CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

(SCREENING, ENROLLMENT, LONG-TERM STORAGE AND FUTURE TESTING)

Sponsor / Study Title:	**US Eunice Kennedy Shriver National Institute of Child Health and Human Development / "A Randomized, Phase 1, Open-Label Study in Healthy HIV-Negative Women to Evaluate the Pharmacokinetics, Safety and Bleeding Patterns Associated with 90-Day Use of Matrix Vaginal Rings Containing 200 mg Dapivirine and 320 mg Levonorgestrel"**
Protocol Number:	**MTN-044/IPM 053/CCN019**
Principal Investigator: (Study Doctor)	**«PiFullName»**
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Additional Contact(s): (Study Staff)	**«AdditionalStaffMemberContacts»**
Address:	**«PiLocations»**

SOURCES OF SUPPORT: US National Institutes of Health (NIH) and conducted by the Microbicide Trials Network (MTN) and the Contraceptive Clinical Trials Network (CCTN). The study rings are supplied by the International Partnership for Microbicides (IPM), a not-for-profit research organization.

Please take time to read this entire form and ask questions before deciding whether to take part in this research project. If you do decide to take part in the trial, you will sign and date your name on this form. A copy of this form will be offered to you. Signing this consent form does not mean you will be able to join the study. You must first complete the screening tests and exams to see if you are eligible. It is important to know that your participation in this research is your decision and taking part in this study is completely voluntary (see *Is my participation in this research study voluntary?* for more information). Take time to ask the study doctor or study staff as many questions about the study as you would like. The study doctor or study staff can explain words or information that you do not understand. Reading this form and talking to the study doctor or study staff may help you decide whether to take part or not.

IMPORTANT INFORMATION ABOUT THE RESEARCH STUDY

You are invited to participate in a research study. In order to participate, you must be a healthy, HIV-negative female between the ages of 18 and 45 years old who has current regular menstrual cycles. Taking part in this research project is voluntary.

Important things you should know:

- The study product in this clinical trial is a vaginal ring (VR) containing a combination of the anti-HIV medication dapivirine (DPV) and an FDA-approved contraceptive hormone called levonorgestrel (LNG)
- The study product is NOT for use to prevent pregnancy in this particular study. You may only participate if you are, and will continue taking steps that prevent pregnancy, or that pose no chance of pregnancy. The study staff will carefully assess this with you and answer your questions to help determine if you may participate.
- You should NOT depend upon the study product to prevent HIV, the virus that causes AIDS. If you are concerned about exposure to HIV you should discuss this with the study staff, who can advise you about your options.
- The purposes of the study are:
    - To find out how the two drugs (DPV and LNG) enter and exit the body when one VR containing the two drugs is inserted into the vagina and worn continuously or cyclically for approximately 90 days
    - To find out if the VR is safe and well-tolerated
    - To look at the effects of the VR on vaginal bleeding
- If you qualify and choose to participate, you will be randomly assigned (like flipping a coin) to one of two groups:
    - Group 1 will use the VR continuously for approximately 90 days
    - Group 2 will use the VR cyclically (use for approximately 28 days, take it out for 2 days and insert the same VR back) for a total of approximately 90 days
- Once enrolled, you will be asked to attend 13 clinic visits at the research clinic over approximately 3 months (94 days) and will be contacted by phone up to 4 times during the 3 months after the ring is removed. The duration of your study participation will be approximately 6 months.
- At the clinic visits, a physical and/or pelvic exam will be performed, blood will be obtained, and vaginal swabs and samples will be collected. At three visits, cervical biopsies will be obtained.
- You may not experience any direct benefit from participation in this study. However, information learned from this study may help in the development of ways to prevent unwanted pregnancy and the spread of HIV in the future.
- Taking part in this research project is voluntary. You don’t have to participate and you can stop at any time.

STUDY PRODUCTS

Dapivirine (DPV)
DPV VRs were recently tested in two large studies and were shown to be safe and helped to prevent HIV acquisition. HIV is the virus that causes AIDS. DPV works by preventing HIV from making copies of itself, which stops the spread of HIV in the body. Study staff can provide you with additional information about these studies if you are interested in learning more.

Levonorgestrel (LNG)
Many contraceptives such as pills and implants contain progestin hormones like LNG. The hormone thickens the mucus of the cervix (the opening to the uterus) to prevent sperm from reaching an egg. It may also keep women from releasing an egg so they do not get pregnant. Currently there is one approved VR available in the United States (called NuvaRing®), which contains a different progestin hormone, etonogestrel, as well as an estrogen hormone, ethinyl estradiol. The new VR being tested in this study contains the progestin hormone LNG.

Dapivirine/Levonorgestrel combination
This is the second study of a VR containing both DPV and LNG. The first study included both a VR containing 200 mg DPV without LNG and the combination DPV-LNG VR (200 mg DPV and 320 mg LNG) used for 14 days in healthy women. There were no safety concerns in that study. **Researchers do not know if LNG prevents pregnancy when combined with DPV in a VR. Therefore, it is important that you use another form of contraception that is non-hormonal during your study participation.**

STUDY GROUPS

Approximately 24 eligible participants will be randomized equally to one of two VR use study groups:

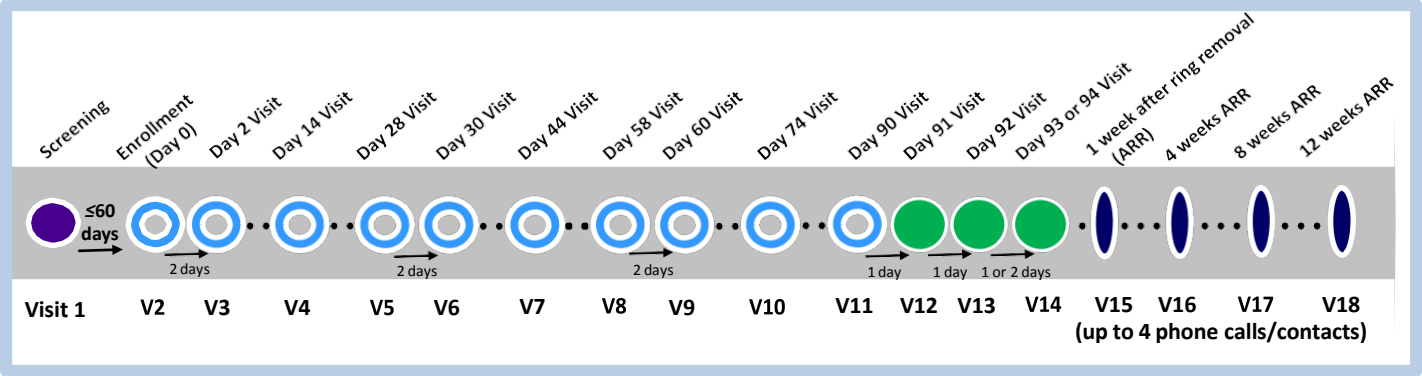
- Group 1 will use the DPV-LNG VR continuously for approximately 90 days
- Group 2 will use the DPV-LNG VR cyclically for approximately 90 days as follows: use the VR for approximately 28 days, then remove, wash and store for 2 days. The same ring will be used for 2 additional cycles in a similar fashion.

Approximately 12 participants will be assigned to each VR use group. Participants will be assigned to a group by random chance (like flipping a coin), and both you and the study staff will know which group you are in. Both study groups are important. No matter which study group you are in, you must remember that we do not know if the drugs contained within the VR will work to protect you against pregnancy or from getting HIV.

WHAT WILL HAPPEN DURING THE STUDY VISITS?

The study includes a total of up to 18 visits or contacts. Fourteen visits will take place at this clinic, including the screening visit, and up to 4 contacts will be conducted with you by phone after ring removal on Day 90.

The study staff will go over the visit schedule chart, below, with you, provide details, and answer any questions you have.



You will discuss with study staff the rules of the study and your understanding of the rules, including but not limited to:

- Keeping the vaginal ring in place and not removing it between study visits.
- Using another form of contraception that is non-hormonal during your study participation.
- Being sexually abstinent and avoiding tampon use for the 24 hours prior to your Enrollment Visit and clinical visits where samples are taken and for one week following cervical biopsies. This means no vaginal sexual intercourse with a male partner, no oral sex or no vaginal finger stimulation.
- Refraining from inserting any non-study vaginal products or objects into the vagina for the 24 hours prior to your Enrollment Visit through completion of Visit 15. These include but are not limited to spermicides, female condoms, diaphragms, other intravaginal rings, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), vaginal douches, non-study lubricants and moisturizers, or sex toys (vibrators, dildos, etc.).
- Avoiding continued use of certain medications and herbal supplements, such as St. John's wort, that may interact with the study drugs.

You will also be asked about your study product use and/or vaginal bleeding or spotting for the duration of your participation. Your answers will be kept private.

What procedures will be performed for research purposes?

The procedures performed in this study are done for research purposes and will be performed by a study doctor, clinician, or other trained member of the study team. The results will become part of your research record. During the study, the study doctors will review the results of all labs, evaluations, and procedures that monitor your health and safety, and you will be given these results after they are available.

At any time during this study, if tests show you might have medical problems, including infections passed through sex, then you may have a physical or pelvic exam; give

blood, urine, or vaginal samples to test for infections; and, if needed, get referrals for medical care and treatment. If HIV, gonorrhea, Chlamydia, or syphilis is identified, we are required to confidentially report this to the local health department with your name and contact information. Someone from the health department may contact you to be sure that you and your partner have been treated.

Visit 1 Screening

This visit may continue today or be done within 60 days before Visit 2 Enrollment to determine if you are eligible to take part in this research study. At this visit, which may take ***[SITE TO INSERT TIME***], you will:

- Answer questions to confirm your understanding of the study requirements and that you are able to join the study
- Study staff will:
    - Ask you about your contact information (for example, where you live and how we can contact you) and other questions about you, including your education, your behavior including your sexual behavior, your medical history (including what medications you are taking) and menstrual history. They may also ask to view your medical records, with your permission.
    - Test your urine for pregnancy and, if needed, for a urinary tract infection.
        - If you are pregnant you cannot join this study.
        - Study staff will talk with you about ways to avoid becoming pregnant.
        - You will answer questions about whether you are using an effective, non-hormonal method of contraception and intend to use this method for the entire time that you are in this study.
        - If needed, study staff will provide and/or refer you to obtain an acceptable contraceptive method for use during your participation in the study. Acceptable methods include:
            - Non-hormonal (for example, copper) intrauterine devices (IUDs) inserted at least 28 days (4 weeks) prior to enrollment
            - Consistent and correct male condom use
            - Sterilization: You or your partner has been sterilized (tubal ligation, vasectomy, etc.)
            - You engage in sex exclusively with women
            - Sexually abstinent for the past 90 days and planning to remain abstinent for the duration of study participation
    - Perform a general physical examination including vital signs (such as blood pressure, heart rate, and temperature), height and weight
    - Perform a breast examination
    - Perform a pelvic examination:
        - The study doctor will use a speculum, a plastic or metal instrument inserted in the vagina. Study staff will ask if you are experiencing symptoms of an infection. They will check your vagina and cervix for signs of infection and other problems.

- A small amount of vaginal fluid will be collected via swab(s), like a Q-tip. These swabs will be used to test for sexually transmitted infections (commonly known as STIs or STDs) and other possible problems.
- If you are 21 years of age or older, samples may be collected from your cervix for a "Pap test" or "Pap smear". If you have a written report confirming a normal Pap test in the past 3 years, or if you had an abnormal Pap test but had follow-up indicating no treatment was required, then you will not need to have a Pap test. The results of your Pap test may affect whether or not you can continue in the study. You will receive the results of this test when it is available.

o Talk with you about HIV and other sexually transmitted infections (STIs), HIV and STI testing, and ways to avoid HIV and STIs.
o Have ***[SITE TO INSERT AMOUNT]*** of blood drawn from a vein in your arm to test the health of your blood, liver and kidneys and to test for HIV and syphilis. These tests are being done to make sure that the blood test results are normal at the start of the study and to test for infections that are typically passed through sex.
    - You will be told your HIV and other test results as soon as they are available. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we know your status for sure. You must receive your HIV test results to be in the study. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need. Medical care for HIV infection will not be part of this study. The study staff will tell you about other studies you may be eligible for, if any.
o If needed, give you treatment or refer you for treatment of STIs or other urinary or reproductive tract infections
o Inform you about other services, if needed
o Provide you with the results of your tests, when available
o Reimburse you for your visit
o Talk with you about the requirements of the study, including the importance of completing clinic visits, and study activities and procedures according to the study schedule
o Give you male condoms, if you need them
o Schedule your next visit to enroll in the study, if you are willing and eligible.

Results of the tests listed above will be available within ***[SITE TO SPECIFY TIMEFRAME]***. The study staff will review your test results with you. If you are not eligible or decide not to participate in this study, no blood collected at Screening will be kept or used for any tests other than those listed above.

Visit 2 Enrollment (Day 0)

The Enrollment Visit is when you join the study. This visit will take about ***[SITE TO INSERT TIME***]. In addition to the procedures listed below, it is possible that study staff may need to perform additional tests if medically necessary (for example, you report having symptoms of a urinary, genital, or other infection and/or other issues).

The following procedures are specific to the Enrollment Visit, which will take place up to 60 days (approximately 8 ½ weeks) after your Screening Visit:

- You will answer questions to confirm you are able to join the study.
- You will update study staff with your contact information (for example, where you live and how we can contact you).
- Study staff will:
    - Talk with you about the requirements of the study and how to follow them, including restrictions on sexual practices. **If you do not think you can abstain from sex as required by the study, then you should not join this study.** Sex for this study is defined as vaginal sexual intercourse with a male partner, oral sex or vaginal finger stimulation.
    - Ask you questions about your vaginal practices that may affect how your body absorbs the study drugs.
    - Ask you questions about your thoughts on the study product
        - A staff member may ask you these questions. It is important that you know that you will answer these questions in private and your responses will be kept confidential.
    - Talk with you about STIs, HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex
    - Discuss any health or medical problems you may have had in the past, are currently experiencing or that have occurred since your last visit (including what medications you are taking)
    - Ask you about any menstrual periods or spotting you may have had since your last visit
    - Give you male condoms, if you need them.
- You will also:
    - Have your urine tested for pregnancy and, if needed, for a urinary tract infection
    - Have a general physical examination
    - Have a breast examination
    - Have about ***[SITE TO INSERT AMOUNT]*** of blood collected before you receive the study VR to test the health of your blood, liver and kidneys; to test for HIV; for study purposes including to test for the amount of DPV and LNG present in your blood when you start using the VR; for sex hormone (progesterone, estradiol), a hormone-related protein (sex hormone binding globulin, or SHBG), and albumin; and for storage in the event there is a question about your lab results in the future. After all testing is done, this stored sample will be destroyed.
    - Have a pelvic examination using a speculum

- Your vagina and cervix will be checked for signs of infection or other problems, and you will be asked if you are experiencing symptoms of an infection. Vaginal fluid will be collected with a swab to test for bacteria and organisms and, if needed, for STIs or other possible problems.
- A small amount of vaginal fluid will be collected via swab before you receive the study VR. A study doctor will insert the swab approximately 3 inches inside your vagina. Swabs will be collected to measure the amount of DPV, LNG, and bacteria present in the vagina when you start using the VR. The same tests will be done when these samples are collected at future visits.
- A cervicovaginal lavage (CVL) will be performed. For the CVL, a study doctor will rinse your vagina and cervix with a small amount of sterile fluid and collect that fluid in a tube for testing. The CVL fluid collected will be used for research purposes only.

o Receive and insert the study VR. Study staff may help you insert the VR if you cannot do it on your own. All participants will have a vaginal examination by a study doctor to ensure the ring is inserted correctly. You will be asked to keep the VR in place and not remove it between visits. Study staff will show you how to take the ring out in case you need to do so. Study staff will talk with you about what to do if you have any problems or symptoms while using the ring

o Be told that you will be asked to answer questions regarding your ring use and any vaginal bleeding or spotting you may experience during the study product use period

o Be given instructions about the short message service (SMS) text message system that will be used in the study. At any time that is convenient for you, this confidential system will send you a few short questions by cell phone via daily text messages that will ask about your vaginal bleeding or spotting and via weekly text messages about your use of the study product. If you do not have a cell phone with texting service, the study team will provide you with one.

o Receive treatment or be referred for treatment for any issues that the study staff may find

o Receive test results, if available

o Talk with study staff about any of your questions. Study staff will talk with you if you encounter any problems or symptoms while undergoing any of the procedures listed above.

o Be reimbursed for your visit

o Schedule your next visit, if applicable.

Follow-Up Visits

After Visit 2 Enrollment (Day 0), you will have Visits 3-14 on Days 2, 14, 28, 30, 44, 58, 60, 74, 90, 91, 92, and 93 or 94 as listed in the chart above. Most study visits will take about ***[SITE TO INSERT TIME]***, except for Visit 11 (Day 90) which may take about ***[SITE TO INSERT TIME]***. Study staff can answer any questions you may have about the procedures listed below.

At each follow-up visit (except where noted otherwise), you will:

- Update study staff with your contact information
- Provide study staff information about your study product use
- Discuss any health or medical problems you may be currently experiencing or that have occurred since your last visit (including what medications you are taking)
- Talk with study staff about STIs, HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex, if needed
- Be asked about any vaginal bleeding or spotting you may have had since your last visit
- Talk with study staff about any problems that you may be experiencing related to using the VR or procedures performed during your last visit
    - As needed, study staff will speak with you again and answer your questions about the requirements of the study and using the VR, including keeping the VR in place and not removing it between visits
- Undergo a targeted physical exam, if indicated
- Have about ***[SITE TO INSERT AMOUNT]*** of blood collected for research purposes:
    - to measure the levels of study drugs
    - to test for serum progesterone and estradiol
- Have a pelvic examination, if indicated
    - Study staff will ask if you are experiencing symptoms of an infection
    - If indicated, the study doctor may use a speculum to check your vagina and cervix for signs of problems due to the ring or infection, and to collect vaginal fluid to test for bacteria and organisms
- Have a breast examination, if indicated
- Have vaginal fluid samples collected via swabs to measure the levels of study drugs
- Receive any available test results
- Be reimbursed for your visit
- Have your next visit scheduled
- Receive male condoms, if you need them.

In addition to the procedures listed above, it is possible that study staff may need to perform additional tests if medically necessary (for example, you report having symptoms of a urinary, genital, or other infection and/or other issues).

Visit 4 (Day 14)

At this visit, you will also:

- Have your urine tested for pregnancy
- Have a pelvic examination with a speculum
- Undergo a cervical biopsy. Study doctors will take approximately 3 small tissue samples from your cervix, each about the size of a grain of rice. These samples will be used to see how much of the study drug is in your tissue and for research purposes. It is important that you do not put anything in your vagina for 24 hours before the collection of the biopsies and one week after, including to avoid sexual intercourse, because you may be at higher risk for getting or spreading an infection until the biopsy sites have healed.

Visits 5 and 8 (Day 28 and 58)

Visit 5 and Visit 8 will take place after you have worn the VR for approximately 28 and 58 days after your Enrollment visit respectively. At these visits, you will also:

- Remove the VR, wash and store it in the clinic for 2 days (Group 2 participants only)

Visits 6 and 9 (Days 30 and 60)

Visit 6 and Visit 9 will take place after you have worn the VR for approximately 30 and 60 days respectively. At these visits, you will also:

- Have your urine tested for pregnancy
- Have a pelvic examination
- Undergo a cervical biopsy (Visit 6 only). Study doctors will take approximately 3 small tissue samples from your cervix, each about the size of a grain of rice
- Re-insert the study VR that had been removed and stored in the clinic for 2 days with a vaginal exam performed by a study clinician after the VR is in place again (Group 2 participants only).

Visits 7 and 10 (Day 44 and 74)

Visit 7 and Visit 10 will take place after you have worn the VR for approximately 44 and 74 days after your Enrollment visit respectively. At these visits, you will also:

- Have a pelvic examination
- Have vaginal fluid samples collected with swabs to test for bacteria
- Have vaginal fluid collected by rinsing your vagina with a small amount of sterile salt water.

Visits 11 – PUEV/Early Study Termination Visit Ring Removal (Day 90)

Visit 11 will take place after you have worn the VR for approximately 90 days. At this visit, you will also:

- Have your urine tested for pregnancy
- Have about ***[SITE TO INSERT AMOUNT]*** of blood drawn for HIV testing; to test the health of your blood, liver and kidneys; and to test for a hormone-related protein (sex hormone binding globulin, or SHBG) and albumin

- Talk with study staff about STIs, HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex
- Have a general physical examination
- Have a breast examination
- Have a pelvic examination
- Have vaginal fluid samples collected to test for bacteria via swabs
- Undergo a cervical biopsy. Study doctors will take approximately 3 small tissue samples from your cervix, each about the size of a grain of rice.
- Remove the study VR
- Be asked to participate in an in-depth interview with a trained staff member to discuss your experiences during study participation. You will be asked questions about your experience with using the ring, your preferences and opinions, any problems you may have had using the ring. The interviews will be audio-recorded to make sure to record your words exactly how you said them. The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or made up names, and the hardware will be physically protected in a locked area. This means that no one other than the study team will have access to your responses. The information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-044/IPM 053/CCN019 study team for the purposes of this research.

Visit 14 (Day 93 or 94)

Visit 14 will take place 3 or 4 days after removing the study VR. At this visit, you will also:

- Talk with study staff about the contraceptive method that you would like to use after this visit
- Schedule your first follow-up phone call
- Receive urine pregnancy test kits to perform at home on the morning of your follow-up phone calls

Visit 15-18/Phone Calls (1, 4, 8 and 12 Weeks After Ring Removal)

For Visits 15-18, you will be contacted by phone at home during the 12 weeks after you have removed the study VR. The Week 1 phone call is required, but the phone calls at 4, 8, and 12 weeks after ring removal will only be conducted if you do not use birth control with hormones or if your menses has not returned since the previous phone call. You will be asked to perform a pregnancy test at home on the morning of each call and will be followed for up to three months to find out when your first period comes after the VR is removed. Each phone call will take between ***[SITE TO SPECIFY TIMEFRAME]*** to complete.

At each applicable phone call, you will:

- Update study staff with your contact information
- Discuss any health or medical problems you may be currently experiencing or that have occurred since your last visit (including what medications you are taking) (Visit 15 only)

- Talk with study staff about STIs, HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex, if needed
- Receive any available test results (Visit 15 only)
- Be asked if you have had your period since your last phone call
- Be asked about the result of the home pregnancy test you perform on the morning of the phone call
- Schedule next visit/contact, if necessary.

If you do not have a period within 3 months after ring removal, you will be referred for medical evaluation.

Additional Visits and Procedures

It may be necessary for you to have additional visit(s) and/or provide additional samples if any of the study procedures at any visit need to be repeated due to one or more of the following:

- Issues with sample processing, testing or shipping
- If you are experiencing any symptoms or changes in your physical condition
- If tests or procedures were missed or not conducted.

Additional testing may be performed as part of quality control.

What are the possible risks, side effects and discomforts of the study?

As with any research study, there may be adverse events or side effects that are currently unknown and could be permanent, severe, or life threatening. The VRs used in this study may have side effects, some of which are listed below. Please note that this list does not include all the side effects that are possible with these VRs. This list includes the more serious or common side effects with a known or possible relationship. If you have questions concerning VR side effects, please ask the study staff at your site. You should report any new or continuing symptoms to the researchers right away. A study doctor is available 24 hours a day, every day of the week in case you have any questions or need to report any problems.

Risks of Vaginal Rings

Use of the study VR may lead to vaginal symptoms, including:

- Irritation
- Increased discharge
- Discomfort (including with vaginal intercourse if it were to occur)

It is possible that a participant may have an allergic reaction to the study product. Symptoms of an allergic reaction include rash or other skin irritation, itching, joint pain, or difficulty in breathing.

Risks of Dapivirine Vaginal Rings

Based on data from the two large studies looking at the effectiveness of the DPV VR, the most commonly reported side effects (occurring in greater than or equal to 10% of

participants) are listed below; it should be noted that a causal association has not yet been determined.

- Metrorrhagia (irregular uterine bleeding)
- Chlamydia (STI)
- Urinary tract infection
- Menorrhagia (heavy or prolonged menstrual bleeding)
- Gonorrhea (STI)
- Upper respiratory tract infection
- Vaginal yeast infection
- Female genital infection
- Bacterial vaginosis (vaginal infection)

As with any product inserted vaginally, the possibility of toxic shock syndrome exists. Toxic shock syndrome is a rare but serious illness caused by poisons (toxins) released by some types of *Staphylococcus aureus*, a common bacterium. While the likelihood of this occurring is rare, it is important that you alert the study staff if you experience any symptoms associated with toxic shock syndrome, such as sudden high fever, a faint feeling, diarrhea, headache, a rash, and muscle aches.

Risks of Levonorgestrel

LNG has been approved for use in contraceptive products for more than three decades including Plan B®, Jadelle®, Norplant®, and Mirena®.

The most common adverse reactions reported in clinical trials of Plan B® were:

- Heavier menstrual bleeding
- Nausea
- Lower abdominal pain
- Fatigue (feeling tired)
- Headache
- Dizziness

The most common adverse reactions reported in clinical trials of an LNG-releasing implant (Jadelle®) were:

- Headache
- Nervousness
- Dizziness
- Nausea
- Changes in menstrual bleeding
- Cervicitis (inflammation of the cervix)
- Vaginal infection
- Vaginal itching
- Vaginal discharge
- Pelvic pain
- Breast pain
- Weight gain

- Acne
- Bleeding at implant insertion site (not applicable to vaginal rings)

The most common adverse reactions reported in clinical trials of a different LNG-releasing implant (Norplant®) were:

- Prolonged, frequent, or irregular bleeding
- Lack of vaginal bleeding (amenorrhea)
- Infrequent bleeding or spotting

The most common adverse reactions in more than 5% of users (more than 5 out of 100 users) for Plan B®, Jadelle®, and the Mirena® IUD are similar and include:

- Uterine/vaginal bleeding alterations including amenorrhea (abnormal absence of menstrual bleeding), menorrhagia (abnormally heavy menstrual bleeding) and intermenstrual bleeding (vaginal bleeding between monthly menstrual periods)
- Abdominal/pelvic pain
- Headache/migraine
- Acne
- Depressed/altered mood
- Breast tenderness/pain
- Vaginal discharge
- Nausea

Other rare and potentially more serious adverse reactions associated with continued LNG use that have been reported are:

- Ectopic pregnancy (a pregnancy outside the uterus)
- Ovarian cysts (fluid-filled sac within the ovary)
- Thrombosis (blood clots)
- Idiopathic intracranial hypertension (increased pressure around the brain, particularly in obese participants)

Risks of Dapivirine-Levonorgestrel Vaginal Ring

Based on preliminary results from the first study of the DPV-LNG VR, reported adverse reactions that are possibly related to the VR include:

- Abdominal distension (expansion due to air (gas) or fluid accumulation)
- Headache
- Uterine cramping
- Nausea
- Increased appetite
- Breast tenderness
- Vaginal discharge
- Vaginal odor
- Vulvovaginal discomfort (discomfort to the vagina or the female external genital area)
- Hot flush (sudden feeling of feverish heat)

It should be noted that a causal association between the above side effects and the study products has not yet been determined.

Risks of Discussing HIV and Sexual Behaviors

You may become embarrassed and/or worried when discussing your sexual practices, ways to protect against HIV and other STIs, and your test results. You may be worried while waiting for your test results. If you have HIV or other infections, learning this could make you worried. Trained study counselors will help you deal with any feelings or questions you have.

Risks of Blood Draws

Whenever your blood is drawn, you may have:

- Discomfort
- Feelings of dizziness or faintness
- Bruising, swelling and/or infection

Risks of Pelvic Exams and Vaginal Fluid Collection

During pelvic exams and cervical and vaginal fluid collection you may feel discomfort or pressure in your vagina, genital area and/or pelvis. You may also have vaginal bleeding or spotting, which should stop shortly after the examination.

Risks of Cervical Biopsy Collection

Cervical biopsies carry the risk of discomfort or pain during the procedure and for a few hours afterwards. You may have mild vaginal spotting (bleeding) for one or two days. Please do not use aspirin (over 81 mg per day) and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours before and after the collection of the cervical biopsies. If you engage in sexual intercourse before the biopsy has healed you may experience some temporary discomfort. If you are sexually active you may also be at increased risk for STIs and HIV acquisition, if exposed. There is a small risk of infection and heavier bleeding.

Risk of Breach of Confidentiality

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. However, it is possible that your involvement in the study could become known to others, and that social harms may result (for example, because participants could become known as HIV-positive or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families, communities, and/or employer(s). Finding out your HIV or STI status could cause depression, suicidal thoughts and/or problems between you and your partner. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

If you are having suicidal thoughts call the study doctor at the telephone number listed on the first page of this form. If you feel in crisis, you can call 911 and/or a Nationwide Suicide Hotline that is answered 24 hours a day with a skilled, trained counselor. One example is the National Suicide Prevention Lifeline at 1-800-273-TALK (8255).

Sexual Practices, Pregnancy, and Breastfeeding:
LNG is widely used in different types of hormonal birth control; however, **it is not known whether the study VR containing LNG can prevent pregnancy**. LNG is not recommended for use by women who are pregnant or may be pregnant. We do not know what effect DPV has on pregnancy, including the effect of DPV on the fetuses of women who use the VR when pregnant, or the babies of women who use the VR when breastfeeding. Because of this, anyone who is pregnant or breastfeeding may not join this study. **Participants who join the study must agree to use an acceptable method of contraception** (see Screening Visit for details). Participants who join this study must also agree to be sexually abstinent starting 24 hours prior to the Enrollment Visit and clinical visits where samples are taken and for one week after each cervical biopsy. Participants who join this study will have pregnancy tests while in the study.

If you become pregnant at any time during the study, study staff will refer you to available medical care and other services you may need.
The study does not pay for this care. You will not receive (or you will stop using) the study VR and you will exit the study. The outcome of your pregnancy is important to study staff; therefore, your pregnancy will be followed until the results of your pregnancy are known. We may contact you to find out about the health of your pregnancy. If you become pregnant and you deliver a baby from that pregnancy, we will contact you up to approximately one year after your delivery to collect information about the health of your baby.

If You Become Infected with HIV
Although a 25 mg DPV VR was recently shown in two large studies to be safe and to help to prevent HIV, **this study is not testing to see if the study VRs prevent HIV infection, and your participation in this study will not cause HIV infection.** The study drugs do not cause HIV. However, there is always a chance that through sexual activity or other activities that you may become HIV-positive. In the unlikely event that you become HIV-positive, study staff will give you counseling and refer you for medical care and other available services. Tests may be performed to see if you have HIV drug resistance. This will allow doctors to know what HIV drugs would be best for the treatment of your type of HIV. If the HIV tests indicate you may be infected with HIV, you will stop using the VR. If HIV infection is confirmed, you will stop your participation in this study. You may be referred to other research studies.

What are the possible benefits from taking part in this study?

You will receive HIV/STI risk reduction counseling, HIV and STI testing, physical and pelvic examinations, and routine laboratory testing, including tests to check the overall health of your liver and kidneys.
You will be offered free male condoms if you need them. This study cannot provide you with general medical care, but study staff will refer you to other available sources of care as needed. If you test positive for HIV, you will be referred for medical care, counseling, and other services available to you. If you have an STI diagnosed, you will

receive medicine or a referral, if needed. Patients in the future may benefit from what we learn in this research study.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

You will be told of any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the VR may be causing bad effects, you will be told about this. Additionally, you will be told of any new information about other effective HIV-prevention products as they become available. You will also be told when the study results are available, and how to learn about them.

May I withdraw, at a future date, my consent for participation in this research study?

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care provided by a hospital or affiliated health care provider or your current or future relationship with a health care insurance provider. If you do not want to be in the study or you stop the study at a later time, you will not be penalized or lose any benefits.

If I agree to take part in this research study, can I be removed from the study without my consent?

The researchers can ask you to stop participating in the study without your permission for the following reasons:

- The study is cancelled by the US FDA, US NIH, International Partnership for Microbicides (IPM, the nonprofit organization that supplies the VRs), the US Office for Human Research Protections (OHRP), the MTN, the Contraceptive Clinical Trials Network (CCTN), the local or other government or regulatory

agency, or the Institutional Review Board. An Institutional Review Board is a committee that watches over the safety and rights of research participants
- The Study Monitoring Committee recommends that the study be stopped early. The Study Monitoring Committee reviews the progress of the study and the kinds of effects that people report while they are participating in the study
- You are found to be infected with HIV
- You become pregnant
- You are found to use recreational injection drugs
- You report the use of PEP for HIV exposure
- You report the use of PrEP for HIV prevention
- Study staff decide that using the VR would be harmful to you, for example, if you have a bad reaction to the study ring
- Other reasons that may prevent you from completing the study successfully, such as inability to consistently keep appointments

If study staff ask you to stop using the VR, you will be asked to complete an interim visit during which time the procedures highlighted to occur at Visit 11 will be completed. Thereafter, you may be asked to continue your regular clinic visit schedule with modified procedures, unless otherwise informed by study staff.

In the event that you are removed from or choose to leave this study, you will be asked to return your VR and complete a final evaluation. If you do not have the VR with you at the time of your contact with staff, staff members will make every effort to assist you in returning the ring as soon as possible. At this visit, you will have the same procedures listed above for Visit 11 (Day 90).

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?

None of the services and/or procedures (study visits, the study VR, physical and pelvic exams, laboratory tests) you receive during this research study will be billed to you or your health insurance. If you receive a bill or believe that your health insurance has been billed for something that is part of the research study, notify a member of the study staff.

You will be referred for treatment for infections passed through sex, including HIV, for the duration of the study, and this treatment will be billed to you and/or your health insurance. You and/or your health insurance will be charged in the standard manner for services and procedures provided for your routine care. You will need to pay any costs for medical care for problems not related to the use of the study VRs. You will need to pay any costs for any visits to the Emergency Room not authorized by one of the researchers unless immediate medical care is needed.

Will I be paid if I take part in this research study?

[*SITE TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT*]: You will receive ***[SITE TO INSERT AMOUNT $XX]*** for your time, effort, and travel to and from the clinic at each scheduled visit. You will receive ***[SITE TO INSERT AMOUNT $XX]*** for responding to text messages. You will receive ***[SITE TO INSERT AMOUNT $XX]*** for the phone call/contact after ring removal. You may receive ***[SITE TO INSERT AMOUNT $XX]*** for any visits which occur in between your normally scheduled visits. You will be paid at the end of each study visit / monthly for completed study visits / quarterly (every 3 months) for completed study visits. If you do not finish the study, you will only be paid for the visits you completed.

Who will pay if I am injured as a result of taking part in this study?

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. If you become ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you for ongoing treatment for the injury, if needed. IPM will be responsible for compensation for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research center or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because you used other medicine during the study that you did not tell us about
- Any injury that happens because you did not follow instructions given by the study doctor or nurse
- Any injury that happens because of negligence on your part

To pay these medical expenses, the sponsor will need to know some information about you, like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

Who will know about my participation in this research study?

Any information about you obtained from this research will be kept as confidential (private) as possible. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. Records related to your involvement in this research study will be stored in a locked file cabinet at the research site. Your records will be maintained in such a manner that it is not possible to link the research data to your identity. Only the investigators and their research staff have access to the research records.
Information from the records will be entered into a computer database. For the computer records, your identity will be indicated by an identification number rather than by your name, and the information linking these identification numbers with your identity will be kept separate from the computer records. Any publication of this study will not use your name or identify you personally.

All HIV testing information will be handled in compliance with the state law on HIV-related confidential information. For visits conducted in person where HIV test results are provided, confidentiality will be maintained by providing the results in a private room. If an HIV test is done at the Day 90/Study Early Termination Visit, you will be given the opportunity to receive results in person, if available. If you decline and prefer to receive results by phone, your identity will first be confirmed before you are given the test results. After you receive the results, you will have the opportunity to have any questions answered, and post-test counseling will be provided.

As part of this study, we are also requesting your authorization or permission to review your medical records to obtain past and current medical information from hospital and other medical facilities.

We will obtain information concerning your diagnosis, age, past medical history, diagnostic procedures, and results of any tests that were already done as part of your standard medical evaluations at hospitals. We will use this information to determine whether you meet the conditions for participation in this study, to compare your earlier test results to the findings from this study and, if possible, to use your previous exam results in place of or in addition to some of the exams needed for this study.
The study staff may use your personal information to verify that you are not in any other research studies. This includes studies conducted by other researchers that study staff may know about. The results of any visits that you make to the Emergency Room because of issues related to the study will become part of your medical records at the hospital. Other information gathered during this study will only be kept at the research site as described above.

Who will have access to identifiable information related to my participation in this research study?

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals and their representatives or designees will or may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study:

- Research Conduct and Compliance Office for the research site
- The sponsors of this research study, the National Institutes of Health (NIH) and the Microbicide Trials Network (MTN)
- The Food and Drug Administration (FDA)
- The Office of Human Research Protection (OHRP)
- Other local, US and international regulatory authorities
- IPM, the organization supplying the study vaginal rings and CCTN, including study monitors
- Health Decisions (a research organization that monitors CCTN sponsored clinical trials for safety and data quality)
- Study staff

- Site Institutional Review Boards or Ethics Committees

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of ***[SITE TO INSERT]*** years and for as long (indefinite) as it may take to complete this research study. Your audio recordings, notes and transcripts will be kept for at least two years after the vaginal ring is approved for marketing or two years after all developmental research on the vaginal ring is stopped.

May I have access to my medical information that results from my participation in this research study?

In accordance with the Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records, filed with your health care provider.

Is my participation in this research study voluntary?

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary.

(Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care provided by a hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your doctor may be involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

[SITE TO INCLUDE/AMEND THE FOLLOWING]:
Following study participation in the study, you may be referred to other research studies.

What additional confidentiality (privacy) protections are provided by a federal Confidentiality Certificate?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose any information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings; for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally-funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. Finally, you should also understand that this federal Certificate does not prevent study doctors from taking steps, including reporting to appropriate authorities, to prevent serious harm to yourself or others. If the study doctors learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by state law, the appropriate agencies.

CLINICALTRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. 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.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046

- or call **toll free**: 877-992-4724

or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00024525.

OPTIONAL CONSENT FOR LONG-TERM STORAGE AND FUTURE TESTING OF SPECIMENS

There might be a small amount of blood, cervicovaginal fluid or cervical tissue left over after we have completed all study related testing. We would like to ask your permission to store these leftover samples and related health information for use in future studies, such as future research to fight HIV and other related diseases. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range.

If you agree, your samples and related health data will be stored safely and securely at facilities that are designed so that only approved researchers will have access to the samples. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you.

The type of testing planned for your leftover specimens is not yet known. However, samples may be used by the MTN Laboratory Center to complete additional quality assurance testing, ensuring that the tests work correctly and supply accurate data. No genetic testing on either a limited set or the full set of genes is planned for leftover specimens that are stored for the purposes of future research. It is important that you know that any future testing or studies planned for these specimens must be approved by an Institutional Review Board before they can be done.

You can still enroll in this study if you decide not to have leftover samples stored for future studies. If you do not want the leftover samples stored, we will destroy them. You can withdraw your consent for the storage and future testing of specimens at any time by providing your request in writing to the principal investigator of this research study at the address listed on the first page of this form. However, researchers will not be able to destroy samples or information from research that is already underway.

_____ Initials and Date	I **DO agree** to allow my biological specimens and health data to be stored and used in future research studies.
_____ Initials and Date	I **DO NOT** agree to allow my biological specimens and health data to be stored and used in future research studies.

VOLUNTARY CONSENT: All of the above has been explained to me and all of my current questions have been answered. I agree that the data collected during this study can be processed in a protected computerized system by a member of the study team. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form. Any questions which I have about my rights as a research participant will be answered by the IRB office. By signing this form, I consent to participate in this research study and provide my authorization to share my medical records with the study team. A copy of this consent form will be given to me.

_____	_____	_____
Participant's Printed Name	Participant's Signature	Date and Time

CERTIFICATION OF INFORMED CONSENT: I certify that I have explained the nature and purpose of this research study to the above-named individual, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual has about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date and Time