaction could be life threatening.

Table 2. Possible Drug Side effects (Placebo)

Common

- Vaginal Discharge

Unknown Frequency

- Contact dermatitis (a red, itchy rash caused by a substance that touches with your skin)

Table 3. Possible Drug Side Effects (Metronidazole)

NOTE: This antibiotic drug is given routinely in Department of Health clinics in South Africa.

Common (but in less than 10% of people)

- Skin – Itching, redness, dryness
- Skin – Irritation or discomfort (burning/pain/stinging)
- Skin – Worsening of rosacea (a chronic skin condition that makes your faceturn red and may cause swelling and skin sores that look like acne)
- Face flushing (warmth and redness), abdominal pain (cramps), nausea and vomiting when drinking alcohol within three days of taking metronidazole.

Uncommon (occur in less than 1% of people)

- Numbness in fingers and toes
- Metallic taste
- Nausea

Rare, but Serious

- Convulsive seizures (body muscles contract and relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body)
- Psychotic reactions (abnormal mental state causing loss of contact with reality)

Table 4. Other Possible Risks from Study Activities

- ***Anxiety****:* You may experience anxiety from not knowing which Study Product you are receiving, LACTIN-V or the placebo drug.
- ***Shyness or embarrassment****:* You may initially feel shy or uncomfortable when you first share details of your sexual practices and/or when you have your pelvic exams ('mucosal"'). The pelvic exam may also make you feel vulnerable.
- ***Discomfort & slight bleeding:*** You may experience discomfort during the pelvic exam, but you should not feel pain. Occasionally you may have slight bleeding from the cervical exam. The study nurses are very gentle, and the sampling is done with a soft cotton swab.
- ***Non-spermicidal condoms:*** The condoms we will provide do not have spermicide (a lubricant that kills sperm). This may slightly increase your chances of getting pregnant, when compared to condoms with spermicide, especially if the condom is not used correctly.
- ***Birth defects to a baby***: The risk of LACTIN-V on a fetus (baby in the womb) is unknown. It is probably safe but has not been tested. You are required to use a reliable birth control method throughout the study (e.g., Depo-Provera injection), but the study will perform pregnancy tests to be sure you are not pregnant. If you do fall pregnant during the study, the Study Product will be discontinued immediately, and you will be referred to your local antenatal clinic. You will continue the study visits without receiving the Study Product and you will keep the FRESH team and LACTIN-V study staff informed about your pregnancy.
- ***Unknown***: Experimental treatments may have side effects 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.

2. Benefits:

- **Free STI Testing**. During the 10-week study, you will have 2 additional pelvic ('mucosal') exams, which will allow us to test for STIs and give you the opportunity to know if you have an STI or bacterial vaginosis (BV) – a type of vaginal inflammation. Because STIs and BV are often "silent" (don't show any side effects

to you), you would not otherwise know about them, and be treated. All study participants will be tested for BV at week 1, 5, and 9. If you have symptoms like an abnormal vaginal discharge and are diagnosed with BV while being enrolled in the study, you will receive a repeated treatment with Metronidazole.

- **Treatment for BV**. The LACTIN-V study will provide you with free antibiotic treatment for BV, dispensed from the FRESH clinic. You will not need to go to your local government clinic and queue for examination and treatment.
- **Free Pregnancy Testing.** You will have periodic urine pregnancy tests performed during the study. If you are found to be pregnant, you will be referred to your local antenatal clinic for care.
- **Free UTI Screening.** Your urine will be tested and you will be screened for symptoms of urinary tract infection (UTI). If clinically indicated, you will be referred for treatment.
- **Benefit to the Community**. Though you personally may not benefit from the administration of LACTIN-V during this study, you will be contributing to research that has the potential to develop a new drug in the future, that will benefit women like you, including women living in Umlazi.
- **Specialist Physician**. You will be under the care of a specialist physician and experienced professional nurses, who will closely monitor your health and safety throughout the trial.

VI. Confidentiality

1. As a participant in this research study, you will be assigned a unique study code. All identifiable information you provide (name, address, date of birth, phone number, etc.) will be kept in a locked file cabinet in a locked room. Only qualified study personnel will have access to this information. Your personal information from your records will not be released without your written permission.
2. Any biological samples collected from you or laboratory test results resulting from your participation in this study, will be labeled with your study code and not your name or any other identifiable information.
3. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.
4. Organizations that may have access to your records for the purpose of research, quality assurance, and data analysis will only have your study code and not your name.These organizations include:

    - South Africa Health Products Regulatory Authority (SAHPRA)
    - Study monitors
    - Study staff
    - Study auditors, including representatives of Osel Inc., the company that is developing LACTIN-V
    - University of KwaZulu-Natal, HIV Pathogenesis Programme Laboratory
    - The University of California San Francisco
    - Massachusetts General Hospital/Harvard Medical School/Ragon Institute
    - University of KwaZulu-Natal Biomedical Research Ethics Committee

5. A description of this clinical trial will be available on *http://www.ClinicalTrials.gov* and South African National Clinical Trials Register on *http://www.sanctr.gov.za/,* as required by U.S. and South African Law. These websites will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

VII. Processing, Storage and Shipment of Samples

Many of the collected samples will be analyzed in laboratories in Durban and at UKZN. But some of your collected vaginal swabs will be shipped to a laboratory located in Boston, USA, headed by Dr. Douglas Kwon of the Ragon Institute at MGH.

Mucosal sampling swabs, and cytobrush cells will all be initially processed and stored at UKZN. Further analysis will be performed at both UKZN and in the U.S. at the Ragon Institute of MGH, MIT and Harvard. Some samples may be stored indefinitely (with no time limit) at either location. All work performed in the U.S. will be done in close collaboration with South African LACTIN-V investigators. Some samples may be stored indefinitely (with no time limit) at either location. Stored samples will be labeled with a code (not your name or other identifiable information) and will only be used in future research that has been approved by an Institutional Review Board (a committee that reviews an investigator's research to ensure it is conducted ethically and that participants' rights are protected).

VIII. Costs, Compensation, Safety, Rights and Key Contacts

1. **Cost**. Participation in the LACTIN-V study will not cost you anything. You will not pay for the Study Product, tests, procedures or for the care you receive from the study doctor, nurses or counsellors.

2. **Compensation.** For participating in the LACTIN-V study, you will receive additional compensation, over and above what you already receive from FRESH, for your time and effort.

   During the LACTIN-V study, you will continue to receive your regular R50 stipend from FRESH and lunch, plus an additional R50 on 15 of the 19 LACTIN-V visits (short visits for dosing only and/or brief check-ins) and additional R150 on the four (4) LACTIN-V visits that require more time, due to additional questionnaires, exams and sampling (Enrolment Visit, Randomization Visit, Follow-up Visit, and Final Visit).

   You will receive a token of R150 should you complete ALL visits that include study product dosing (Randomization Visit, Visits 4, 5, 6, 7, 8 and 9), and another token of R150 at the end of the study, should you complete all 19 study visits.

   All study stipends will be received on the day of the study visit.

3. **Safety.** It is important that you tell a member of the study team if you experience any side effects during the study or feel you have been harmed as a result of participation in the LACTIN-V study. If you have an adverse event (any harm) as a result of being in this study, the LACTIN-V study will either provide you with medical care or ensure you are linked to appropriate care. All costs associated with that care and treatment will be paid for by the LACTIN-V study.

4. **Rights.** Research studies include only people who voluntarily choose to participate. You may decide not to participate and withdraw from the LACTIN-V study at any time without losing the benefits of your standard medical care, nor will it affect your continued participation in the FRESH study. (You may not, however, withdraw from FRESH and continue participation in LACTIN-V. Only FRESH participants are eligible for the LACTIN-V study.)

   The LACTIN-V product is still in early stages of testing and may not be available to you or other women (outside of this study), for many years, if at all. If this study shows promising results, much larger studies would need to be conducted before this product could be approved for use in the treatment of Bacterial Vaginosis or prevention of

sexually transmitted infections. We will tell you about new information or changes in the LACTIN-V study that may affect your health or your willingness to continue participating.

You have the right to privacy. Test results, medical records and personal details about you collected during this study will be treated as confidential and only qualified study personnel will have access to this information. Your name/identity will not be associated in any publication or presentation with the information collected about you or with the research findings from this study.

5. **Conflicts of Interest Disclosure.** Two of the researchers contributing to this study are employed by Osel, Inc., the company that makes LACTIN-V. Osel employees (Laurel Lagenaur and Tom Parks) will not be directly involved in the conduct of the trial, will not interact with participants, and will not have access to identifiable data. Their role is to provide the Study product, advice on its use, aid in the development of pharmacy/shipping documents, and to provide input on the interpretation of results.

6. Approvals

- This study has been approved by the South African Health Products Regulatory Authority (SAHPRA).
- This study has been ethically reviewed and approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BFC160/19) and by the UCSF Institutional Review Board (19-27732) and Partner's Human Research Committee (2020P002237).
- A community advisory board (CAB) comprised of key stakeholders and community members from Umlazi, has been informed about the LACTIN-V study and is satisfied that this research will be conducted responsibly and appropriately, and will have some benefit to the community.

7. Key Contacts

Throughout the study, you are welcome to contact any member of the study staff. The study number is (076) 412 0329, which will be answered by the nurse on-call, 24 hours per day, 7 days per week. If you need to speak with the study doctor, or any of the study investigators, the nurse will assist you.

If you have problems or questions with which the nurse is unable to assist you, you may also contact the Investigators in South Africa, members of the CAB or the Research Ethics Boards directly.

Study Nurse: (076) 412 0329
Investigators (South Africa):

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- Prof. Thumbi Ndung'u / Email: ndungu@ukzn.ac.za Tel: +27 (0)31 260-4173
- Dr. Krista Dong / Email: kdong@mgh.harvard.edu Tel: +27 (0)33 395-4523

Dr. Craig Cohen / Email: craig.cohen@ucsf.edu Tel: +1(415) 476-5874 UCSF Investigator (USA)

BIOMEDICAL RESEARCH ETHICS COMMITTEE (BREC) University of KwaZulu-Natal Research Office Govan Mbeki Building Westville Campus Private Bag X 54001 Durban 4000 KZN, SOUTH AFRICA Tel: +27 31 2604769 Email: BREC@ukzn.ac.za	**MASSACHUSETTS GENERAL BRIGHAM (MGB) IRB** Massachusetts General Hospital 800 Boylston Street, 11th Floor Boston, MA 02199 USA Tel: +1-800-856-1983	**UCSF HUMAN RESEARCH PROTECTION & IRB** University of California San Francisco (UCSF) Program, Box 0962 3333 California Street, Suite 315 San Francisco, CA 94143 USA Tel: +1 415-476-1814

If you have questions about this trial, you should first discuss with the study doctor [Dr. Vaneshree Govender] or the Ethics Committee (contact details as provided on this form). After you have consulted the study doctor or the Ethics Committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

THE CHIEF EXECUTIVE OFFICER, SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY
Department of Health, Private Bag X828, PRETORIA 0001
Email: Boitumelo.Semete@sahpra.org.za Tel: +27 12 3958126

CONSENT TO PARTICIPATE

FRESH / LACTIN-V Study

☐ I,_____have been informed about the
(Print Name) (Print Surname)

LACTIN-V study by _____
(Print Name and Role of Study Staff)

☐ I understand the **purpose** of the study and all of **my questions have been answered** to my satisfaction.

☐ I understand **what is expected of me** as a participant in the LACTIN-V study and I understand all of the associated **risks and benefits** of participating in the study

☐ I understand that my participation in this study is **voluntary** and that **I may withdraw** at any time without any negative consequences or impact on my enrolment at FRESH.

☐ I understand I will receive compensation for my participation in the LACTIN-V study, and that if I have any harm or injury that requires medical attention as result of study-related procedures, the cost of the **medical care and treatment will be provided by the LACTIN-V study.**

☐ I understand that I may contact the study team at any time if I have any further questions or concerns related to the study, including the study counselors and nurses, as well as the study doctor and investigators associated with the study. All of their contact details are included on this form.

☐ I have been offered a printed copy of this Informed Consent Form.

☐ I understand who I can contact if I have any questions or concerns about my rights as a study participant, or if I am concerned about any aspect of the LACTIN-V study or the researchers.

Participant Name (print)	Participant Signature	Date
Clinic Staff Conducting Consent Name (print)	Clinic Staff Signature	Date

Option 1 – *Collection and Future Use of Stored Samples*

If you agree, the study investigators would like to collect up to two additional vaginal swabs at each of the 3 visits that includes a pelvic ('mucosal') exam and store these extra samples for future use. (Collected at Visit 1 - Enrolment, Visit 11 and Visit 19)
These swabs will be in addition to the swabs being collected to test for sexually transmitted infections and BV. The additional swabs may be used for future testing to understand factors that may put women at risk of HIV infection, or other conditions related to women's health. Upon request, these samples may also be made available to other scientists to test for the bacteria. Your samples will be identified only by a code (not your name) and released only with your written permission on this form, and only for research that has been approved by an Institutional Review Board (a committee that reviews an investigator's research to ensure it is conducted ethically and participants' rights are protected).

Please indicate below "yes" or "no" and initial and date whether you approve the collection and use of stored samples. Note that you can withdraw your consent for research on stored specimens at any time and the specimens will be discarded. Your refusal or withdrawal of consent for the storage of these samples will not affect your study participation since storage of leftover samples is not a requirement for the study.

Option 1, initial and date, Yes or No:

☐ Yes, I agree. ☐ No, I do not agree.

Option 2 – *Consent To Be Contacted For Future Research*

There may be studies in the future that would be appropriate for you and that you would be interested in joining. If you agree, a qualified member of the study staff may contact you in the future to invite you to participate in any future studies. You have no obligation to actually participate in any study.

Please indicate below "yes" or "no" and initial and date whether you approve to be contacted in the future about future research opportunities. If you agree, you are giving consent for information to be taken from your LACTIN-V study records. This information may include your name, date of birth, diagnosis and contact information. This information will be kept indefinitely, unless you withdraw your permission. You may withdraw permission to be contacted at any time by contacting the study coordinator.

Option 2, initial and date, Yes or No:

☐ Yes, I agree. ☐ No, I do not agree.

Participant Name (print)	Participant Signature	Date
Clinic Staff Conducting Consent Name (print)	Clinic Staff Signature	Date