FAME-103B: A Randomized Double-Blind Cross-Over Study of Self-Insertion of Two Formulations of a Placebo Vaginal Film

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National Institutes of Health

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Protocol Signature Page

Protocol Title: FAME-103B: A Randomized Double-Blind Cross-Over Study of Self-Insertion of Two Formulations of a Placebo Vaginal Film

Protocol Version: Version 1.0

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

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Protocol Chair (PRINT NAME)

_____

Signature of Protocol Chair

_____

Date (Month/Day/Year)

_____

Protocol Co-Chair (PRINT NAME)

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Signature of Protocol Co-Chair

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Date (Month/Day/Year)

FAME-103B

LIST OF ABBREVIATIONS

AE	adverse event
ARV	Antiretroviral
CRF	case report form
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
STI	sexually transmitted infection

FAME-103B

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FAME-103B

PROTOCOL SUMMARY

Short Title:	FAME-103B
Chairs :	Sharon Hillier, PhD; Katherine Bunge, MD MPH
Sample Size:	30 pre-menopausal women without urogenital complaints
Study Population:	The recruitment strategy is likely to capture a diverse population as this community is comprised of approximately 48% White, 48% African-American and 4% other ethnicities including Hispanic, Asian, Indian and Native American. Persons below the age of 18 will not be recruited.
Study Sites:	UPMC Magee-Womens Hospital, Pittsburgh, PA
Study Design:	Randomized cross-over study of self-insertion of two formulations of a placebo vaginal film
Study Duration:	One study visit lasting approximately 90 minutes
Study Film Products:	Two formulations of a placebo vaginal film (high and low level ammonio-methacrylate copolymer type B (Eudragit®)

Key Roles

1.1 Protocol Identification

Protocol Title: FAME-103B

1.2 Sponsor and Monitor Identification

Funding Agency: DAIDS/NIAID/NIH
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2 Introduction

2.1 Vaginal films for HIV prevention

Sexual transmission accounts for the majority of new HIV infections worldwide. While most cases of sexual transmission involve both a male partner and a female partner, women are disproportionately impacted by the sexual transmission of HIV[1]. This disproportionate impact arises from a combination of biologic, social, and economic factors. Women at risk face formidable challenges in protecting themselves from HIV infection, including power differentials, gender norms, and economic dependence.

Topical microbicides are agents designed to prevent or substantially reduce the acquisition and transmission of HIV when applied to the genital or gastrointestinal mucosa. In addition to preventing HIV infection, topical microbicides may satisfy two critical needs: affordability and female control. Topical microbicides also have the potential for high acceptability for both male and female partners. Acceptability and utility of topical microbicides can be maximized by the development of an array of dosing formulations.

Vaginal films are an attractive dosing option for several reasons. In terms of manufacturing, films are inexpensive, scalable, physically and chemically stable, uniform with regards to product content, and amenable to combinations of active ingredients. In terms of use, films are discreet, portable, and easy to store. Vaginal films can deliver fixed doses of microbicidal agents with minimal mess and without an applicator. The small volume of vaginal films may also result in less dilution of endogenous antiviral or antibacterial properties of vaginal fluids compared to vaginal gels. In studies of spermicidal film, women have found vaginal films to be acceptable[2,3,4]. When Vaginal Contraceptive Film (VCF) was compared to foaming tablets containing nonoxynol-9 (N-9), contraceptive film was preferred in three different countries[2]. Ninety-seven percent of 59 Mexican women, 60 percent of 52 Dominican women, and 86 percent of 51 Kenyan women reported liking contraceptive film. In particular, they cited the following favorable characteristics: ease of use, general feel or comfort, additional lubrication, and lack of side effects. Over eighty percent of Cameroonian sex workers, who participated in a large randomized placebo-controlled trial of N-9 film, reported that they would use the film were it found to be effective against HIV[3]. In Zambian focus groups, placebo vaginal film was preferred over placebo vaginal tablets and soft-gel capsules after each product was used once daily for one week [4]. In a study evaluating the acceptability of placebo microbicidal film, soft gel capsule and tablet, African women were instructed to use each of the three products once daily for 7 consecutive days. The film and soft-gel capsule were chosen significantly more often than the tablet as the preferred dosage form (39%, 37% and 25%, respectively). In this particular study, film and soft gel were preferred because of faster dissolving time and easier insertion[4]. In other studies, participants found vaginal films to be less messy than foaming tablets or gel[2,5].

2.2 Integrated Preclinical/Clinical Program

The Film Antiretroviral Microbicide Evaluation (FAME) program brings together an inter-disciplinary group of research scientists from four academic institutions: University of Pittsburgh, University of Washington, Carnegie Mellon University, and the University of Colorado. The long-term goal of the program is to develop and evaluate an extended delivery vaginal film containing an integrase inhibitor which could provide protection from HIV for one week or more following a single application. The first iteration of the FAME IPCP established proof of concept that vaginal films containing the antiretrovirals (ARVs) dapivirine and tenofovir could deliver drug to target

tissues as effectively as gel formulations of those same ARVs. The second iteration strives to develop an extended release formulation of an integrase inhibitor MK-2048 which will provide coverage for 7 days after each use. FAME-103 is the backbone of this effort.

2.3 FAME-103

FAME-103 is clinical study of a vaginal film containing the integrase inhibitor MK-2048 in a formulation containing either high or low concentrations of the extended release polymer Eudragit®. MK-2048 is a potent 2nd generation integrase inhibitor; the extended platform film to be used in FAME-103 is intended to provide 7 days of protection. The primary objective of FAME-103 is to evaluate the safety of the two formulations of MK-2048 vaginal film. A key secondary objective is to evaluate the pharmacokinetics of the two film formulations.

Because safety and pharmacokinetics are key study outcomes, the active vaginal film will be inserted by a clinician. Product misplacement was noted in the last four clinical trials of vaginal film previously conducted at the University of Pittsburgh. While most participants could successfully insert the vaginal films, incorrect film placement was noted for some. In some instances, the vaginal film stuck to the finger after attempted insertion and in other instances the film was visualized on the external genitalia.

2.4 FAME-103B Rationale

The objective of the FAME-103B study is to evaluate whether study participants can self-insert the high and low Eudragit® content placebo films. In previous vaginal film trials conducted at the University of Pittsburgh, participants have had variable success with self-insertion. As the Eudragit® film formulation as an extended platform moves forward with other active pharmaceutical ingredients in clinical trials, understanding whether the level of Eudragit® in the film impacts ease of insertion is vitally important.

In order to evaluate whether Eudragit® content impacts ease of self-insertion, participants will be asked to self-insert each placebo film and complete a survey reporting their perceptions and experience. Within 10 minutes of the insertion, clinical staff will perform a speculum exam to assess the location of the film and remove the residual film. This study poses minimal risks to participants as the safety of the high Eudragit® placebo film has already been evaluated in FAME-101 and found to be safe. The risk to study participants will also be minimized because the film will be removed immediately after insertion thereby limiting exposure to under 10 minutes for each film. The feasibility of easy film removal after self-insertion has been established by the clinical staff at the Reproductive Infectious Disease Unit at Magee-Womens Hospital who have removed film within 15 minutes of insertion in at least 40 prior participants. Thus, no technical or safety issues with film removal are anticipated.

2.5 Safety Data: Eudragit® platform

The Eudragit® film has a proven safety record.

Pre-Clinical Safety Data
Safety evaluation of the extended release placebo film was performed in a nonhuman primate model. Six pigtailed macaques were exposed to two films per week for two weeks, which is double the proposed human dosing (intended dosing is one film per week). In total, four films were delivered to each macaque over fourteen days. The vaginal microbiota, vaginal pH, and

number of PMNs on gram stained vaginal smears were assessed before the first film placement and after the fourth film placement. The integrity of the cervicovaginal tissues was assessed by colposcopy at each film placement. Of note, there was visible film in the vagina with each film placement. No adverse events were noted by colposcopy; microbiota remained stable with no effect noted on the beneficial H_20_2 producing microorganisms; vaginal pH remained within normal range; and PMN counts remained within the normal range even after more frequent administration than intended for use (Patton, personal communication). The entire study report is presented in Appendix IV.

Clinical Safety Data

FAME-101 was a safety and acceptability study of the higher Eudragit® level. Sixty-four HIV uninfected, healthy women were enrolled. At enrollment the participants were randomized to timing of the follow-up visit. They then attempted self-insertion of the film. Immediately after this attempt, a clinician performed a visual inspection. If most of the film was visualized outside of the introitus, the film was removed by the clinician and a second film placed by the clinician during a speculum examination. Participants returned either 3,7,10 or 14 days after film placement depending on their randomization and then all participants returned for a final safety assessment three weeks after enrollment. Safety assessments, acceptability parameters, and changes to the vaginal microenvironment were assessed at each visit. The persistence of the film was noted.

Eighty-four participants were screened and 64 enrolled. The median age was 26.5 years; 56% were white and 27% non-Hispanic black. The primary endpoint was Grade 2 or higher AEs. There were 6 Grade 2 events; these included bacterial vaginosis, vaginal itching, pelvic cramping (2), friable cervix and adnexal pain. Of these, only bacterial vaginosis and vaginal itching were attributed to study product use. Forty-seven AEs were reported amongst 64 participants. Thirty-one participants (48.5%) reported at least one AE; 22 reported at least one urogenital event. For the women randomized to the 3 and 7 day follow up visit approximately 50% of the participants had visible film on speculum exam (44% and 56%). In summary, the high Eudragit® film was very well tolerated with no concerning safety signals.

3 Study Objectives

3.1 Primary Objective:

- To assess women's ability to successfully insert two formulations of a vaginal placebo film containing differing concentrations of Eudragit®

3.2 Primary Endpoint:

- Visual assessment of film location after insertion attempt (completely inserted, partially inserted, unable to insert)

3.3 Secondary Objectives:

- To explore participants' preference for vaginal film formulation
- To explore participants' challenges with self-insertion

3.4 Secondary Endpoints

- Percentage of participants who prefer the low level Eudragit® film to the high level Eudragit® formulation film with respect to insertion

- Participants' description of identified challenges

4 Study Population

4.1 Selection of the Study Population

The inclusion and exclusion criteria in this section will be utilized to ensure the appropriate selection of study participants.

4.2 Recruitment

For this study, 30 pre-menopausal women, 18 – 45 years of age, will be enrolled over approximately a 3-month period. Participants may be recruited from medical clinics, local colleges, a list of previous study participants and the community by members of the Reproductive Infectious Disease Research staff. This recruitment strategy is likely to capture a diverse population as this community is comprised of approximately 48% White, 48% African-American and 4% other ethnicities including Hispanic, Asian, Indian and Native American. An IRB approved screening script may be used to provide study information and assess minimum eligibility during the recruitment process. After the study has been presented and questions have been answered, participants will be scheduled for an enrollment visit at UPMC Magee-Womens Hospital.

4.3 Study Design Summary

After providing written informed consent, the participant will provide answers to a brief questionnaire, have urine collected for pregnancy testing, and have saliva collected for rapid HIV testing (unless a result from previous 6 months is available). Once deemed eligible, vaginal swabs will be collected (without a speculum) for sexually transmitted infection testing (gonorrhea, chlamydia and trichomonas).

The participant will then be randomized to insertion order for the two formulations of a placebo vaginal film [high and low ammonio-methacrylate copolymer type B (Eudragit®)]. Once a participant is randomized to the film, she is considered enrolled.

Clinic staff will obtain the films from the pharmacy and will provide instruction to the participant on the proper technique of self-insertion. The clinician and the participant will be in the same room during self-insertion of the films but will be separated by a privacy curtain. The clinician will be available to answer questions and document concerns/comments. The participant will attempt self-insertion of the first film and immediately afterward (within 10 minutes) the clinic staff will perform a speculum exam to determine the location of the film. The clinical staff will remove all visible film and ask the participant to complete a brief questionnaire regarding her experience with that specific film. The participant will then be asked to self-insert the second film. After the second film insertion, the clinical staff will perform another speculum exam to determine the film's location and remove any visible film. The participant will then answer another brief questionnaire regarding her experience with the second film as well as additional questions regarding her preference of film and questions surrounding challenges with self-insertion. It is anticipated that gonorrhea, chlamydia and trichomonas testing will be resulted within the week. Participants will be notified of any positive STI test reported by telephone, and necessary treatment and referrals will be provided. It should be noted that STI testing is provided in this study as a courtesy to the participants and not for eligibility purposes.

4.4 Inclusion Criteria

1. Ages 18-45
2. Intact uterus by participant report
3. Agrees to abstain from inserting anything into the vagina for 24 hours prior to the study visit

4.5 Exclusion Criteria

Women who meet any of the following criteria by participant report will be excluded from the study. Of note, the study is limited to premenopausal women with an intact uterus because the mucosal environment differs substantially between pre- and post- menopausal women. Therefore, inclusion of post-menopausal women would introduce heterogeneity into the population.

1. Menopausal (as defined as amenorrhea for one year or more without an alternative etiology)
2. Hysterectomy (including total and supracervical)
3. Currently pregnant or pregnancy within 90 days of enrollment
4. Lactating
5. Symptoms of a urogenital infection including vaginal discharge, pain, odor, or itching
6. Menses at the time of enrollment
7. Known allergy or hypersensitivity to any of the components of the placebo film
8. Any condition that, in the opinion of the Investigator, would preclude provision of consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

5 Study Procedures

This section describes visit-specific study procedures.

5.1 Pre-screening

As part of participant outreach and recruitment strategies, study staff may pre-screen potential study participants (e.g. via telephone). During these interactions, study staff may use an IRB approved telephone script to explain the study to participants and ascertain elements of presumptive eligibility, to be confirmed at the time of enrollment. If the participant is eligible based on a screening script her name and appointment time will be placed on the script. If she

signs consent, the telephone script will then become part of her research record. If she does not sign consent, the form will be de-identified.

5.2 Study visit

The participant will present to the study clinic. Written informed consent will be obtained. A brief medical history will be taken to ensure eligibility. Height and weight will be obtained and participants will be asked a brief baseline questionnaire, which will include questions related to previous film use. Saliva for HIV antibody testing (unless a negative result is available from the past 6 months), urine for pregnancy testing and vaginal swabs for *Neisseria gonorrhoeae, Chlamydia trachomatis*, and *Trichomonas vaginalis* nucleic acid amplification testing will be collected. The urine pregnancy test result will be available before the participant is randomized. Counseling and referral will take place as necessary. HIV test results will be available before the end of the visit and will be provided to the participant. Given the very low risk of the women being enrolled in this study, HIV test result will not be needed prior to randomizing. In the very unlikely event of a positive rapid HIV test, a blood sample will be drawn to send to the main UPMC laboratory for confirmatory testing. The vaginal STI testing results will not be available in real time and will not impact eligibility.

Clinic staff will obtain study product from the pharmacy and will instruction the participant on the proper technique of self-insertion. The participant will attempt self-insertion of the first film and immediately afterward the clinic staff will perform a speculum exam to determine the location of the film. The clinical staff will remove all visible film.after the clinician verifies placement. The clinician will use an instrument as needed (e.g. forceps) to grab and remove the film. This method was successful in removing the entire piece of film from previous studies. The study staff will then ask the participant to complete a brief questionnaire regarding her experience with that specific film. The participant will then be asked to self-insert the second film. After the second film insertion, the clinical staff will perform another speculum exam to determine the film's location and remove any visible film. The participant will then answer another brief questionnaire regarding her experience with the second film as well as additional questions regarding her preference of film and questions surrounding challenges with self-insertion.

It is anticipated that gonorrhea, chlamydia and trichomonas testing results will be reported within the week. Participants will be notified of any positive STI test result by telephone, and necessary treatment and referrals will be provided. It should be noted that STI testing is provided in this study as a courtesy to the participants and not for eligibility purposes

The table below outlines procedure to take place at the Study Visit.

Table 1: Study Visit Procedures

Study Visit	
Component	Procedures
Administrative/ Interview	Informed consent document Collect contact information Eligibility questionnaire Demographics Visit Questionnaire (including experience using films) Height and Weight HIV pre- and post-test counseling Randomization Verbal self-insertion instructions Product questionnaire Insertion challenges discussion Reimbursement
Saliva*	Rapid HIV test if no confirmed negative HIV test is available from the previous 6 months
Urine	Pregnancy test
Vaginal Swab (w/o speculum)	*Neisseria gonorrhoeae, Chlamydia trachomatis*, and *Trichomonas vaginalis* nucleic acid amplification testing
Study Product	Self-insertion of two formulations of a placebo vaginal film [high and low ammonio-methacrylate copolymer type B (Eudragit®)]
Pelvic Exam	Visual Inspection of vaginal film placement and removal of residual film following each film insertion

*If rapid HIV testing using saliva is positive, confirmatory testing will be performed by collecting a small blood sample to be sent to the UPMC Central Laboratory

5.3 Telephone follow-up

Clinic staff will call participants with the results of the *Neisseria gonorrhoeae, Chlamydia trachomatis*, and *Trichomonas vaginalis* nucleic acid amplification testing when available if resulted positive. This is consistent with standard clinical care. Treatment will be provided per CDC recommended guidelines, as necessary.

6 Study Product

6.1 Regimen

Each participant will receive one vaginal film containing high level Eudragit® and one vaginal film containing low level Eudragit®.

6.2 Administration

After eligibility is confirmed, site staff will randomize the participant to sequence of film insertion. The site staff will retrieve two films from the pharmacy. The site staff will provide insertion instructions to the participant and the participant will self-insert the vaginal films in the order assigned by randomization. Neither the participant nor the study staff will know which film is the higher level or lower level film. The order of use will be documented in the participant's record.

6.3 Study Product Formulation

Participants will receive two placebo films that differ in the content of Eudragit. The films are 2" x 2."

6.4 Study Product Supply and Accountability

Study product was manufactured and package by Benefit Coatings, Stratford, CT, in compliance with cGMP. The packaged study product will be provided to the UPMC Magee-Womens Hospital Pharmacy and will be labeled to maintain the blind of the films (e.g. film A and film B). All study product will be available to the study staff through the Magee Investigational Drug Service Pharmacy.

The Magee research pharmacist will maintain complete accountability records of all study products received for this protocol and dispensed to participants.

The film is packaged into a foil-lined pouch and stored at room temperature.

In the event that a participant is unable to insert the film (e.g. sticks to her finger), insertion will be deemed unsuccessful and the participant will not be dispensed another replacement film.

However, if a film is dropped or damaged, the film will be discarded and accounted for by the clinical staff in the participant record and a new replacement film will be obtained from the pharmacy.

6.5 Study Product Dispensing

Study products will be dispensed only to enrolled participants upon receipt of a written study product order form signed by an authorized prescriber.

7 Laboratory Evaluations

7.1 Laboratories

<u>UPMC Magee-Womens Hospital Clinical and Translational Research Center</u>

- Rapid HIV test (saliva)
- Pregnancy Test (urine)

<u>Presbyterian/Shadyside Laboratory- UPMC Central Laboratory</u>

- Confirmatory HIV test (blood)

Magee-Womens Research Institute- Hillier Laboratory

- *Chlamydia trachomatis* (vaginal)
- *Neisseria gonorrhoeae* (vaginal)
- *Trichomonas vaginalis* (vaginal)

7.2 Specimen Collection and Processing

The site will adhere to the standards of good clinical laboratory practice and site standard operating procedures for proper collection, processing, labeling, handling, and transport of specimens. In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to recollect specimens.

7.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated fluid, appropriate secretion precautions will be employed by all personnel in the handling of all specimens for this study as recommended by the CDC and NIH.

8 Assessment of Safety and Clinical Management

8.1 Safety Monitoring

The study site investigators are responsible for continuous close safety monitoring of all study participants and for alerting the Protocol Chairs if unexpected concerns arise. Appropriate safety monitoring will be contingent upon excellent communication between study participants and study staff, and upon cooperation among study staff, and the physician investigator.

Given this study involves a single study visit, use of placebo films which are immediately removed after insertion, and poses minimal risk to the participant, adverse events are not expected. In the very unlikely event that an unanticipated event occurs, the protocol chair and the DAIDS medical officers will be made aware of the event, and the event will be reported as applicable to the policies outlined on the IRB website: www.irb.pitt.edu.

8.2 Adverse Events Definitions

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. The term “investigational product” for this study refers to the two placebo films.

Given that the study product is a placebo product and the product will be removed immediately after insertion, it is exceptionally unlikely that any adverse events will be noted during the single visit. Nonetheless, should one occur study site staff will document any AEs in source documents regardless of severity and presumed relationship to study product.

The PI/designee will grade the severity of each AE and the relationship of the AE to study product:

AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version2.0, November 2014 and the Female Genital Grading Table for Use in Microbicide Studies (Appendix 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, December 2014). AEs not included in the Female Genital Grading Table will be graded by the DAIDS AE Grading Table Version 1.0, December 2004. In cases where a genital AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

The relationship of all AEs reported on CRFs will be assessed based on the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 1.0, dated January 2010), the product Package Inserts and Investigators Brochures, and the clinical judgment of the PI/designee. Per the Manual for Expedited Reporting of Adverse Events to DAIDS, the relationship categories that will be used for this study are:

- *Related*: There is a reasonable possibility that the AE may be related to the study agent(s)
- *Not related*: There is not a reasonable possibility that the AE is related to the study agent(s)

The DAIDS Table for Grading Adult and Pediatric Adverse Events, the Female Genital Grading Table for Use in Microbicide Studies, and Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS are available on the DAIDS Regulatory Support Center (RSC) web site: http://rsc.tech-res.com/
All AEs will be captured on an AE log form.

8.3 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The Site PI/designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures.

9 Statistical Considerations

9.1 Sample Size and Accrual

The primary aim of the study is to assess proper placement of two vaginal placebo films containing two levels of polymer. Secondary aims are to gather women's preference and experiences through questionnaire and discussion.

In a previous cross-over study of placebo film products, the proportion of 32 women that misplaced a 2" x 2" cellulose film was 41% and 78% misplaced a 1" x 2" film product, with 50% placement concordance between the two films. Twenty-five women will have 80% power to determine whether there is a difference between polymer types of vaginal placebo films based on a McNemar's test evaluated at the .05 significance level. The sample size of 30 women will allow for additional input regarding challenges.

9.2 Statistical analyses

McNemar's test will be used to assess differences in the proportion of misplaced films, defined as partial or unable to insert the vaginal film product based on visual assessment. McNemar's test will also be used to assess differences in preference for the two film products. Conditional logistic regression will be used to assess whether demographic characteristics such as age, race, and BMI are associated with product placement or product preference. Descriptive statistics will be used to summarize participants' challenges with self-insertion of the film products.

9.3 Blinding

All participants will receive a single vaginal film containing high level and low level Eudragit® content placebo films. They will be blinded to the formulation with respect to Eudragit® content and the sequence of insertion. Evaluators of the study endpoints will also be blinded to the film formulation and sequence of insertion.

9.4 Random assignment

The randomization scheme will be generated and maintained by a member of the Data Management Center at the study site and supplied to the Pharmacy. Women will be randomized to the sequence of insertion of the two films, low followed by high Eudragit® content or high followed by low Eudragit® content in a 1:1 ratio using a permuted block design with random block sizes of 2 and 4. In order to minimize bias in group assignment, participants will be given study identification numbers. A study staff member will allot the identification numbers in sequential order as participants become eligible to enroll in the study. Participants will be randomized using REDCap's randomization module to obtain the sequence of product insertion. The film product will be labeled in order to mask the Eudragit® content to the participants and study staff. The randomization scheme will be created for a total of 34 participants; the overage will be created to compensate for participant withdrawals or unusable products.

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